

# Developing new comorbidity indices for cancer populations using administrative data

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# Abstract

## Background

Comorbidity has an important impact on cancer outcomes, but the optimal approach to measuring comorbidity at a population level has not been established.

## Aims

- To review evidence relating to the importance of comorbidity in relation to cancer care and outcomes; and to examine previously developed approaches to measuring comorbidity in this context.
- To assess the usefulness of routinely collected comorbidity data in New Zealand,
- To develop and validate optimised measures of comorbidity using these data for patients with cancer,
- To develop, and compare more simplified measures against the optimised measures.

## Methods

Studies describing methods to measure comorbidity in epidemiological studies related to cancer were identified and reviewed. For this study, development and validation cohorts included patients diagnosed with colorectal, breast, gynaecological, upper gastrointestinal, or urological cancers identified from the national Cancer Registry between July 2006 and June 2008 for the development cohort (n=14096) and July 2008 to Dec 2009 for the validation cohort (n=11014). Data on comorbid conditions identified in administrative hospitalisation and pharmaceutical data were compared with data from manual clinical notes review for a subset of patients. Fifty conditions using administrative hospitalisation and twenty conditions using pharmaceutical data were identified prior to cancer diagnosis. Three sets of indices were developed 1) site-specific indices using hospitalisation data ('C3' indices), 2) a single all-cancer index using pharmaceutical data (PBCI) and 3) three simplified versions of the hospitalisation indices; an all-cancer version and two versions including a subset of conditions (SI1, 2 and 3 respectively). Conditions were weighted according to their log hazard ratios from age and stage adjusted Cox regression models of non-cancer death; and indices were calculated by summing these weights. Performance of these indices was compared

with the Charlson index, a combination of the C3 and pharmacy-based indices, and with each other.

## Results

The review of previously developed comorbidity measures for cancer populations identified 21 separate approaches, with none identified as gold standard. Administrative data were found to be adequate for measuring comorbidity in cancer populations. Comorbidity was associated with poorer survival but the impact varied by condition and across cancer site. No single index clearly outperformed all others for all sites. The best performance overall was achieved with the combined hospitalisation and pharmaceutical indices, particularly for all sites combined, colorectal and upper GI cancers. Generally hospitalisation indices outperformed the pharmaceutical-based index, but the converse was true for non-cancer death for breast and gynaecological cancers. Site-specific weights did not add appreciably to the validity of the indices. Among the simpler indices, the SI2, SI3 and PBCI approaches tended to outperform the Charlson index for all sites combined, although there was little difference between these indices in some sites.

## Conclusion

Measuring comorbidity in cancer populations is important, and the C3-based and PBCI indices provide a useful and valid cancer-specific approach based on administrative data. Site-specific indices were not found to be necessary. Future work includes validating these indices in other cancer populations, preferably outside New Zealand; and potentially working to extend the use of these indices beyond cancer.

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Finally, to the thousands of patients who have made the cancer journey and whose stories are represented in the palest of outlines in the data here, you are not forgotten.

# Statement of participation

This thesis is part of a larger programme of work led by the author of the thesis; the Cancer, Care and Comorbidity (C3) projects. There are two C3 projects, one based on quantitative methods and the other on qualitative methods. The overall hypotheses of the two C3 projects are that: 1) comorbidity has a measurable negative impact on treatment quantity and quality, and cancer survival among cancer patients in New Zealand; 2) Māori diagnosed with cancer receive both a lesser quantity and quality of treatment, and consequently have worse survival than similar non-Māori people with cancer with the same level of comorbidity; and 3) substantial improvements in health outcomes are possible for all, and particularly for Māori, if treatment quality and quantity meet the best standards for all. Both C3 projects were conceived and initiated by me. Associate Professor Louise Signal joined the team in 2010 to lead the qualitative project which is unrelated to the work in this thesis.

The work presented in this thesis was carried out by me to address the question of how best to measure comorbidity in the context of cancer populations in New Zealand. To ensure the adequacy of routinely collected hospitalisation data for measuring comorbidity in the New Zealand context, I compared data that had been manually collected from hospital notes from an earlier study relating to colon cancer patients<sup>1</sup>. I initiated that study, obtained funding for it, and led it as Principal Investigator. Dr Sarah Hill was co-Principal investigator and collected the clinical data. The comorbidity aspects of these data were managed and analysed by me. Gordon Purdie (biostatistician) assisted with the analysis involving comparison of these data with administrative hospitalisation data using an analysis plan developed by me.

Other than this early stage of the work, all data used in this thesis was collected for the purpose of addressing the questions posed in this thesis, as well as the broader questions of the C3 project. For the C3 project, patients diagnosed with specified cancers were identified from the New Zealand Cancer Registry and their data linked to hospitalisation, pharmaceutical and mortality data. The required data variables were identified by me (with input from the C3 team), and Jason Gurney coordinated the communication with the Ministry of health to obtain the data under my supervision.

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<sup>1</sup> Hill, S., D. Sarfati, et al. (2010). "Ethnic disparities in treatment of Māori and non-Māori New Zealanders with colon cancer." *Cancer* **116**: 3205-3214.

Sarfati, D., S. Hill, et al. (2009). "The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study." *BMC Cancer* **9**: 116.

Additional data on treatment were collected from Cancer Centres and private hospitals, but these latter data were not used in this thesis. Detailed hospital notes review was carried out on a subset of patients with liver, stomach and rectal cancers. The protocol for this process was developed by me, and the data were collected by an oncology-trained nurse, Virginia Signal, under my supervision. The day-to-day data management for the full C3 project was carried out by a Research Fellow (Jason Gurney) who was responsible for linking and cleaning the data, as well as data analysis for the main C3 project. Clare Salmond provided assistance with, and checking of, the coding of individual clinical conditions from the hospitalisation data. Additional clinical and pharmaceutical advice was provided by Jonathan Koea (hepatobiliary surgeon), Liz Dennett (colorectal surgeon), Andy Simpson (medical oncologist) and Claire McSherry (oncological pharmacist).

All analyses presented in the thesis were carried out by me except as specified here. Jason Gurney repeated some analyses that had been previously run by me in the development dataset using the validation dataset as a quality assurance measure. The bootstrapping estimates of confidence intervals around c-statistics were provided by a biostatistician, James Stanley. The supervisors of this thesis were not part of the C3 research team, but acted in an advisory capacity.

# Contents

<b>Abstract</b>	<b><i>i</i></b>
<b>Acknowledgements</b>	<b><i>iii</i></b>
<b>Statement of participation</b>	<b><i>v</i></b>
<b>List of Tables</b>	<b><i>xiii</i></b>
<b>List of Figures</b>	<b><i>xvii</i></b>
<b>Chapter 1. Introduction</b>	<b><i>1</i></b>
<b>Chapter 2. Comorbidity and related constructs</b>	<b><i>7</i></b>
<b>What is comorbidity?</b>	<b><i>7</i></b>
<b>Constructs related to comorbidity</b>	<b><i>13</i></b>
Multimorbidity	<i>13</i>
Functional (or performance) status:	<i>14</i>
Disability	<i>15</i>
Allostatic load	<i>16</i>
Frailty	<i>17</i>
Burden of disease/ illness	<i>19</i>
Complexity	<i>21</i>
<b>How are the comorbidity-related constructs linked?</b>	<b><i>22</i></b>
<b>Why focus on comorbidity?</b>	<b><i>23</i></b>
<b>Why might we want to measure comorbidity accurately?</b>	<b><i>24</i></b>
Comorbidity is common.	<i>24</i>
Impact on health services.	<i>26</i>
Impact on patients.	<i>27</i>
Impact on inequities.	<i>28</i>
<b>Summary</b>	<b><i>29</i></b>
<b>Chapter 3: How does comorbidity relate to cancer?</b>	<b><i>31</i></b>
<b>Why might cancer and comorbidity coexist?</b>	<b><i>31</i></b>
<b>Prevalence of comorbidity among cancer patients</b>	<b><i>33</i></b>
<b>Impact of comorbidity on diagnosis of cancer</b>	<b><i>41</i></b>

<b>Impact of comorbidity on treatment for cancer</b>	<b>45</b>
<b>Impact of comorbidity on outcomes from cancer</b>	<b>49</b>
Survival	49
Quality of life	52
Cost of care	53
<b>Impact of comorbidity on inequalities in cancer care and outcomes</b>	<b>53</b>
<b>Summary</b>	<b>54</b>
<b>Chapter 4. Measuring comorbidity: Review of comorbidity indices</b>	<b>57</b>
<b>Review of approaches to measuring comorbidity</b>	<b>59</b>
Methods	59
Results of review	62
Individual conditions or counts of conditions	67
<b>Early approaches to measuring comorbidity (pre 1980s)</b>	<b>68</b>
Cumulative Illness Rating Scale (CIRS)	68
Kaplan-Feinstein Index (KFI)	71
<b>Developments during 1980s</b>	<b>73</b>
Charlson Comorbidity Index (CCI)	73
Diagnostic Cost Group/ Hierarchical Condition Categories (DCG/HCC)	76
<b>Progress during the 1990s</b>	<b>78</b>
Adjusted Clinical Groups (ACG) System	78
Chronic Disease Score (CDS) and RxRisk	79
Index of Coexistent Disease (ICED)	82
Satariano approach	85
Total Illness Burden Index (TIBI)	87
NIA/NCI Collaborative Study: Yancik	89
Elixhauser (comorbidity count and index)	91
Fleming (Comprehensive Prognostic Index)	94
<b>Recent attempts to measure comorbidity</b>	<b>96</b>
NCI (combined) Comorbidity Index	96
American Society of Anesthesiologists' class (ASA)	98
Alcohol-tobacco related comorbidities index	100
Washington University head and neck comorbidity index (WUHNCI)	101
Adult comorbidity evaluation-27 (ACE-27)	102
Tammemagi approach	105

Multipurpose Australian Comorbidity Scoring System (MACSS)	107
Simplified Comorbidity Index	110
<b>Summary and conclusions</b>	<b>112</b>
Content and face validity	112
Criterion validity	113
Reliability	114
Feasibility	114
So which index is best?	119
<b>Chapter 5: Methods</b>	<b>125</b>
<b>Overview:</b>	<b>125</b>
Aims	126
<b>Section 1: Data sources, subjects and variables used</b>	<b>128</b>
Data sources	128
Subjects	132
Variables used in study analyses	133
<b>Section 2: Use of hospitalisation data to measure comorbidity</b>	<b>136</b>
Validation of comorbidity identified using administrative hospitalisation data	136
Optimising the identification of comorbid conditions using hospitalisation data	140
Developing hospitalisation-based comorbidity indices	143
Validation of hospitalisation-based indices	146
<b>Section 3: Use of community pharmaceutical data to measure comorbidity</b>	<b>148</b>
Identification of comorbid conditions from Pharmaceutical database	148
Comparison of pharmaceutical data with hospital notes review data	150
Developing pharmaceutical-based comorbidity indices	153
Validation of pharmaceutical-based comorbidity indices	153
<b>Section 4: Development of simplified comorbidity index, and comparison with other indices</b>	<b>155</b>
Development of simplified indices	155
Comparison of simplified indices with other approaches	156
<b>Summary</b>	<b>159</b>
<b>Chapter 6: Results</b>	<b>161</b>
<b>Outline</b>	<b>161</b>
<b>Section 1: Description of (main) study cohorts</b>	<b>162</b>

Development cohort _____	162
Validation cohort _____	166
<b>Section 2: Use of hospitalisation data to measure comorbidity _____</b>	<b>167</b>
Results of the validation exercise for hospitalisation data _____	167
Prevalence of comorbid conditions using hospitalisation data _____	174
Impact of comorbid conditions on mortality among cancer cohorts _____	177
Development of the site-specific hospitalisation-based comorbidity indices _____	190
Performance and validation of the site-specific hospitalisation-based comorbidity indices _____	193
<b>Section 3: Use of pharmaceutical data to measure comorbidity _____</b>	<b>199</b>
Results of the comparison exercise of pharmaceutical data with hospital notes review data _____	199
Prevalence of comorbid conditions using pharmaceutical data _____	201
Impact of comorbid conditions on mortality among cancer cohorts _____	202
Development of the pharmaceutical-based comorbidity index _____	209
Performance and validation pharmaceutical-based comorbidity index _____	209
<b>Section 4: Development and validation of simplified comorbidity index _____</b>	<b>215</b>
Comparison of indices using Discrimination slopes and Integrated Discrimination Improvement (IDI) _____	227
<b>Summary of Results _____</b>	<b>237</b>
<b><i>Chapter 7. Discussion: Strengths and weaknesses of the data and methods used _____</i></b>	<b><i>243</i></b>
Data sources used _____	243
Strengths and limitations of using weighted index to measure comorbidity _____	257
Strengths and weaknesses of the specific methods used in developing the weighted indices (C3, PBCI and simplified indices) _____	261
Strengths and weakness of weights and weighting procedures _____	263
Strengths and weaknesses of the validation approaches used _____	267
Summary of strengths and weaknesses _____	270
<b><i>Chapter 8. Discussion: Interpretation and implications of results _____</i></b>	<b><i>273</i></b>
Summary of key findings _____	273
Prevalence and impact of comorbidity among cancer populations _____	274
Patterns of comorbidity _____	274
Impact of comorbidity on survival _____	276
Interpretation of the index results: _____	277

Content and face validity _____	277
Concurrent criterion validity _____	279
Predictive criterion validity _____	279
Reliability _____	280
<b>Implications of (mis)measuring comorbidity _____</b>	<b>281</b>
Comorbidity as an exposure variable _____	283
Comorbidity as an outcome variable _____	284
Comorbidity as a confounding variable _____	285
Comorbidity as a mediating variable _____	287
<b>Pulling it all together _____</b>	<b>288</b>
Comorbidity is common and has adverse impacts on patients _____	288
Which comorbidity index should be used? _____	288
<b>Generalisability of findings _____</b>	<b>292</b>
<b>Concluding statement and recommendations _____</b>	<b>294</b>
<b><i>Appendices</i> _____</b>	<b>299</b>
<b>Appendix 1: Conditions included in other comorbidity indices _____</b>	<b>300</b>
<b>Appendix 2: List of comorbid conditions identified from NMDS data and their ICD-10 codes     _____</b>	<b>306</b>
<b>Appendix 3: Conditions included in PBCI and drug classes included _____</b>	<b>327</b>
<b>Appendix 4: Evaluating the impact of multiple simultaneous conditions. _____</b>	<b>328</b>
<b>Appendix 5: Association of all-cause and non-cancer mortality with categories of C3 and     PBC indices _____</b>	<b>332</b>
<b>Appendix 6: Weights for simplified indices. _____</b>	<b>334</b>
Background _____	334
<b>Appendix 7: Boxplots Predicted non-cancer death Development cohort _____</b>	<b>336</b>
<b>Appendix 8: Publications and papers submitted for publication arising from this thesis (to     date) _____</b>	<b>342</b>
<b><i>References</i> _____</b>	<b>343</b>



# List of Tables

Table 1: Prevalence of specific conditions among patients with prostate cancer from selected studies (%).....	37
Table 2: Prevalence of specific conditions among patients with colorectal cancer from selected studies(%) .....	38
Table 3: Prevalence of specific conditions among patients with lung cancer from selected studies (%).....	39
Table 4: Prevalence of specific conditions among patients with female breast cancer from selected studies (%) .....	40
Table 5: Summary of sources of data for development of measures of comorbidity ....	63
Table 6: Scoring approaches for measures of comorbidity.....	65
Table 7: Scoring system for the Index of Coexistent Disease (OECD) .....	83
Table 8: Table of articles comparing predictive validity of measures of comorbidity in the context of cancer.....	115
Table 9: Qualitative criteria used to assess measures of comorbidity. ....	121
Table 10: Qualitative assessment of validity of indices in relation to cancer patient populations .....	122
Table 11: Diagnostic codes used for mapping in NMDS validation exercise .....	137
Table 12: Categories of comorbid conditions from clinical notes and PBCI categories .....	151
Table 13: Crude and age/sex standardised proportions of patients by specific cancer site, and sex, age, ethnicity, stage and Charlson scores.....	164
Table 14: Crude sex, age, ethnicity and Charlson scores of patients included in the development and validation cohorts by cancer site .....	165
Table 15: Comparison of ascertainment of comorbidity using data from medical notes or administrative data from index admission and one year prior.....	169
Table 16: Comparison of ascertainment of comorbidity using data from medical notes or administrative data from index admission and eight years prior .....	170
Table 17: Table showing hazard ratio of all-cause mortality for Māori compared with non- Māori .....	172
Table 18: Prevalence n (%) of conditions identified in administrative hospitalisation data in 9 (development) cancer Cohorts .....	175
Table 19: Crude and age/stage standardised hazard ratios (HR) of all-cause mortality by C3 condition and cancer site .....	180

Table 20 : Crude and age/stage standardised hazard ratios (HR) of non-cancer mortality by C3 condition and cancer site.....	184
Table 21: Crude and adjusted hazard ratios (HR) of all-cause and non-cancer mortality by C3 condition for all sites combined.....	188
Table 22: List of conditions in the site-specific C3 indices, coefficient estimates and HRs from site specific age/ stage-adjusted models or age/sex/site/stage adjusted all-site models with non-cancer death as outcome in development cohorts .....	191
Table 23: Score distributions of C3 indices and comparison with Charlson index scores from development cohorts .....	195
Table 24: Concordance statistics from logistic regression models predicting death from all-causes or non-cancer causes, within one year of diagnosis using the validation cohorts: median (2.5th percentile from bootstrapped c-indices, 97.5th percentile) ....	197
Table 25: Akaike Information Criteria (AICs) from logistic regression models predicting death from all-causes or non-cancer causes, within one year of diagnosis using the validation cohorts.....	198
Table 26: Comparison of comorbid conditions identified in hospital notes review and community pharmaceutical data .....	201
Table 27: Prevalence n (%) of conditions included in the PBCI index by site, and coefficient estimates and hazard ratios from age/site and stage-adjusted Cox regression models with non-cancer mortality as outcomes in the full (combined) development cohort .....	204
Table 28: Crude and age/stage standardised hazard ratios (HR) of all-cause mortality by PBCI condition and cancer site .....	205
Table 29: Crude and age/stage standardised hazard ratios (HR) of non-cancer mortality by PBCI condition and cancer site .....	207
Table 30: Score distributions of PBCI Index, and correlation with Charlson index scores in development cohort .....	212
Table 31: Bootstrapped c-indices (median, 95% CI) for comorbidity-adjusted models by site (10,000 bootstrap estimates) predicting deaths from all and non-cancer causes within one year of diagnosis using the validation cohort.....	213
Table 32. Reduction in AIC from Cox proportional hazard models predicting deaths from all- cause and non-cancer causes within one year of diagnosis using the validation cohort.....	214
Table 33: Score distributions of simplified indices and correlation with Charlson index scores in development cohort by site .....	219

Table 34 Comparison of concordance statistics and AICs from logistic regression models predicting deaths from all- and non-cancer causes within one year of diagnosis using the validation cohorts by cancer site and for all sites combined.....	223
Table 35: Differences in concordance statistics (95% confidence intervals) from baseline logistic regression models including each simplified index compared with Charlson or with 'gold standard' approach for 1-year all and non-cancer mortality....	226
Table 36 showing Integrated Discrimination Improvement (IDIs) comparing baseline, Charlson and Gold standard approaches to measuring comorbidity with other approaches for each site and all sites combined for all-cause death in validation datasets.....	235
Table 37 showing Integrated Discrimination Improvement (IDIs) comparing baseline, Charlson and Gold standard approaches to measuring comorbidity with other approaches for each site and all sites combined for non-cancer death in validation datasets.....	236
Table 38: Odds ratios for likelihood of having missing stage (or extent of disease at diagnosis) data by comorbidity category. ....	247
Table 39: hazard ratios of Māori compared with non-Māori cancer survival adjusted for age, sex and stage, and sequentially with different measures of comorbidity.....	287
Table 40: Summary of recommendations for choice of measure of comorbidity by cancer site. ....	292
Table 41: Hazard ratios and 95% confidence intervals (CI) from Cox regression models of non-cancer death (selected conditions only) .....	330
Table 42 Interaction effects from model 3. ....	330
Table 43: C-statistics from logistic regression models of one-year all-cause and non-cancer death among patients with colorectal cancer.....	331
Table 44: Hazard ratios of death by C3 index categories adjusted for age, sex (where relevant) and stage. ....	332
Table 45: Hazard ratios of death by PBCI index categories adjusted for age, sex (where relevant) and stage. ....	333
Table 46: Weights used in calculation of simplified indices 1, 2 and 3. First nineteen conditions (shaded) included in SI 2 and 3.....	334



# List of Figures

Figure 1: Process of categorisation of ACG groups .....	10
Figure 2: Three pathways to disability: senescence leading to frailty; disease; and environmental, psychological and social factors (A, B and C). .....	19
Figure 3: Conceptual model of Total Illness Burden .....	20
Figure 4: Vector Model of Complexity .....	22
Figure 5: Comorbidity and related constructs .....	23
Figure 6: Comparison of number of patients with Charlson index scores of 0, 1, 2 or 3+ calculated using medical notes and administrative data (1 or 8 year lookback) for the same cohort of patients with colon cancer .....	171
Figure 7: Distribution of site-specific C3 index scores .....	194
Figure 8: Distribution of PBCI by site .....	211
Figure 9: Score distribution of simplified index 1 by site .....	216
Figure 10: Score distribution of simplified index 2 by site .....	217
Figure 11: Score distribution of simplified index 3 by site .....	218
Figure 12 Boxplots Predicted all-cause death from baseline (age, site and stage) model, and baseline combined with various measures of comorbidity. Development cohort: All sites combined .....	229
Figure 13: Boxplots showing predicted all-cause death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: CRC cancer. ....	230
Figure 14: Boxplots showing predicted all-cause death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Breast cancer .....	231
Figure 15: Boxplots showing predicted all-cause death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Gynaecological cancers .....	232
Figure 16: Boxplots showing predicted all-cause death from baseline (age, sex and stage) model, and baseline combined with various measures of comorbidity. Development cohort: upper GI cancer .....	233
Figure 17: Boxplots showing predicted all-cause death from baseline (age, sex and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Urological cancer .....	234
Figure 18: Unadjusted Kaplan-Meier curves for one-year survival, by proportion unknown stage group.....	246



# Chapter 1. Introduction

Comorbidity is the co-existence of disorders in addition to a primary disease of interest (Feinstein 1970). While this concept appears relatively simple, the study of comorbidity is complicated by the fact that comorbidity is difficult to define, and even more difficult to measure (Bonavita and De Simone 2008; Valderas, Starfield et al. 2009). Comorbidity, in this context, is defined by the concomitant presence or absence of chronic disease. There has been little work carried out in New Zealand to date to investigate the best way of measuring comorbidity given our data sources, or that has attempted to investigate the detailed impacts of comorbidity on cancer outcomes. Furthermore, while many approaches have been used to measure comorbidity in the context of cancer, none have been shown to be clearly better than all others (Extermann 2000).

Understanding the role of comorbidity in cancer outcomes is important. Why?

*Comorbidity is common.* The exact prevalence of comorbidity among cancer patients varies both by cancer site, and by the method used to measure comorbidity, but regardless, comorbidity is common among cancer patients (Extermann 2000; Lee, Cheung et al. 2011). In New Zealand, 70% of those with colon cancer and 72% of those with lung cancer had at least one comorbid condition (Stevens, Stevens et al. 2008; Sarfati, Hill et al. 2009; Hill, Sarfati et al. 2010). As the population ages, comorbidity will become even more common.

- *Comorbidity affects outcomes.* Comorbidity has a major negative effect on the likelihood of survival from cancer (Newschaffer, Bush et al. 1997; Coebergh, Janssen-Heijnen et al. 1998; Extermann 2000; Yates 2001; Fleming, Pearce et al. 2003; Piccirillo, Tierney et al. 2004; Tammemagi, Neslund-Dudas et al. 2004; Baldwin, Dobie et al. 2005; Hall, Jani et al. 2005; Lemmens, Janssen-Heijnen et al. 2005; Gross, Guo et al. 2006; Stevens, Stevens et al. 2008; Sarfati, Hill et al. 2009). Comorbidity acts on survival both through direct mechanisms related to the increased physiological burden of disease, and through indirect mechanisms related to the effects comorbidity has on treatment choice and/or effectiveness. Cancer patients with comorbidity are considerably less likely to be offered active therapy (Hall, Jani et al. 2005; Lemmens, Janssen-Heijnen et al. 2005; Baldwin, Klabunde et al. 2006; Gross, McAvay et al. 2007; Stevens, Stevens et al. 2007; Etzioni, El-Khoueiry et al. 2008; Sarfati, Hill et al. 2009). Furthermore, there is growing evidence that many such treatments are both

tolerated and effective among those with comorbidity (Yancik, Wesley et al. 2001; Velanovich, Gabel et al. 2002; Hall, Jani et al. 2005; Lemmens, Janssen-Heijnen et al. 2005; Tammemagi, Nerenz et al. 2005; Cronin, Harlan et al. 2006; Gross, McAvay et al. 2007; Etzioni, El-Khoueiry et al. 2008; Sarfati, Hill et al. 2009). For example, among New Zealanders with stage III colon cancer, patients with comorbidity were considerably less likely to be offered adjuvant chemotherapy than those without (84% with a Charlson score of 0 compared with 19% of those with a Charlson score of 3). Moreover, among those with the highest level of comorbidity, there was a 60% reduction in excess mortality if they were offered chemotherapy (Sarfati, Hill et al. 2009). This suggests that at least part of the burden of comorbidity on cancer mortality is reversible. Comorbidity also has an important impact on other outcomes such as functional status, quality of life, length of stay in hospitals, quality and costs of care (Gijssen, Hoeymans et al. 2001; Davis, Lay-Yee et al. 2002; Perkins, Kroenke et al. 2004; Nardi, Scanelli et al. 2007; Valderas, Starfield et al. 2009; Parekh and Barton 2010).

*The impact of comorbidity is modifiable.* There is evidence that focusing at a clinical level on more complex patients with comorbidity can result in benefits in terms both of improved outcomes and satisfaction with care for patients (Wagner, Austin et al. 1996; Redelmeier, Tan et al. 1998; Fried, Ferrucci et al. 2004; Safford, Allison et al. 2007). Systems can be redesigned to optimise healthcare processes for complex patients, and from a policy perspective, incorporating complexity of patient mix into quality measurement and performance profiling results in a more comprehensive understanding of health service quality and processes (Haggerty 2012; Mangin, Heath et al. 2012; Salisbury 2012; Tinetti, Fried et al. 2012).

There is a balance between simplicity of use, and accuracy of measurement in estimating the comorbidity status of individuals in a population. On one end of the spectrum, patients might be individually assessed, medical notes and laboratory results reviewed, and on the basis of this information, patients classified according to their comorbidity status. On the other end of the spectrum, comorbidity status may be estimated on the basis of the number of conditions identified at a particular hospital admission using routinely collected discharge data. Whilst the first approach is likely to provide considerably better data, and more accurately categorise individual patients according to comorbidity, the latter approach is considerably less resource intensive, and can be applied easily to many more patients. The goal of this thesis is to develop a relatively simple index of comorbidity that can be used for patients with cancer, using administrative data, but that has been validated against more comprehensive

approaches. The emphasis will be on identifying those variables that are most important in the accurate estimation of comorbidity status, and that can be identified using administrative data.

This thesis will focus on patients with breast, colon, rectal, stomach, uterine, ovarian, liver and renal cancers diagnosed between 30 June 2006 and 1 July 2008. These cancers provide a range in terms of prognosis, and in terms of treatment type and complexity. The focus of the work will be on indices that are designed to measure the impact of (predominantly) physical comorbidity on outcomes for cancer patients, and that can be calculated using routine data sources. Similarly, the New Zealand specific comorbidity index will be designed for those with cancer, and for use with New Zealand data sources. However, it is envisaged that this work may be able to be generalised to patients outside New Zealand, and with primary conditions other than cancer in the longer term.

This work is part of a larger programme of work led by the author of the thesis; the Cancer, Care and Comorbidity (C3) projects. These projects aim to disentangle the impacts of comorbidity and ethnicity on the unequal outcomes from cancer that have been demonstrated between ethnic groups in New Zealand. I initiated the planning for these projects in 2009 with an interested group of clinicians, epidemiologists and Maori health researchers. My own interest stemmed both from my early clinical training and interest in oncology, and my more recent research on ethnic inequities in cancer outcomes in New Zealand (Sarfati, Blakely et al. 2006; Sarfati, Hill et al. 2009; Hill, Sarfati et al. 2010; Hill, Sarfati et al. 2010; Sarfati, Shaw et al. 2010). The broader C3 projects have retained their focus on ethnic inequities in cancer outcomes, but the work here relates to the question of how best to measure comorbidity in the context of cancer.

### **The main aims of this thesis are:**

1. To review evidence relating to the importance of comorbidity in relation to cancer care and outcomes.
2. To examine and describe approaches to measuring comorbidity in the context of cancer, and to identify the strengths and weaknesses of these approaches.
3. To assess how well data on comorbidity are captured in routine databases in New Zealand by comparing detailed comorbidity data extracted from hospital records

with routinely collected hospitalisation and pharmaceutical data from the same patients.

4. To develop and validate optimised ('gold standard') measures of comorbidity using routinely collected data for patients with cancer. These measures would be:
  - a. Site- and outcome-specific;
  - b. Use more than one source of data;
  - c. Include all important conditions and exclude those that may be complications of the primary disease;
  - d. take account of the severity of conditions and their likely impact on survival and;
  - e. consider the impact of clustering of conditions.
5. To develop and validate a simplified comorbidity index using routinely collected data on comorbidity; and to compare the performance of this 'user-friendly' index with the comprehensive 'gold-standard' approach.

The thesis is divided into eight chapters, as follows:

**Chapter 1: Introduction.** This outlines the focus, and provides the main aims of the thesis. It describes the scope of the work including what is, and what is not included. It provides a brief outline of the structure and content of the chapters included in the thesis.

**Chapter 2: Comorbidity and related constructs.** This introduces the concept of comorbidity and briefly describes how this has changed over time. It introduces other related constructs specifically multimorbidity, functional status, disability, allostatic load, frailty, burden of disease and patient complexity. It provides a rationale for the choice of comorbidity as the most appropriate construct to measure for this thesis.

**Chapter 3: The impact of comorbidity on cancer care and outcomes.** This chapter provides a rationale for focusing on cancer, and summarises research relating to the impact of chronic disease on cancer diagnosis, treatment and outcomes. It also describes the impact of comorbidity on inequalities in cancer care and outcomes.

**Chapter 4: Measuring comorbidity: Review of comorbidity indices.**

This chapter comprehensively describes and appraises approaches used to measure comorbidity in the context of cancer.

**Chapter 5: Methods.** The first part of this chapter describes the methods used to measure comorbidity using administratively collected hospitalisation data including their validation for this purpose, the optimisation of identification of conditions and the development and validation of site-specific comorbidity indices. The second part describes the measurement of comorbidity using administrative pharmaceutical data including the identification of conditions, comparison with hospital notes data and the development and validation of pharmaceutical-based comorbidity indices. The final part describes the development and validation of simplified comorbidity indices and their comparison with the other measures.

**Chapter 6: Results.** This chapter begins with a description of the cohorts of cancer patients whose data are used in this thesis. This is followed by results relating to the hospitalisation-based comorbidity indices including results of the validation exercise, prevalence and impact of comorbid conditions identified in hospitalisation data and results of the development and validation of the site-specific comorbidity indices. Next, similar results relating to the pharmaceutical-based comorbidity indices are presented. Finally, the results relating to the simplified indices, and their comparison with the other measures are presented.

**Chapter 7: Discussion: Strengths and limitations.** This chapter provides an exploration of the strengths and limitations of the data and methods used in the thesis.

**Chapter 8: Discussion: Interpretation and implications.** This chapter provides a brief summary of the results of the thesis then discusses the implications of these results and makes recommendations for measuring comorbidity in the context of cancer patient populations.



# Chapter 2. Comorbidity and related constructs

*I am a little deaf, a little blind, a little impotent, and on top of this are two or three abominable infirmities, but nothing destroys my hope. ~Voltaire*

This chapter introduces the concept of comorbidity, and outlines how the definitions of comorbidity have developed over time. It describes constructs that are related to, but distinct from comorbidity, specifically multimorbidity, functional status, disability, allostatic load, frailty, burden of disease and patient complexity. Finally it provides a rationale for why comorbidity is the most relevant construct to investigate in this thesis, and why it is important to measure it accurately.

## What is comorbidity?

As the populations age, the prevalence of chronic disease increases. Almost all chronic diseases are more common among the elderly than younger adults, and many of these conditions are not life threatening in the short term. Consequently, many people live with, rather than die from chronic health conditions. Cancer is often a chronic disease, and is itself more prevalent among the elderly. Concomitant chronic disease in addition to cancer is now, therefore, the norm rather than the exception and it can have a profound effect on individuals (Extermann 2000; Extermann 2000; Satariano and Silliman 2003). Comorbidity results in increased risk of hospitalisation, adverse effects of treatment, multiple competing demands on both patient and health care professionals, high health care costs, reduced quality of life and higher mortality (Feinstein 1970; Wagner, Austin et al. 1996; Gijssen, Hoeymans et al. 2001; Mandelblatt, Bierman et al. 2001; Satariano and Silliman 2003; Fortin, Bravo et al. 2006; Valderas, Starfield et al. 2007; Yancik, Ershler et al. 2007; Valderas, Starfield et al. 2009; Parekh and Barton 2010). Despite this, much of the research and planning relating to cancer and cancer care assume a single disease paradigm. For example, patients with comorbidity are often excluded from randomised controlled trials which means that it is difficult to generalise the findings of such trials to those with chronic health problems, or to predict the difficulties or complications from treatment that such patients may face (Fortin, Dionne et al. 2006; Starfield 2006; Mangin, Heath et al.

2012; Tinetti, Fried et al. 2012). Partly as a consequence of this, clinical practice guidelines tend to be very poor at addressing the needs of older patients with comorbidity (Boyd, Darer et al. 2005; Vitry and Zhang 2008; Mangin, Heath et al. 2012). Health care service providers, policy makers and researchers need to be able to respond adequately to the requirements of individuals with complex health needs (van Weel, Schellevis et al. 2006). Despite the importance of comorbidity in the care of cancer patients, there is no consensus about how to define it, and even less on how to measure it.

## **The evolution of the concept and measurement of comorbidity**

In 1970 Feinstein noted that *'[a]lthough patients with more than one diagnosed disease are frequently encountered in modern medical practice, the inter-relationships and effects of multiple diseases have not received suitable taxonomic attention in clinical science'* (Feinstein 1970). Feinstein argued that this *'neglect of comorbidity'* had many detrimental effects, although his focus was largely on defining comorbidity in order to ensure comparability between study groups in studies of treatment effectiveness, and to ensure that *statistics* relating to disease were accurate. Feinstein defined comorbidity as *"any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient that has the index disease under study"*. He noted the importance of comorbid disease in terms of its potential effects on diagnosis, treatment and outcomes of patients. This first paper focused on classifying comorbid disease according to the timing and location of the comorbid condition, but did not discuss the more practical aspects of how comorbidity could be measured.

Subsequent work by Kaplan and Feinstein in 1974 (Kaplan and Feinstein 1974) resulted in possibly the first attempt to measure comorbidity as a separate construct in its own right. They focused on patients with diabetes mellitus and classified comorbid conditions into vascular (e.g. hypertension, cardiac disorders) and non-vascular, and by severity based on the likely prognostic impact of each condition ranging from 1 (slight decompensation) through to 3 (recent full decompensation or life threatening). They found that comorbidity was related to increased risk of mortality, and higher severity of comorbidity with increased risk. Risk of death was more related to severity of comorbidity than type (vascular versus non-vascular). Five-year fatality rate was 7%

in 41 patients with prognostically unimportant comorbidity, 33% in 79 patients with moderate comorbidity and 69% in 68 patients with severe comorbidity.

During the 1980s and early 1990s, the measurement of comorbidity developed into two distinct branches; diagnostic –based risk (or case-mix) adjustment systems, and clinically-based comorbidity indices. These approaches differed both in the underlying assumptions and constructs relating to comorbidity, and in the approaches that were used to measure comorbidity. While this dichotomy is clearly distinguishable, it is important to note that both approaches have been used in a variety of study types with varying aims and objectives (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991; Extermann 2000; Reid, MacWilliam et al. 2001; Duckett and Agius 2002; de Groot, Beckerman et al. 2003; Perkins, Kroenke et al. 2004).

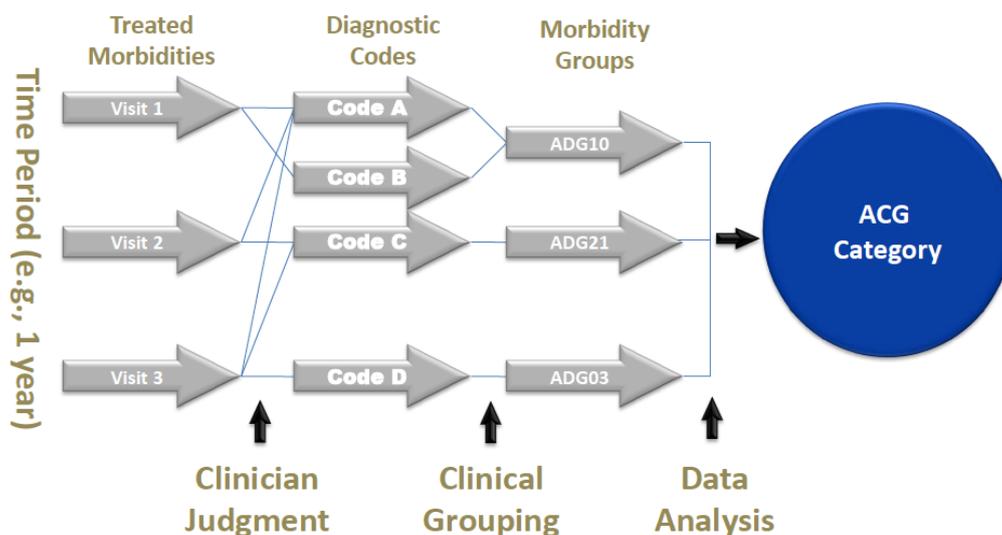
## **Diagnostic-based risk (or case-mix) adjustment systems**

These were developed largely in the United States in response to the need to allocate health care resources in managed care environments where populations were enrolled in health care organisations. There was pressure to develop systems which could predict future cost and utilisation of healthcare. These systems were based on routinely collected data that could be applied to large populations, and often included factors other than comorbidity. The concept of comorbidity for these tended to be focused conditions or categories of conditions that were associated with increased health service utilisation or health care costs (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991; Duckett and Agius 2002).

The ACG system developed at John Hopkins University is an example of a diagnosis-based risk adjustment system. It was developed in response to the recognition of increasing costs of health care, the rapid expansion of managed and capitated care in the US, and an increasing emphasis on ambulatory care (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991). This system used administrative data to categorise individuals into groups with similar health resource use expectations. It initially used only ambulatory care data, but more recently the system has been refined and extended to include data from other sources including hospitalisation and pharmaceutical data, and the term Ambulatory Care Group was amended to Adjusted Clinical Group (both ACG) (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991;

Reid, MacWilliam et al. 2001). The system works by grouping specific diagnoses over specified time periods based on ICD codes from administrative data sources on the basis of expected duration, severity, diagnostic certainty, aetiology and speciality care involvement of each condition (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991). These are then divided into adjusted clinical groups (ACGs) based on factors such as age, sex, presence of specific ADGs, and number of ADGs with each group including individuals that would be expected to experience a similar pattern of resource use (Weiner, Starfield et al. 1991). This system has been used in a number of settings primarily for health care management purposes including setting capitation rates and profiling the efficiency of health care organisations and clinicians (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991; Fowles, Weiner et al. 1996; Greene, Barlow et al. 1996; Tucker, Weiner et al. 1996; Orueta, Lopez-De-Munain et al. 1999; Reid, MacWilliam et al. 2001; Duckett and Agius 2002; Perkins, Kroenke et al. 2004; Chang and Weiner 2010).

**Figure 1: Process of categorisation of ACG groups**



From: John Hopkins University

[http://www.acg.jhsph.org/index.php?option=com\\_content&view=article&id=55&Itemid=149](http://www.acg.jhsph.org/index.php?option=com_content&view=article&id=55&Itemid=149) (downloaded 6 Dec 2010)

## Clinically-based comorbidity indices

Clinically-based comorbidity indices were developed primarily for clinicians and researchers to assess the role of comorbidity in outcomes for their patients, often in the

context of clinical or epidemiological studies. They tend to employ a range of approaches and data sources in an attempt to optimise the measurement of comorbidity (de Groot, Beckerman et al. 2003; Hall 2006). Comorbidity in this context tends to be focused on conditions that have an impact on patient outcomes, most commonly mortality.

The best known example of a clinically-based comorbidity index is the Charlson Comorbidity Index (CCI) developed by Mary Charlson and colleagues in 1987 (Charlson, Pompei et al. 1987). The Charlson index was developed using medical notes data from a cohort of 607 medical patients at a single New York hospital over a one month period in 1984, and validated against a population of 685 breast cancer patients diagnosed between 1962 and 1969. Seventeen conditions (in 19 categories) were identified and allocated a weight of 1 to 6 depending on the adjusted relative risk of 1-year mortality, and summed to give an overall score. The higher the individual's score, the higher was the level of comorbidity.

The Charlson index has subsequently been validated and used in a huge variety of clinical and research settings, and has been adapted for use with administrative data,(Deyo, Cherkin et al. 1992; Romano, Roos et al. 1993; Romano, Roos et al. 1993; Quan, Sundararajan et al. 2005) and for use with patient self-report,(Katz, Chang et al. 1996; Fan, Au et al. 2002; Byles, D'Este et al. 2005). However there are problems with the Charlson Index in general, and in relation to measuring comorbidity in the context of cancer. The index includes some conditions that have not been shown to have an impact on survival among patients with cancer (e.g. peptic ulcer disease), it may exclude some that do have such an impact (e.g. non-cerebrovascular neurological conditions), and it assumes that the impact of multiple conditions is additive on a relative scale (Sarfati, Hill et al. 2009). Because of these and other issues, a number of approaches to measuring comorbidity have been subsequently developed (Extermann 2000; de Groot, Beckerman et al. 2003; Hall 2006; Lash, Mor et al. 2007). These are described in detail in Chapter 4, but in general can be divided into those that are simple counts of conditions (Verbrugge, Lepkowski et al. 1991; Davis, Lay-Yee et al. 2002; Sarfati, Hill et al. 2009), weighted indices that adjust for seriousness of conditions (Kaplan and Feinstein 1974; Charlson, Pompei et al. 1987; Greenfield, Kaplan et al. 1988; Fleming, Rastogi et al. 1999; Piccirillo, Tierney et al. 2004), and systems that depend on models involving varying numbers of individual conditions (Elixhauser, Steiner et al. 1998; Tammemagi, Neslund-Dudas et al. 2003; Holman, Preen et al. 2005). Data sources used to estimate comorbidity have also varied including

administrative data, medical charts, physical examination, personal interviews and self-report (Extermann 2000; Humphries, Rankin et al. 2000; Gijzen, Hoeymans et al. 2001; Lash, Mor et al. 2007).

## **Recent evolution relating to the concept of comorbidity**

In October 2003, the National Institute on Aging (NIA) Geriatrics and Clinical Gerontology Program convened a taskforce on comorbidity. The objective of this taskforce was to *'explore conceptual and methodological complexities of comorbidity'* (Yancik, Ershler et al. 2007). There was general consensus that comorbidity was a complex and heterogeneous concept, and that no single measure would be likely to adequately serve all research and clinical purposes. The taskforce determined that the definition and measurement of comorbidity depended on the objective that was being addressed, the setting and population/s of interest, the extent to which comorbid conditions inter-relate, and the severity and timing of conditions. The conclusion, then, was that more research was needed on the measurement and impact of comorbidity, but that a balance needed to be maintained on advancing the conceptual and theoretical aspects of comorbidity on one hand, and not losing sight of the practical issues of measuring comorbidity on the other.

Subsequent work has tended to shift into more complex conceptualisations of comorbidity. For example, Karlamangla et al (2007) suggested a categorisation of comorbidity that was based on body systems (i.e mental function, sensory, pain, voice and speech functions, and movement, skin, cardiovascular, haematological, immunological, respiratory, digestive, metabolic, endocrine, GU/ reproductive/ sexual, and neuromusculoskeletal systems) (Karlamangla, Tinetti et al. 2007). They suggested each could be classified on a spectrum ranging from high-functioning, through subclinical abnormalities through to clinically manifest disease of various severities. For example, for endocrine system, an abnormal fasting blood glucose may be categorised as a subclinical abnormality, overt diabetes mellitus controlled by diet may be considered disease on the less severe end of the spectrum, while insulin dependent diabetes mellitus with complications may be on the more severe end of the spectrum. The authors also suggested that interactions between domains could be included, for example, the known synergies between hypertension and diabetes could be included in the estimate of overall patient comorbidity, although it was unclear how this would be achieved. In this way, sub-clinical disease could be explicitly recognised, disease

clusters would be accounted for, the system would not depend solely on diagnosed disease and high functioning would be measured as well as low functioning. Whilst these aims are laudable, the collection of data required for such a measurement tool would be intensive, expensive and often not feasible.

In their narrative review, Valderas et al (2009) attempted to 'define and measure the concept of comorbidity' (Valderas, Starfield et al. 2009). They identified four distinctions that could be made in relation to comorbidity. The first three are related to the definition of comorbidity itself, and are expanded on in chapter 5. These are 1. the requirement to be clear about what a comorbid entity is, and how these can be identified and defined; 2. the relative importance of the primary condition, and given the co-existence of multiple conditions, which can be considered primary; and 3. the chronology of the conditions, i.e are they co-occurring, does the order in which they occur affect genesis, prognosis or treatment. The fourth distinction highlighted was that related to 'expanded conceptualisations' relating to comorbidity. Such conceptualisations included those of *multimorbidity* where no one condition is considered primary, *burden of disease* which includes elements of multimorbidity and functional status, and *patient complexity* which expands this idea further into other factors which may influence patient outcomes and healthcare resource requirements such as socioeconomic status, lack of social support or language difficulties. Other related constructs not explicitly included in the paper by Valderas et al include allostatic load, disability and frailty (Nagi 1976; Verbrugge and Jette 1994; Seeman, Singer et al. 1997; Fried, Ferrucci et al. 2004).

## Constructs related to comorbidity

### ***Multimorbidity***

Multimorbidity is the "*the co-occurrence of multiple chronic or acute diseases and medical conditions within one person*" (van den Akker, Buntinx et al. 1996). It is distinct from comorbidity in that the latter implies an index disease under study. The concept of multimorbidity shifts the focus from a single disease paradigm to one where the causes and effects of multiple combined conditions are explored.

Multimorbidity is a particularly useful concept in the context of primary care, where practitioners are responsible for the overall health of their patients rather than the

management of a single disease entity (Fortin, Soubhi et al. 2007). However more recently, there have been strong calls to reorient the health system in general away from a single-disease orientation (Haggerty 2012; Mangin, Heath et al. 2012; Salisbury 2012; Tinetti, Fried et al. 2012). Much of the research of multimorbidity has focused on the epidemiology and effects of multimorbidity. For example, Van der Akker et al (1998) used data from a network of family health practitioners in the Netherlands to identify permanent, chronic or recurrent conditions (van den Akker, Buntinx et al. 1998). They found that 29.7% of the population had two or more conditions, and that multimorbidity was more common among older people, women and those with lower education, or no private health insurance. There was also evidence that certain conditions tended to cluster. They concluded that this clustering of diseases was likely to be due to a combination of *causal* mechanisms such as common genetic, immunological, environmental or behavioural risk factors, or *artifactual* mechanisms particularly chance clusterings, or detection bias where a patient is more likely to have a second condition diagnosed because of health service contact related to a first condition. More recently, Barnett et al analysed data from primary care databases in the United Kingdom for 1.75 million patients (Barnett, Mercer et al. 2012). They found that nearly a quarter of all patients had more than one chronic condition, the likelihood of this increased with increasing deprivation and that whilst multimorbidity was more common among those aged over 65 years, in absolute terms there were more people under 65 years with multimorbidity.

Multimorbidity, like comorbidity, has been found to be associated with an increased risk of disability, poor functional status, higher health expenditure, polypharmacy, and complications of care (van den Akker, Buntinx et al. 2001; Byles, D'Este et al. 2005; Noel, Parchman et al. 2007; Britt, Harrison et al. 2008; Tooth, Hockey et al. 2008; Barnett, Mercer et al. 2012; Guthrie, Payne et al. 2012; Haggerty 2012; Mangin, Heath et al. 2012; Smith, Soubhi et al. 2012; Tinetti, Fried et al. 2012).

### ***Functional (or performance) status:***

Functional limitations are defined as limitations in performance at the level of the whole organism or person (Nagi 1976). Functional status is broader than this, and is the ability or otherwise to carry out everyday tasks. Scrag (2008) articulately describes it as "*captur[ing] much of what seasoned clinicians ascertain in an instant as they watch*

*a patient enter a room, rise from a chair, or clamber onto an exam table” (Schrag 2008).*

The presence of chronic disease is directly related to functional status. Pain and stiffness in arthritis, shortness of breath in chronic respiratory disease, dysphasia or dyspraxia as a result of a stroke all lead to loss of ability to carry out every day tasks. Functional status is measured by the ability or otherwise to carry out such tasks, and is often related to both the presence and the consequences of chronic disease (Lash, Mor et al. 2004). Assessment of functional status may be based on self-report or proxy report of ability to carry out specified tasks, for example the World Health Organisation performance status instrument (WHO-PS) or the physical functioning scale of the SF-36, or physical performance tests such as ability to open and close fasteners, gait speed, ability to climb stairs or rise from a chair (Guralnik and Ferrucci 2003). Functional status is a predictor of morbidity, mortality, length of hospital stay and hospital charges independent of other characteristics including age and comorbidity (Pompei, Charlson et al. 1991; Parmelee, Thuras et al. 1995; Mandelblatt, Bierman et al. 2001; Wedding, Rohrig et al. 2007). The measurement of functional status as an outcome is also useful in determining the impact of the consequences of chronic disease,

## ***Disability***

Disability is closely related to the concept of functional status. It is defined as *“limitation in performance of socially defined roles and tasks within a sociocultural and physical environment.”* (Nagi 1976) Functional impairments can lead to disability, but the extent to which this occurs depends on the social and psychological environments in which people live (Verbrugge and Jette 1994). Environments can be more or less disabling. For example, an individual with severe arthritis may be considerably less disabled if they have access to mobility aids, and aids to assist with tasks requiring dexterity.

The concepts of functional limitations, and disability, as well as those of disease, dysfunction and other related concepts have evolved markedly over time (Minaire 1992; Masala and Petretto 2008). One of the major changes is a shift in emphasis from disability being a function of the individual’s physical, emotional and mental capacity, to one that emphasises the role of the social and physical environment in which an individual lives (Minaire 1992; Verbrugge and Jette 1994; World Health Organization 2002; Masala and Petretto 2008). A second important change has been

an increasing awareness of the lack of linearity in the relationships between these key concepts. Early models tended to emphasise a more or less simple stepwise progression starting with disease or impairment leading to functional limitation and, finally, disability. However, increasingly, it has become recognised that the relationships between these concepts are considerably more complex. (Nagi 1976; Verbrugge and Jette 1994; Masala and Petretto 2008) Disability can both cause and be caused by chronic disease. The pathway from disease to disability is intuitively obvious, but recent research suggests that chronic disease in those with disability may progress more quickly, either because of lower levels of physical activity, or through some shared biological mechanisms (Fried, Ferrucci et al. 2004). Similarly, the associations between pathological change, functional impairment and disability can be complex and unpredictable. For example, the World Health Organization states “...*diagnosis alone does not predict service needs, length of hospitalization, level of care or functional outcomes. Nor is the presence of a disease or disorder an accurate predictor of receipt of disability benefits, work performance, return to work potential, or likelihood of social integration*” (World Health Organization 2002).

Disability, like functional status, is most commonly assessed using self-reported difficulty in specific tasks, and these are assessed in the clinical setting by screening tools such as Activities of Daily Living (ADLs) and Instrumental Activities of daily Living (IADLs) (Fried, Ferrucci et al. 2004).

## ***Allostatic load***

While disability takes explicit account of a person’s environment, allostatic load is a purely physiological measure of ill-health. It is a measure of cumulative, chronic physiological dysfunction across multiple body systems (Seeman, Singer et al. 1997). Seeman’s hypothesis was that organisms must adapt body systems to alter their internal milieu in response to environmental challenges. When these adaptive responses are no longer able to cope with such challenges, progressive dysregulation occurs and can be measured. Allostatic load is related to but is not the same as comorbidity. Chronic disease may result in cumulative physiological burden which results in increasing allostatic load. Seeman et al see the measure of allostatic load as an indicator that an individual may be decompensating as a result of various internal and external challenges including comorbid disease:

*“No single form of comorbidity occurs with high frequency, but rather a multiplicity of diverse combinations are observed (e.g. osteoarthritis and diabetes, colon cancer, coronary heart disease, depression and hypertension). This diversity underscores the need for an early warning system of biomarkers that can signal early signs of dysregulation across multiple physiological systems.”* (Seeman, Singer et al. 1997)

Allostatic load was initially measured using 10 biological parameters which are physiologically related to a number of homeostatic metabolic processes such as the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, and the cardiovascular system. The parameters were systolic and diastolic blood pressure, waist/hip ratio, serum high density lipoprotein and total cholesterol, plasma glycosylated haemoglobin, serum dihydroepiandrosterone, 12 hour cortisol excretion and urinary norepinephrine and epinephrine excretion (Seeman, Singer et al. 1997). In later work, serum fibrinogen, C-reactive protein and interleukin 6, all measures of chronic inflammation, were added to the measure of allostatic load (Seeman, Singer et al. 1997; Gruenewald, Seeman et al. 2009).

In the development of the measure of allostatic load, each of these parameters was measured in a group of 70 to 79 year olds. Each parameter was categorised into quartiles, and the number of parameters that each individual fell into the highest risk quartile was summed to give a total score. Higher scores were cross-sectionally, and longitudinally related to all-cause mortality, cardiovascular disease, and poorer cognitive and physical functioning, and frailty (Seeman, Singer et al. 1997; Seeman, McEwen et al. 2001; Gruenewald, Seeman et al. 2009).

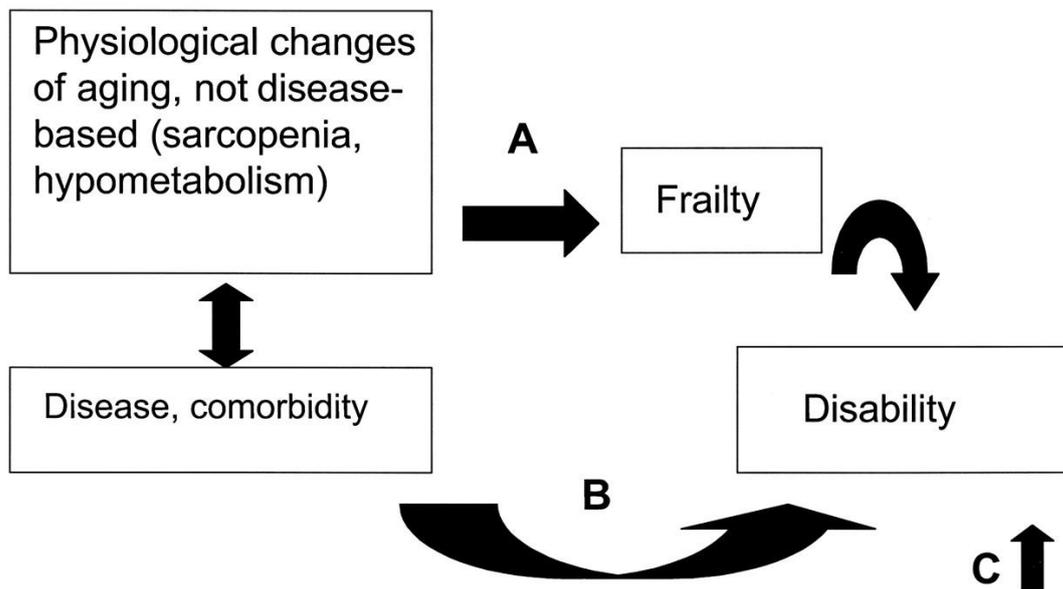
## ***Frailty***

Frailty has been defined as a *“physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and ... dysregulation, of multiple physiologic systems”* (Fried, Ferrucci et al. 2004). Frailty is considered a physiological syndrome related to, but separate from comorbidity and disability (Fried, Ferrucci et al. 2004; Balducci 2007). Frailty is characterised by weakness, decreased endurance and slowed performance. It is related to poor nutrition, concurrent chronic disease, loss of muscle mass, reduced metabolic rate, decreased activity and energy expenditure (Fried, Tangen et al. 2001). It has been measured in a variety of ways, for example Fried (2001) categorised those with frailty as having any three of unintentional weight

loss, weakness, poor endurance, slowness or low physical activity (Fried, Tangen et al. 2001), whereas Balducci used age greater than 85 years, high ADL score, three or more comorbidities and diagnosis of a geriatric syndrome (any one of delirium, dementia, depression, osteoporosis, incontinence, falls etc) (Balducci and Stanta 2000; Balducci 2007). Frailty is strongly related to increasing age, and is most common in the very elderly. It has also been found to be more common among cancer patients than similar aged patients without cancer (Mohile, Xian et al. 2009). Frailty may cause disability independently of coexisting disease and may be caused by comorbidity (Fried, Ferrucci et al. 2004). Frailty is strongly associated with adverse outcomes including disability, mortality and dependency (Balducci and Extermann 2000; Fried, Tangen et al. 2001; Fried, Ferrucci et al. 2004; Koroukian, Murray et al. 2006; Balducci 2007; Pal, Katheria et al. 2010).

There are clear relationships between physiological change (measured by allostatic load), chronic disease, frailty and disability. This is shown graphically in the Figure taken from Albert et al (2002) (Figure 2). It shows three pathways to disability. The first (A) is through the direct effects of aging. These effects can result in frailty which can be present in older people even without any identifiable disease. These factors are likely to result in disability measured by a lack of ability to carry out everyday tasks. The second pathway (B) is the direct effect of chronic disease on disability. Pathway C reflects other factors within the environment that can be variably enabling or disabling, for example, access to mobility aids and social support.

**Figure 2: Three pathways to disability: senescence leading to frailty; disease; and environmental, psychological and social factors (A, B and C).**



Albert, S. M. et al. Am J Public Health 2002;92:1214-1216

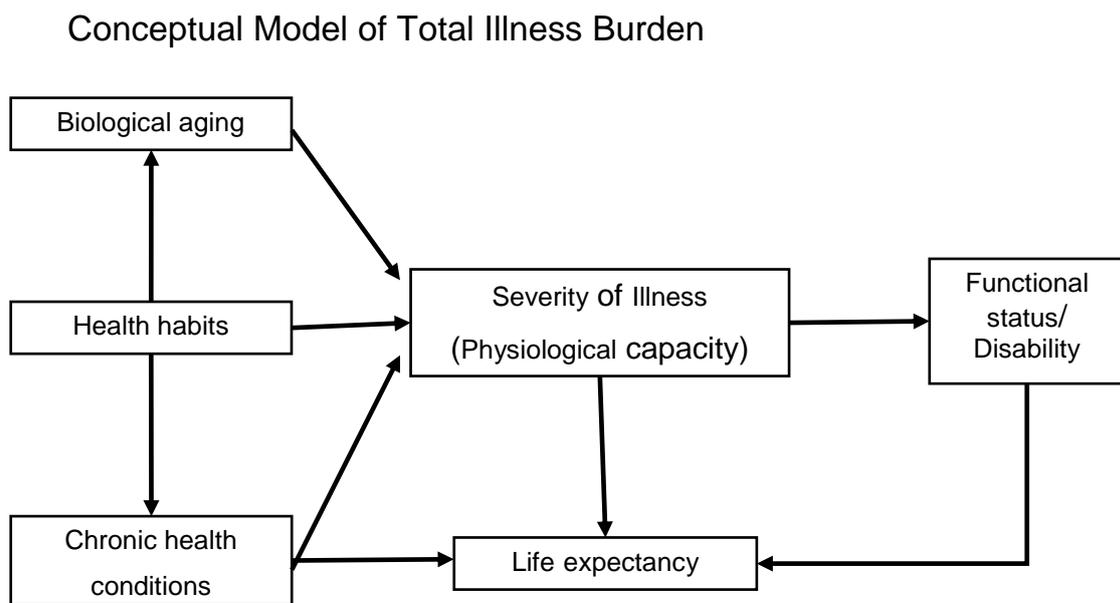
## ***Burden of disease/ illness***

Burden of disease (in this context) expands the concept of multimorbidity to include functional status of individuals. Burden of disease is a combined measure of number of chronic diseases, their severity and their impact on functional status (Mandelblatt, Bierman et al. 2001). It is therefore a measure of chronic disease, and its impact on the individual concerned. There is no gold standard measure for burden of disease. The first attempt to measure this construct was in 1995 by Greenfield et al (Greenfield, Sullivan et al. 1995). Their aim was to measure a “*composite illness-based measure of risk for substantial declines in health*” (Total Illness Burden Index or TIBI). They did this by identifying the presence of chronic disease among a cohort of patients divided into categories (such as pulmonary disease, heart disease, stroke and neurological disease, gastrointestinal disease, other cancers, arthritis, eye problems, hearing problems, hypertension, diabetes mellitus and arthritis). For each category or condition, they assessed the likely impact on functional status both through clinician assessment, and through statistical assessment of the association of each with outcomes such as the physical functioning scale of the SF-36 instrument. TIBI scores

have been associated with poorer outcomes in general, and among cancer patients specifically (Greenfield, Sullivan et al. 1995; Litwin, Greenfield et al. 2007).

Mandleblatt (2001) assessed burden of disease by examining the separate roles of comorbidity and functional status as well as life-expectancy and self-rated health on treatment patterns and outcomes for a cohort of older women with early stage breast cancer (Mandelblatt, Bierman et al. 2001). They posited that biological aging and the effects of chronic disease would result in physiological dysregulation, which is in turn a determinant of functional status and disability (Figure 3). These three components of total illness burden (number of chronic conditions, physiological dysregulation and functional status) would then impact on life expectancy and other health outcomes. They found that whilst each of these separate constructs were correlated with each other, the strength of correlation varied considerably suggesting that each was capturing a different dimension of illness burden. However they also found that even in combination, these variables did not explain much of the variance in number of treatments received among this cohort of patients. Of note, though, is that this group of patients were healthier than average breast cancer patients, so the authors concluded that their estimates of the effects of burden of illness on cancer treatment were likely to be somewhat conservative.

**Figure 3: Conceptual model of Total Illness Burden**



Source: Buchner and Wagner 1992; cited in Mandleblatt et al 2001

Clinically, total illness burden may be measured using instruments such as the Comprehensive Geriatric Assessment (CGA) tool (Balducci and Extermann 2000). This tool combines measures of functional performance, cognitive status and depression, and presence of chronic disease. Studies that have used the CGA tool among older patients with cancer have found that it is associated with poorer survival, higher levels of treatment toxicity, and higher mortality (Extermann 2003; Brunello, Sandri et al. 2009; Girones, Torregrosa et al. 2010; Pal, Katheria et al. 2010).

## ***Complexity***

Complexity is the broadest related construct (Safford, Allison et al. 2007; Schaink, Kuluski et al. 2012). It includes not only comorbidity and functioning, but all determinants of health at an individual level. These include a broad range of factors including, but not limited to socioeconomic, cultural, and environmental factors that are likely to impact on patient care and outcomes.

Safford (2007) developed a graphical model of patient complexity that involved a series of vectors each relating to individual determinants of health, and each with a force and magnitude resulting either in increasing or decreasing complexity (Figure 4)(Safford, Allison et al. 2007). The concept of complexity reflects the intricate interactions between a multitude of factors that impact on care and outcomes at an individual level. The presence of chronic disease is one of these, but is only one part of a highly complex and dynamic system (Nardi, Scanelli et al. 2007; Schaink, Kuluski et al. 2012).

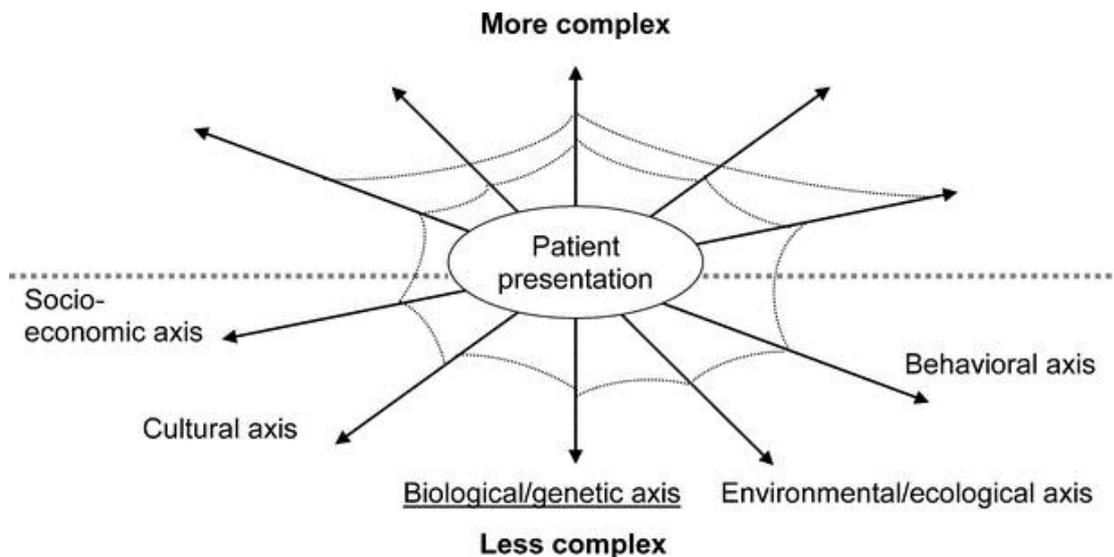
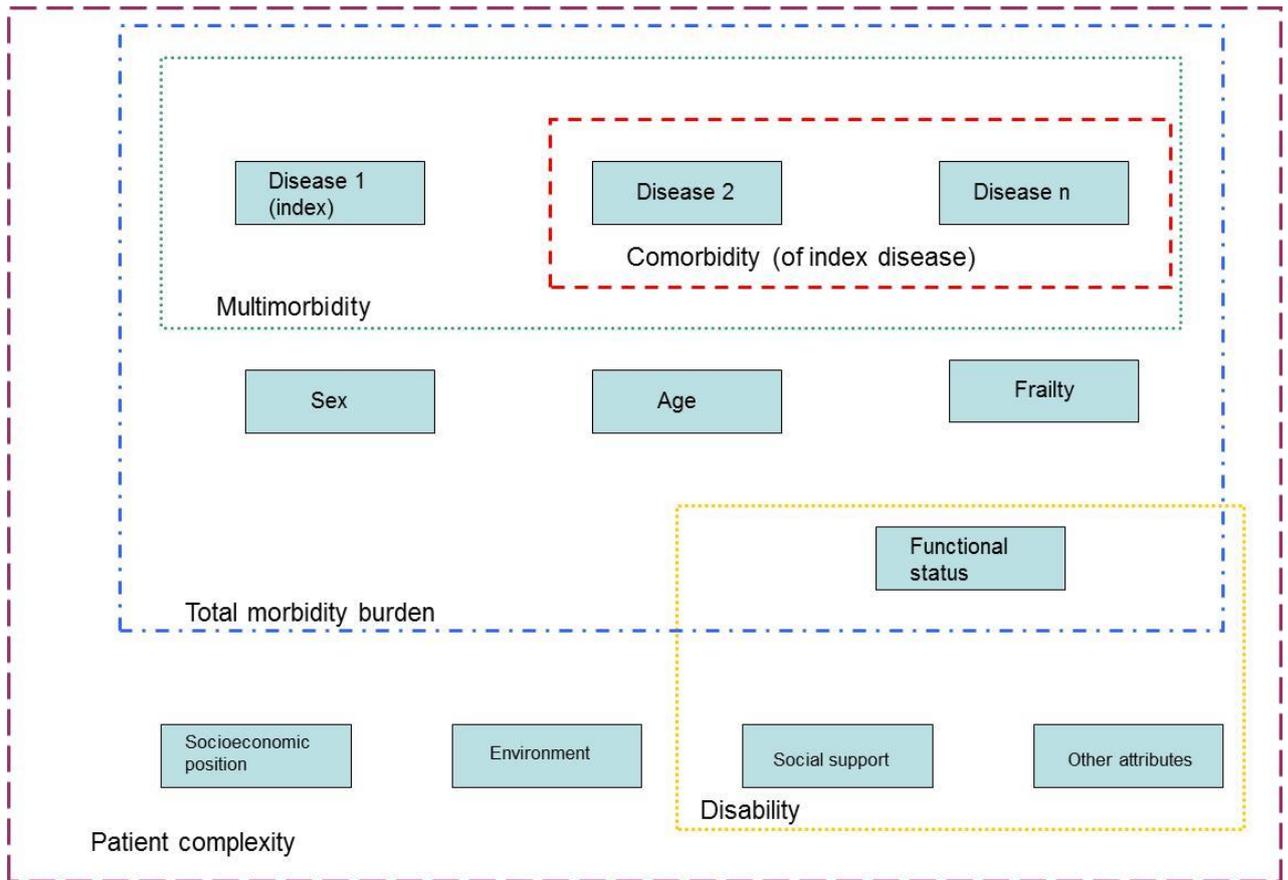


Figure 4: Vector Model of Complexity

## How are the comorbidity-related constructs linked?

There is considerable overlap between these inter-related concepts, and the boundaries between them is blurred. Figure 5 is amended and expanded from Valderas et al 2009 (Valderas, Starfield et al. 2009). It shows the close relationship between *comorbidity* and *multimorbidity*, with the difference being that comorbidity is measured in relation to a primary index disease, whilst multimorbidity is a total measure of all diseases occurring concurrently in an individual. In this figure, *functional status* and *frailty* are represented as separate constructs, but clearly they are both strongly related to each other and to other factors particularly increasing age, and presence of chronic disease. *Total morbidity burden* is a broader concept encompassing elements of comorbidity, frailty and functional status. *Disability* is closely related to the concept of functional status, but includes broader elements such as the degree of social support, and other disabling or enabling features of the environment. Finally at the broadest level, patient complexity encompasses all previous elements, as well as other factors that determine health outcomes in an individual.

**Figure 5: Comorbidity and related constructs**



Model showing comorbidity and related constructs

Expanded from Valderas et al 2009

## Why focus on comorbidity?

This thesis focuses on measuring comorbidity in the context of a primary diagnosis of cancer at a population level. Comorbidity is common among people with cancer, it affects cancer outcomes, and its impact is, at least in part, modifiable. However, to a degree, all these points could be made in relation to any of the constructs above. So why comorbidity?

Multimorbidity is simply the co-existence of two or more conditions. It is an aggregate measure, with no primary condition identified. This concept can be very useful in some contexts, for example in primary care, but is less so when the interest lies in identifying the role of comorbid conditions specifically in relation to treatment and outcomes for cancer. Functional status and disability are separate and useful constructs. Both

poorer functional status, and disability are correlated with higher levels of comorbidity. Ideally it would be useful to measure both comorbidity and functional status or disability at a population level, however currently there are no such data available for cancer patients in New Zealand. For similar reasons, calculation of measures of total illness burden, which combine measures of comorbidity and functional status, are unlikely to be feasible at a population level. So for the time being, these constructs will be put to one side.

Allostatic load is a physiologically based index which requires detailed clinical data to calculate. It is likely to be useful at this clinical level, but again population level data are not available. Frailty is particularly relevant in the very elderly population, and the presence of frailty identifies those at highest risk of adverse outcomes. This thesis is focused on all adults with cancer, and the aim is to quantify comorbidity throughout the spectrum, so frailty is less relevant in this context.

Complexity extends well beyond the concept of comorbidity. Each of the factors that relate to an individual's level of clinical complexity can theoretically be measured separately. The accurate measurement of comorbidity is one element of this, and is the focus of this work.

The measurement of comorbidity allows us to focus specifically on the role of chronic disease in the context of cancer. The next chapter will outline the importance of comorbidity among cancer patients specifically, but first it is useful to consider briefly why we might want to measure comorbidity in general.

## **Why might we want to measure comorbidity accurately?**

### ***Comorbidity is common.***

Comorbidity is common, particularly in the older population. A number of studies show high prevalence of comorbidity among various populations of hospitalised patients (Davis, Lay-Yee et al. 2002; Holman, Preen et al. 2005). A detailed discussion of the prevalence of comorbidity among patients with cancer is given in Chapter 3, but

comorbidity (or multimorbidity) is common even among community populations. In the context of communities, multimorbidity is often the most appropriate measure of chronic disease burden because outside of specialist secondary services it is usually the combination of coexistent conditions that is important. However, the frequency of multimorbidity in the community gives an indication of how common comorbidity is likely to be in the context of cancer. Some examples of such studies are given here but it is noteworthy that studies are often not comparable because of different populations used, different age ranges and, most importantly, different measures of morbidity. As a general rule, self-reported morbidity surveys find higher prevalence than notes review or administrative data-based studies because less serious morbidity is often included (such as vision and hearing problems). In spite of this, the key point is that regardless of how it is measured, multimorbidity is common among older people.

There is little work on the prevalence of comorbidity or multimorbidity in community samples in New Zealand, although two-thirds of adults who completed the 2006/07 New Zealand Health Survey reported they had been diagnosed with at least one chronic health condition (Ministry of Health 2008). Several studies on the prevalence of comorbidity or multimorbidity in older communities have been carried out in Australia (Brown, Brauner et al. 1993; Byles, D'Este et al. 2005; Caughey, Vitry et al. 2008; Tooth, Hockey et al. 2008). The 2004/05 Australian Health Survey found that among those aged over 65 years, almost all had at least one chronic condition, and 88% were on prescription medications (Australian Institute of Health and Welfare 2006). Two studies have specifically focused on the prevalence of morbidity among older women in Australia. In the first, Byles et al 2005 reported on a survey carried out as part of the Department of Veteran's Affairs Preventative Care Trial of veterans and war widows (Byles, D'Este et al. 2005). They found that among women over 70 years, 99% had at least one self-reported condition, the most common being arthritis, and vision, back or hearing problems. Tooth et al reported on the Australian Longitudinal Study on Women's Health, and also found high prevalence of self-reported chronic conditions among older women (Tooth, Hockey et al. 2008). Britt et al carried out a survey of 305 general practitioners, who provided data on 9156 patients throughout Australia (Britt, Harrison et al. 2008). They used a measure called the Cumulative Illness Rating Scale which categorised diseases in domains based on organ systems. Multimorbidity was defined as disease in more than one domain. They found that 37% of their sample met this criterion, and they calculated that if they applied their data to the general population, approximately 25% of the population would have multimorbidity. They

pointed out that multimorbidity was more common than any single condition among patients aged over 60 years.

High prevalence of multimorbidity has been confirmed in community samples in many other studies around the world for example Holland (van den Akker, Buntinx et al. 1998); UK (Barnett, Mercer et al. 2012); US (Fan, Au et al. 2002; Wolff, Starfield et al. 2002; Smith, Reeve et al. 2008); Spain (Rius, Perez et al. 2004); and Canada (Fortin, Bravo et al. 2005).

### ***Impact on health services.***

Gijssen et al (2001) carried out a literature review relating to the consequences of comorbidity (Gijssen, Hoeymans et al. 2001). They identified 13 studies that examined the consequences of comorbidity for health care services, specifically health care utilisation, including hospital costs and length of stay, and disposition at discharge (e.g. discharge to home or to rehabilitation services) or readmission rates. Primary conditions were most commonly cardiovascular disease or cancers, but also diabetes and rheumatoid arthritis. All studies that investigated health service utilisation found a significant relationship with comorbidity. The five studies that investigated the impact of comorbidity on readmissions or disposition at discharge were less consistent with three out of five showing some effect. For example, a high comorbidity index score was associated with an increased chance of readmission for patients with congestive heart failure (Chin and Goldman 1997; Krumholz, Parent et al. 1997), but not for stroke patients (Ween, Alexander et al. 1996; Stukenborg 1997).

More recent work in Australia and New Zealand has confirmed the relationship between higher comorbidity and longer length of stay. Davis et al found that length of stay increased linearly with increasing comorbidity score among 1575 patients from three Auckland hospitals (Davis, Lay-Yee et al. 2002). Mean length of stay was 4.4 days among those with a Charlson comorbidity score of 0, and 7.6, 8.7 and 10.0 days for those with a score of 1-2, 3-4 and 5+ respectively. Similarly Holman et al (2005), and Preen et al (2006) found an association between multimorbidity and both length of stay and 30-day readmission rate among more than a million individuals admitted to Western Australian hospitals between 1989-96 (Holman, Preen et al. 2005; Preen, Holman et al. 2006). Zhang et al 2009, found comorbidity was associated with

readmission rates, and that adverse drug reactions were more common among those with higher Charlson scores (Zhang, Holman et al. 2009).

## ***Impact on patients.***

It is perhaps not surprising that there is considerable and consistent evidence that comorbidity has a strong influence on mortality and the quality of life of individuals. Higher mortality is observed among those with multimorbidity in community samples (eg (Byles, D'Este et al. 2005; Rius, Perez et al. 2008), and among those admitted to hospital with comorbidity and a variety of primary (non-cancer) conditions (Davis, Lay-Yee et al. 2002). For example, Davis et al found that the odds of inpatient mortality increased with increasing Charlson comorbidity score among hospital inpatients in Auckland (crude odds ratio for those with any comorbidity compared to none was 3.64 (1.77-7.46); adjusted for age, gender, case mix OR=1.77 (0.78-4.04))(Davis, Lay-Yee et al. 2002).

Comorbidity is associated with poorer self-reported quality of life, functional status and higher levels of disability (Fortin, Lapointe et al. 2004; Byles, D'Este et al. 2005; Fortin, Bravo et al. 2006; Noel, Parchman et al. 2007; Rius, Perez et al. 2008; Mukherjee, Ou et al. 2011; McDaid, Hanly et al. 2013). In their review of the association between multimorbidity and quality of life in the primary care context, Fortin et al (2004) found an inverse relationship between the number of chronic medical conditions and measures of quality of life relating to physical functioning (Fortin, Lapointe et al. 2004). The findings were somewhat less consistent for social and psychological domains, but the authors note major limitations in many of the studies including a lack of uniform definition of multimorbidity or comorbidity, inconsistent use of data sources, lack of controlling for confounding and exclusion of psychiatric diagnoses. The findings of their own study, which was designed to deal with some of these shortcomings, found associations with higher levels of multimorbidity and dimensions of physical functioning, which were stronger than associations with mental components (Fortin, Bravo et al. 2006). Other authors have found that, in addition to the number and severity of conditions, the nature of the condition is also important in the extent to which quality of life is affected. For example Sprangers et al (2000) found that musculoskeletal, renal and neurological conditions had a more severe impact on self-reported quality of life than cardiovascular disease, endocrine conditions, cancer or chronic respiratory conditions (Sprangers, de Regt et al. 2000).

There are also the more intangible adverse effects of multiple conditions on patients and their carers. Older people with comorbidity report difficulties in coping with juggling multiple clinical appointments and polypharmacy, they often experience poor continuity of care, and they have difficulty in assessing when they need to seek care, or the urgency with which such help should be sought (Wagner, Austin et al. 1996; Fleming, Pursley et al. 2005; Noel, Parchman et al. 2007).

## ***Impact on inequities.***

Comorbidity may produce or exacerbate inequities in health outcomes between population groups. The focus here will be on ethnic inequities, particularly between Māori and non-Māori New Zealanders because these are the most marked disparities currently occurring in New Zealand (Blakely, Tobias et al. 2007), but there is evidence internationally for the role of comorbidity in social class inequities also (Frederiksen, Osler et al. 2009). Comorbidity disproportionately affects Māori for two reasons. First and most obviously, Māori have higher prevalence of comorbidity, and are more likely to have multiple, complex comorbidity than non-Māori (Stevens, Stevens et al. 2008; Hill, Sarfati et al. 2010). Second, even for a given level of comorbidity, Māori may be more impacted than non-Māori. An explanation for this phenomenon can be found in the comprehensive and scientifically rigorous report entitled *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* published by the Institute of Medicine in the United States in 2002 (Smedley, Stith et al. 2002). This report found that racial and ethnic disparities in health care in the United States exist, and are associated with worse outcomes. The reasons for unequal treatment were complex and multifaceted, and included *structural barriers* such as the geographical location and type of institution where care was received; *individual patient factors* including socioeconomic position, and individuals' preferences and decisions, and *physician/clinical factors*. The authors of the Institute of Medicine report concluded that in combination with systemic issues, discrimination at the provider level contributed to disparities in healthcare (Smedley, Stith et al. 2002). They argued that this discrimination tended to be exacerbated with increasing uncertainty relating to the patient. Uncertainty is likely to be higher when clinicians are dealing with people from other racial or ethnic groups than their own and will be particularly high in the context of multiple chronic conditions. For these reasons, people from minority ethnic groups

tend to be disadvantaged, and within these groups those with multiple medical problems will be most disadvantaged.

No detailed work has been carried out on this in the New Zealand context, however there is increasing evidence in New Zealand that health systems tend to work better for non-Māori compared with Māori (Tukuitonga and Bindman 2002; Cormack, Ratima et al. 2005; Stevens, Stevens et al. 2008; Hill, Sarfati et al. 2010; Robson, Purdie et al. 2010). These issues will be expanded in the next chapter in relation to cancer specifically, but for the reasons outlined here, it is reasonable to assume that the burden of comorbidity will be carried disproportionately by Māori patients, and that comorbidity has a role in both producing and exacerbating inequalities in the New Zealand context.

## Summary

Comorbidity is the coexistence of disorders in addition to a primary disease of interest. There is a general consensus in the literature that comorbidity is a complex construct that is difficult to define fully, or to measure accurately. There are a number of constructs that are closely related to, and overlap with comorbidity, including multimorbidity, functional status, disability, allostatic load, frailty, burden of disease, and patient complexity. Given the focus of this thesis is on the impact of chronic disease on cancer outcomes, comorbidity is the most appropriate concept to measure. Comorbidity is common among cancer patients, has a major impact on health services, and patient outcomes.



# Chapter 3: How does comorbidity relate to cancer?

*It is in moments of illness that we are compelled to recognize that we live not alone but chained to a creature of a different kingdom, whole worlds apart, who has no knowledge of us and by whom it is impossible to make ourselves understood: our body. ~Marcel Proust*

This chapter describes how comorbidity is related to cancer. It provides a summary of the prevalence of comorbidity among different cancer sites and discusses potential reasons for the coexistence of cancer and other conditions. It summarises the evidence relating to the influence of comorbidity on the prevention, diagnosis and treatment of cancer, and its subsequent deleterious impact on cancer related outcomes.

## Why might cancer and comorbidity coexist?

The previous chapter described how comorbidity (or multimorbidity) is common among older people in general. Because cancer is largely a disease of the elderly, it is therefore unsurprising that comorbidity is common among cancer patients. However there are several other reasons that cancer may co-occur with other chronic conditions.

1. Cancer and comorbid conditions share many common risk factors. Age is the most obvious example, but there are many others. Smoking, poor diet, lack of physical activity, obesity and alcohol abuse are all risk factors for a range of common non-cancer conditions including diabetes, hypertension, respiratory, cardiovascular and peripheral vascular disease and liver disease. They are also risk factors for many cancers including cancers of lung, bladder, head and neck, colorectum, liver and breast (Adami, Hunter et al. 2008).
2. Comorbidity may cause cancer. There are a number of chronic conditions, in particular chronic infections, diseases of the immune system and diabetes that are causally associated with an increased risk of cancer. For example,

Hepatitis B can cause chronic liver disease which is strongly associated with hepatocellular carcinoma, and tuberculosis patients have an increased risk of lung cancer (Wu, Hu et al. 2011). Conditions associated with immune suppression (such as HIV/AIDS) or dysregulation of the immune system (such as rheumatoid arthritis) are associated with a number of cancers (Extermann 2007; Chen, Chang et al. 2011; Hensel, Goetzenich et al. 2011). HIV/AIDS is related to Kaposi's Sarcoma, Hodgkin's disease and anal cancers (Hensel, Goetzenich et al. 2011) and rheumatoid arthritis is associated with non-Hodgkin's lymphoma and other haematological malignancies (Extermann 2007; Chen, Chang et al. 2011). The exact mechanisms through which these associations might occur have yet to be fully clarified, but are likely to be multifactorial (Extermann 2007). Diabetes is also associated with an increased risk of several cancers including colorectal, pancreatic, liver, endometrial and bladder cancers (Extermann 2007; Friberg, Orsini et al. 2007; Bartosch-Harlid and Andersson 2010; Tabares-Seisdedos, Dumont et al. 2011). Whilst in part these associations may be related to common risk factors between diabetes and cancer (such as obesity), there is also evidence that there are specific biological pathways that directly link diabetes with cancer (Extermann 2007; Bartosch-Harlid and Andersson 2010; Tabares-Seisdedos, Dumont et al. 2011). Diabetes is caused (in part) by insulin resistance which in turn is associated with hyperinsulinaemia (high circulating levels of insulin) and high levels of other insulin-like growth factors, which promote cellular proliferation and affect programmed cell death (apoptosis) increasing the risk of cancer.

3. Cancer may cause comorbidity. This is considerably less common and most conditions caused by cancer would be considered complications of cancer rather than comorbid conditions per se. However, while diabetes is known to cause pancreatic cancer, the reverse is also true. Pancreatic cancer is a cause of diabetes in a small fraction of cases through destruction of the insulin producing Islet cells of the pancreas (Extermann 2007; Bartosch-Harlid and Andersson 2010).
4. Comorbidity may protect from cancer directly or indirectly. Whilst patients with diabetes are at increased risk of a number of cancers, they are also at lower risk of lung and prostate cancers and Hodgkins disease (Tabares-Seisdedos, Dumont et al. 2011). Whilst it is not known exactly why this is the case, it is postulated to be due to changes in hormone profiles, growth factors and steroids. Patients with hypothyroidism have also been found to have lower rates of breast cancer (Extermann 2007). Treatment for comorbid conditions may

also be protective, for example, the use of non-steroidal anti-inflammatory drugs used commonly in arthritis is associated with a reduced risk of colorectal cancer (Huls, Koornstra et al. 2003; Flossmann, Rothwell et al. 2007; Din, Theodoratou et al. 2010).

5. There may be common genetic or physiological pathways between cancer and comorbidities. A well-established example of this is the inverse relationship between neurodegenerative disorders (such as Alzheimer's and Parkinson's disease) and cancer (Olsen, Friis et al. 2005; Roe, Behrens et al. 2005; West, Dawson et al. 2005; Driver, Kurth et al. 2007; Driver, Logroscino et al. 2007; Driver, Kurth et al. 2008; Yashin, Ukraintseva et al. 2009; Roe, Fitzpatrick et al. 2010). For example Roe et al 2010 found that there was both a low risk of cancer among Alzheimer's disease patients (HR=0.31; 0.12-0.86) and low risk of Alzheimer's disease among cancer patients (HR=0.57; 0.36-0.90) after adjustment for demographic, smoking and other factors (Roe, Fitzpatrick et al. 2010). Neurodegenerative diseases are related to neuronal loss and cellular destruction, while cancer is a disease of unchecked cellular proliferation. At the cellular level, there is a fine balance between mechanisms that repair DNA and promote cell growth, and those that stop cellular replication and apoptosis. The hypothesis relating to the negative correlation between cancer and neurodegenerative disorders is that if the balance favours cell growth and repair, then an individual may be protected from neurodegenerative disorders but may be at increased risk of cancer, whilst if the balance favours effective inhibition of cell growth and replication the opposite will be true.

## **Prevalence of comorbidity among cancer patients**

Whilst there is general agreement that comorbidity is common among cancer patients, it is remarkably difficult to state with any certainty how common it is. This is because the prevalence of measured comorbidity varies, sometimes dramatically, depending on the measure of comorbidity used, the data available, the study population, and the cancer site. In their review of the impact of comorbidity on chemotherapy use and outcomes among patients with solid tumours, Lee et al reported an unhelpfully wide prevalence range for comorbidity of 0.4% to 90% among cancer patients (Lee, Cheung et al. 2011). Not surprisingly, studies that use a more inclusive measure of comorbidity demonstrate a higher prevalence of comorbidity than those that use a more restrictive

approach. For example, Tammemagi et al used an extensive and inclusive approach to identifying comorbid conditions from computerised medical records in their cohort of patients with breast cancer, and found that 72% had at least one condition (Tammemagi, Nerenz et al. 2005). This compares with Gonzalez et al who used data extracted only from routine discharge abstracts and found 13% of women with breast cancer had at least one Charlson index-related comorbid condition (Gonzalez, Ferrante et al. 2001). Even if the approach to measuring comorbidity is limited to a single comorbidity index, the Charlson index, there is still a large range of prevalence estimates. Most studies that use the Charlson index report that 10-75% of cancer patients have at least one Charlson index-related condition (Coebergh, Janssen-Heijnen et al. 1999; Gonzalez, Ferrante et al. 2001; Miller, Taub et al. 2003; Janssen-Heijnen, Smulders et al. 2004; Janssen-Heijnen, Houterman et al. 2005; Cronin-Fenton, Norgaard et al. 2007; Iversen, Norgaard et al. 2009; Sarfati, Hill et al. 2009; Patnaik, Byers et al. 2011). The variation is largely due to characteristics of the study population and to the data collected. For example, studies that are restricted to older patients generally demonstrate higher levels of comorbidity. Comorbidity also tends to be higher among patients with certain cancers, particularly smoking-related cancers such as lung, head and neck and bladder cancers (Coebergh, Janssen-Heijnen et al. 1998). Studies based on administrative data often (but not always) report lower levels of comorbidity than those based on medical notes review or self-report (Romano, Roos et al. 1993; Malenka, McLerran et al. 1994; Newschaffer, Bush et al. 1997; Kieszak, Flanders et al. 1999; van Doorn, Bogardus et al. 2001; Sarfati, Hill et al. 2010).

Despite these uncertainties, there is universal agreement that comorbidity is common among cancer patients in general. It is less clear whether cancer patients have higher rates of comorbidity than similarly aged non-cancer populations. Some authors have noted generally similar prevalence rates of comorbid conditions among cancer patients compared with non-cancer populations (Zeber, Copeland et al. 2008; Harlan, Klabunde et al. 2009). In contrast, other studies have reported that cancer patients have somewhat higher levels of comorbidity than the general population (Hewitt, Rowland et al. 2003; Smith, Reeve et al. 2008). Two studies compared the self-reported prevalence of conditions from the US National Health Interview Study among those with a history of cancer to those without (Hewitt, Rowland et al. 2003; Smith, Reeve et al. 2008). Hewitt et al found that among those aged over 65 yrs, 3.9% of cancer patients reported having three or more chronic medical conditions, compared with 2.3% of those without a history of cancer (Hewitt, Rowland et al. 2003). Similarly, Smith et al found that with the exception of patients with melanoma, non-Hodgkin's lymphoma and

prostate cancer, cancer patients were more likely to report two or more conditions than others (Smith, Reeve et al. 2008). There are two studies that have reported that cancer patients actually have lower levels of comorbidity than age matched controls. The first by Repetto et al compared cancer patients to patients admitted to hospital medical or geriatric services who would be expected to have higher levels of multimorbidity than people of a similar age in the general population (Repetto, Venturino et al. 1998), and the second by Piccirillo et al compared comorbidity data extracted from hospital notes for cancer patients with self-reported national data on similar conditions. Both these sets of authors concluded that the differences between the cancer and non-cancer populations were likely to reflect inadequacies in the data comparison (Piccirillo, Costas et al. 2003).

One obvious reason for the inconsistent results is likely to be that the prevalence of comorbidity varies considerably by cancer site. In their matched case-control study of men with newly diagnosed cancer, Driver et al found that the overall (modified Charlson) comorbidity scores were similar for men with and without cancer (Driver, Yung et al. 2010). However, they found that there was variation by cancer type. In particular, men who had been diagnosed with screen-detected cancers (such as prostate cancer and melanoma) had lower comorbidity scores than age-matched population controls, whilst those with smoking-related cancers had higher scores (Driver, Yung et al. 2010). Similarly two recent studies have found that those with lung cancers had higher likelihood of comorbidity, while those with breast cancer had similar or lower likelihood (Jorgensen, Hallas et al. 2012; Cho, Mariotto et al. 2013).

Tables 1 to 4 show a range of prevalence estimates for the most common conditions for patients with lung, breast, colorectal and prostate cancers respectively. They show that there is variation in prevalence estimates of specific conditions even within cancer sites. For example, estimates of the prevalence of diabetes among colorectal cancer patients range between 6 and 18%, of hypertension between 16 and 47% and of chronic respiratory disease between 5 and 22%. As with global comorbidity measures, these variations are a function of the study populations, the data collected and the definitions used for specific comorbid conditions. These tables do usefully show that the most common concomitant conditions include hypertension, respiratory disease, heart disease, cerebrovascular disease, previous cancer, arthritis and diabetes. They also show that the prevalence of some comorbid conditions varies between sites, for example, respiratory conditions are (not surprisingly) particularly high among patients

with lung cancer with estimates ranging from 15-47 % compared with prostate (1-30%), colorectal cancer (5-22%) and breast (all 3-14% except for one outlier at 52%).

**Table 1: Prevalence of specific conditions among patients with prostate cancer from selected studies (%)**

<b>Paper</b>	<b>Driver 2010</b>	<b>Janssen- Heijnen 2005</b>	<b>Janssen- Heijnen 2005</b>	<b>Klabunde 2007</b>	<b>Piccirillo 2008</b>	<b>Fleming 2006</b>	<b>Fleming 2006</b>	<b>Fan 2002</b>	<b>Putt 2009</b>	<b>Putt 2009</b>
<b>Age range (yrs)</b>	40-84	65-79	80+	66 +	All	67+, White men	67+, Black men	All	65+, White men	65+, Black men
<b>Data source</b>	From Dr	Medical Notes	Medical Notes	Admin Data	Medical notes	Admin data	Admin data	Self- report	Admin data	Admin data
<b>Hypertension</b>	19	17	12		37	55	88	59	40	58
<b>Other cancer</b>		9	14		6	9	11	13		
<b>CHF/Heart disease</b>		24	27	10	2	13	20	9	4	6
<b>COPD/Respiratory</b>	21	12	15	16	8	26	30	24	1	13
<b>Diabetes</b>		8	9	19	10	16	27	24	14	23
<b>Cerebrovascular disease</b>				7	3	11	12		2	4.2
<b>Angina</b>					13			31		
<b>Previous MI</b>				3	7			22		
<b>PVD</b>				5		13	17		6	7
<b>Arthritis</b>	20							59		

**Table 2: Prevalence of specific conditions among patients with colorectal cancer from selected studies(%)**

<b>Paper</b>	<b>Driver 2010</b>	<b>Janssen- Heijnen 2005</b>	<b>Janssen- Heijnen 2005</b>	<b>Gross 2006</b>	<b>Klabunde 2007</b>	<b>Klabunde 2007</b>	<b>Ogle 2000</b>	<b>Piccirillo 2008</b>	<b>Sarfati 2009</b>
<b>Age range (yrs)</b>	40-84	65-79 Males	65-79 Females	67 +	66 + Males	66 + Females	All (Colon)	All	>25 (Colon)
<b>Data source</b>	From Dr	Medical notes	Medical notes	Admin data	Admin data	Admin data	Self- report	Medical notes	Medical notes
<b>Hypertension</b>	16	21	25				47	41	38
<b>Other cancer</b>		15	14					14	5
<b>CHF/Heart disease</b>	15	28	14	19	4	5		5	11
<b>COPD/Respiratory</b>	19	15	8	21	5	5	15	12	22
<b>Diabetes</b>		10	14	18	6	7	6	16	16
<b>Cerebrovascular disease</b>				10	2	2	7	5	7
<b>Angina</b>								12	12
<b>Previous MI</b>					1	<1		8	8
<b>PVD</b>				7	2	2			4
<b>Arthritis</b>	15						5		

**Table 3: Prevalence of specific conditions among patients with lung cancer from selected studies (%)**

<b>Paper</b>	<b>Driver 2010</b>	<b>Janssen- Heijnen 2005</b>	<b>Janssen- Heijnen 2005</b>	<b>Klabunde 2007</b>	<b>Klabunde 2007</b>	<b>Ogle 2000</b>	<b>Piccirillo 2008</b>	<b>Tammemagi 2003</b>	<b>Blanco 2008</b>	<b>Colinet 2005</b>	<b>Stevens 2008</b>
<b>Age range (yrs)</b>	40-84	65-79 Males	65-79 Females	66 Males	66 Females	All	All	All	>70	All	All
<b>Data source</b>	From Dr	Medical notes	Medical notes	Admin data	Admin data	Self- report	Medical notes	Computerised medical records	Medical notes	Medical notes	Medical notes
<b>Hypertension</b>	16	15	21			37	38				
<b>Other cancer</b>		16	16				18	1.2	13	12	
<b>CHF/Heart disease</b>	21	34	22	7	5		5	8			
<b>COPD/Respiratory</b>	28	24	24	19	15	37	29	29	42	44	47
<b>Diabetes</b>		10	12	8	5	5	11		16	9	13
<b>Cerebrovascular disease</b>				4	3	9	5		12		
<b>Angina</b>							14				
<b>Previous MI</b>				2	2		10				
<b>PVD</b>				4	2			10			
<b>Arthritis</b>						5					

**Table 4: Prevalence of specific conditions among patients with female breast cancer from selected studies (%)**

<b>Paper</b>	<b>Janssen-Heijnen 2005</b>	<b>Harlan 2009</b>	<b>Klabunde 2007</b>	<b>Patnaik 2011</b>	<b>Piccirillo 2008</b>	<b>Fleming 1999</b>	<b>Mandelblatt 2001</b>	<b>Satariano 1994</b>	<b>Wang 2000</b>
<b>Age range (yrs)</b>	65-79	All	66 +	66 +	All	67 +	67 +	40-84	20 +
<b>Data source</b>	Medical notes	Medical notes	Admin data		Medical notes	Admin data	Medical records	Medical records	Admin records
<b>Hypertension</b>	29	28			35	69	48	44	
<b>Other cancer</b>	10			16	12	9	10	6	
<b>CHF/Heart disease</b>	12	1.2	6	7		25			1
<b>COPD/Respiratory</b>	6	10	7	9	8	52	14	5	3
<b>Diabetes</b>	13	8	11	13	10	32	11	8	4
<b>Cerebrovascular disease</b>			4	4	3	16		3	1
<b>Angina</b>		1			4	8			
<b>Previous MI</b>		1.4	1	2	3			1	1
<b>PVD</b>			2	3		15			<1
<b>Arthritis</b>		14					34	21	

# Impact of comorbidity on diagnosis of cancer

There are contrasting and not necessarily mutually exclusive possibilities regarding the impact of comorbidity on the detection and diagnosis of cancer (Ogle, Swanson et al. 2000; Vaeth, Satariano et al. 2000; Fleming, Pursley et al. 2005). On one hand, patients with comorbidity may be diagnosed earlier and/or be more likely to be offered screening for cancer because they tend to be accessing health services more regularly and to be under a higher level of medical scrutiny than people without chronic conditions. In contrast, the concomitant existence of chronic disease may mask early symptoms of cancer and may distract either or both the patient and clinician from considering a diagnosis of cancer. Equally, it is reasonable to assume that in some cases a rational decision is made for a patient with severe chronic disease not to undergo screening or investigations for cancer because of their reduced life expectancy.

The review of the literature suggests that more than one of these mechanisms may be at play at the same time, and the balance between them may vary depending on health system and patient factors. Consistent with these ideas, Fleming et al (2005) put forward four separate hypotheses to explain the varying associations between comorbidity and stage of cancer at diagnosis. These are 1) The *competing demands* hypothesis in which comorbidities distract the clinician or the patient from a diagnosis of cancer thereby delaying diagnosis and resulting in later stage at diagnosis; 2) the *pathological hypothesis* in which comorbidities impact biologically on the aggressiveness of the cancer; 3) the *surveillance hypothesis* in which those with comorbidity are more likely to access health services facilitating early diagnosis and 4) the *death from other causes hypothesis* in which patients with major comorbid illness are likely to have reduced life expectancy and therefore are not offered screening or diagnostic investigations.

## 1. Competing demands hypothesis

If health professionals and/or patients are distracted from the possibility of cancer because of other health-related demands, one would expect a delay in the diagnosis of

cancer, and thus more advanced stage at diagnosis. There are numerous studies reporting this pattern (Miller, Taub et al. 2003; Koppie, Serio et al. 2008; Tetsche, Dethlefsen et al. 2008; Teppo and Alho 2009; Grann, Froslev et al. 2013). For example, Koppie et al reported that locally extensive bladder cancer was present at diagnosis in 43% of patients with Charlson index score <3, 49% of those with score 3-5 and 56% among those with scores >5 (Koppie, Serio et al. 2008). In the largely unscreened New Zealand population, Sarfati et al also found an association of more advanced stage colorectal cancer with higher comorbidity (Sarfati, Tan et al. 2011). Consistent with the hypothesis of competing demands on doctors and patients, Teppo et al found that both patient delay and long professional delay were related to later stage of diagnosis among those with higher levels comorbidity for patients with head and neck cancers (Teppo and Alho 2009).

## **2. The physiological hypothesis.**

The general findings of later stage at diagnosis for those with chronic disease are also consistent with the theoretical possibility that cancer is somehow more aggressive among those with comorbidity (Fleming, Pursley et al. 2005). Aksoy et al suggested that some comorbidities may be related to higher levels of proangiogenic growth factors which may encourage cancer growth (Aksoy, Aksoy et al. 2006). Similarly insulin resistance seen in type II diabetes is associated with high levels of blood insulin, growth factors and activation of pathways that may also promote cancer growth (Extermann 2007). In contrast, it may be that some conditions or their treatment are associated with slower cancer growth. For example, non-steroidal anti-inflammatory drugs used in arthritis may slow the growth of colorectal and other cancers (Gonzalez-Perez, Garcia Rodriguez et al. 2003; Extermann 2007).

## **3. The surveillance hypothesis**

The surveillance hypothesis suggests that those with comorbidity are more likely to access health services because of their high health needs, and are therefore more likely to be offered screening and/or have symptoms noticed and investigated than others. Consistent with this hypothesis, some authors have reported either no difference in stage distribution according to comorbidity, or a pattern of earlier stage at diagnosis with higher comorbidity levels (Satariano and Ragland 1994; Vaeth, Satariano et al. 2000; Yancik, Wesley et al. 2001; Zafar, Abernethy et al. 2008;

Yasmeen, Xing et al. 2011; Corkum, Urquhart et al. 2012). Walter et al (2009) found that higher number of visits to health clinics was related to higher rates of screening, supporting the contention that those with high levels of medical surveillance due to chronic disease may be more likely to be offered screening (Walter, Lindquist et al. 2009). Vaeth et al (2000) found that women with one or more of five functionally limiting comorbid conditions were less likely to present with late stage breast cancer (Vaeth, Satariano et al. 2000). They concluded that these conditions are likely to be associated with higher levels of medical surveillance, which resulted in more opportunity for referral to screening. Furthermore, there may also be an element of 'reverse causality' where patients who tend to access health care services frequently are more likely to be diagnosed with minor comorbidity and may also be more likely to undergo screening.

#### **4. The death from other causes hypothesis**

This hypothesis relates to the possibility that those with comorbidity might be less likely to be offered screening (or diagnostic investigations) due to an explicit decision on the part of the health professional or patient that there is little point to such investigations due to their risk of death from other causes. The evidence to support this hypothesis is difficult to disentangle from that of the competing demands hypothesis. Patients may be less likely to be referred for screening either because of competing demands of care for their comorbidity or because of a rational decision on the part of the health professional and patient that screening may not be worthwhile given that the mortality reduction benefits of screening for cancer tend not to accrue until many years after the initial screening test (Zappa, Visioli et al. 2003; Schonberg, McCarthy et al. 2004; Gross, McAvay et al. 2006; Walter, Bertenthal et al. 2006; Wolf, Wender et al. 2010).

There is, however, good evidence that those with comorbidity are less likely to be offered screening, and as a result have later stage at diagnosis of screen-detectable cancers. For example, Gonzalez et al (2001) studied the association of higher levels of comorbidity with late stage at diagnosis among patients with potentially screen-detected cancers (breast, colorectal, prostate and melanoma). They found that for all four sites, comorbidity was a significant predictor of late stage at diagnosis cancers ('any' comorbidity compared with none was associated with 17% greater odds for late stage diagnosis for CRC, 24% for breast, 30% for prostate and 62% for melanoma) (Gonzalez, Ferrante et al. 2001). To assess whether chronic disease reduced breast and cervical cancer screening uptake, Kiefe et al carried out a review of medical records amongst a cohort of primary care patients (Kiefe, Funkhouser et al. 1998).

They found that higher Charlson index scores were associated with a reduced rate of screening for these cancers (each unit increase in Charlson score resulted in a 17% lower likelihood of mammography and 20% lower cervical smear after adjustment for demographics, clinic use and insurance status). Of note is that reduced screening among those with limited life expectancy is entirely consistent with best practice relating to screening (Gross, McAvay et al. 2006; Leach, Klabunde et al. 2012).

## **How to make sense of the evidence?**

The summary of evidence relating to the impact of comorbidity on diagnosis above suggests that there are different mechanisms at play and they vary depending on specific circumstances. Key characteristics that are likely to be important are:

*Type of cancer:* the impact of comorbidity may vary between cancers where there is screening available and not, and between cancers for which early symptoms may be mistaken for symptoms relating to comorbidity. For example, a patient with chronic respiratory disease may report increasing shortness of breath or cough to their health professional who may assume this is an exacerbation of their underlying disease rather than investigating the possibility of lung cancer.

*Type of comorbidity:* Patients with unstable and/or life threatening comorbidity may be more likely to have symptoms overlooked and less likely to undergo screening because of diversion of resources to manage the active condition(s) rather than considering new ones. In contrast, patients with stable or less severe comorbidities may be more likely to access health services, and therefore have greater opportunity to undergo screening or to have early symptoms of cancer investigated. There is some evidence to support this contention. Yasmineen et al (2011) studied a cohort of 118,742 women with breast cancer (Yasmineen, Xing et al. 2011). They identified comorbid conditions and divided them into those that could be classified as stable (those that effect daily activities) and unstable (those that may be life-threatening or difficult to control). They found that the presence and number of stable conditions were associated with higher screening mammography rates and earlier stage at diagnosis while the converse was true for unstable conditions.

*Health service structure, funding and organisation.* Health services with a strong focus on screening or where funding is attached to screening coverage may be associated with less difference in screening rates between those with and without comorbidity compared with other services. A number of studies have investigated the uptake of CRC screening within the equal access Veterans Administration health system in the

US (Fisher, Judd et al. 2005; Sultan, Conway et al. 2006; Fisher, Galanko et al. 2007; Walter, Lindquist et al. 2009). All found that there was little or no difference in rates of screening for men with life-limiting comorbidity, concluding that physicians may not be taking account of shortened life expectancy when they offer screening. This may be because colorectal cancer screening rates are used as a performance measure in the VA health system which may have had the unforeseen consequence of encouraging inappropriate screening (Fisher, Judd et al. 2005).

## **Impact of comorbidity on treatment for cancer**

One of the most consistent findings in relation to cancer and comorbidity is that those with comorbidity are less likely to receive curative treatment for their cancer than those without comorbidity. This phenomenon has been reported across different health settings, cancer sites and treatment types (Newschaffer, Penberthy et al. 1996; Mandelblatt, Bierman et al. 2001; Lash, Thwin et al. 2003; Tammemagi, Neslund-Dudas et al. 2004; Hall, Jani et al. 2005; Janssen-Heijnen, Houterman et al. 2005; Tammemagi, Nerenz et al. 2005; Blanco, Toste et al. 2008; Etzioni, El-Khoueiry et al. 2008; Koppie, Serio et al. 2008; van der Aa, Siesling et al. 2008; Sarfati, Hill et al. 2009; Crawford, Grubb et al. 2011; Lee, Cheung et al. 2011; Chen, Royce et al. 2012; Land, Dalton et al. 2012; Rodrigues and Sanatani 2012). Taking colorectal cancer as an example, there is strong evidence that those with comorbidity are less likely to receive recommended treatment for their cancer. Numerous studies have found that the offer and receipt of chemotherapy among colorectal cancer patients is lower among patients with comorbidity (Janssen-Heijnen, Houterman et al. 2005; Lemmens, Janssen-Heijnen et al. 2005; Baldwin, Klabunde et al. 2006; Cronin, Harlan et al. 2006; Gross, McAvay et al. 2007; Sarfati, Hill et al. 2009; Quipourt, Jooste et al. 2011). A systematic review of studies analysing the use of chemotherapy among stage III colon cancer patients in the US reported that seven out of nine studies found that comorbidity had a deleterious effect on chemotherapy receipt. The magnitude of the effect was large with the odds ratios comparing the uptake of chemotherapy among patients with Charlson scores of 2 or 3+ with those with scores of 0 ranging from 0.38-0.44 in one large study. No summary estimate was given because of the heterogeneity of the studies (Etzioni, El-Khoueiry et al. 2008).

In the New Zealand setting, Sarfati et al found that among patients with stage III colon cancer, those with a Charlson score greater than two compared with zero were less likely to be offered chemotherapy (19% compared with 84%) despite such therapy being associated with a 60% reduction in excess mortality for both all-cause and cancer specific survival in these patients (Sarfati, Hill et al. 2009). Radiotherapy is generally used only for a subset of patients with rectal carcinomas, but comorbidity has also been shown to be associated with lower receipt of radiotherapy among this group (Janssen-Heijnen, Houterman et al. 2005; Lemmens, Janssen-Heijnen et al. 2005).

While no difference in receipt of surgery was found among colorectal cancer patients in some studies (Janssen-Heijnen, Houterman et al. 2005; Lemmens, Janssen-Heijnen et al. 2005), Iversen et al (2009) found the proportion of resected cancers in Denmark decreased with increasing comorbidity for colon cancer (83.8% for Charlson score =0 compared with 63.2% for Charlson score 3+) (Iversen, Norgaard et al. 2009). A similar pattern was seen for rectal cancers. Zhang et al reported that those CRC patients with comorbidity were less likely to undergo surgery at high (compared with low) volume institutions in the US, which they postulated may result in poorer quality surgery for those with comorbidity (Zhang, Ayanian et al. 2007).

Vignette-based studies that ask clinicians to consider decisions on the basis of summarised information about hypothetical patients have also consistently found that surgeons and oncologists are less likely to refer or recommend treatment for cancer patients with comorbidity (Keating, Landrum et al. 2008; Krzyzanowska, Regan et al. 2009; Ring 2010). There are several reasons that may explain the impact of comorbidity on treatment for cancer. Clinicians may be concerned that concomitant conditions will increase the toxicity and side effects of treatment, that treatments may be less effective in these groups, or that the life expectancy of these patients is insufficient to justify the use of potentially toxic agents (Newcomb and Carbone 1993; Kutner, Vu et al. 2000; Schrag, Cramer et al. 2001; Lemmens, Janssen-Heijnen et al. 2005; Gross, McAvay et al. 2007). It is also possible that these patients themselves are more likely to decline treatment (Newcomb and Carbone 1993; Yellen, Cella et al. 1994; Kutner, Vu et al. 2000).

This issue is important because it is not entirely clear the extent to which comorbidity acts on survival directly or through its impact on treatment choice or effectiveness. Intuitively it is likely that both play a part. This is a significant distinction because the latter pathway is amenable to intervention. There is some debate about the tolerability

of treatment among those with comorbidity. There is a paucity of studies that have investigated this issue directly. However, there is some evidence that those with comorbidity have longer lengths of hospital stay after treatment for cancer which may suggest lower treatment tolerance (Extermann 2000; Sarfati, Tan et al. 2011). A recent New Zealand study of 11,524 patients with colon cancer which investigated the impact of comorbidity on length of stay found that there was a significant association only seen among those with Charlson scores of 3+, compared with 0. That is, people with a Charlson score of 3 or more had a 15% (95% CI 8%-22%) increase in length of stay compared to those with a Charlson score of 0. Those with chronic respiratory disease, diabetes and previous myocardial infarction had significantly longer length of stays compared to those without the specified condition, while those with recorded essential hypertension had significantly shorter stays.

Equally, the evidence among cancer patients relating to the risk of complications from treatment among those with comorbidity is conflicting. Several authors have reported that there was no or minimal difference in rates of complications between those with and without comorbidity (Meyerhardt, Catalano et al. 2003; Gross, McAvay et al. 2007; Lemmens, Janssen-Heijnen et al. 2007; Gronberg, Sundstrom et al. 2010; LoConte, Smith et al. 2010; Peters, van der Laan et al. 2011; Seymour, Thompson et al. 2011). Loconte et al (2010) identified 242 cancer patients representing 27 cancer types who were enrolled in randomized controlled trials for phase 1 chemotherapy within their institution (LoConte, Smith et al. 2010). They did not find that comorbidity as measured by CIRS-G was predictive of dose limiting toxicity either in univariate or multivariate analyses, however their cohort was a relatively young and healthy one so they may have underestimated the effect of comorbidity on complications. Similarly Meyerhardt et al (2003) investigated the role of treatment toxicity within a cohort of patients enrolled in a randomised controlled trial (Meyerhardt, Catalano et al. 2003). In their study they compared overall survival, cancer recurrence and treatment toxicity among stage IIb and III colon cancer patients with and without diabetes mellitus. Patients with diabetes had 42% increased risk of death from any cause, and 21% increased risk of recurrence after adjustment for other factors at five years, but treatment toxicities were similar between the groups. Gronberg et al investigated complications after chemotherapy for patients with advanced non-small cell lung cancer (Gronberg, Sundstrom et al. 2010). They found that those with comorbidity identified using CIRS-G had similar rates of neutropenia but were somewhat more likely to develop neutropenic fevers and related deaths than those without comorbidity. Those with comorbidity also had more thrombocytopenia (low platelet counts) but were not more

likely to develop problems with bleeding. These authors concluded "*[w]ithholding chemotherapy from all patients with severe comorbidity [accounting for 40% of the study population] does not seem to be a reasonable precaution to avoid neutropenic infection among a few*". Lemmens et al found that comorbidity overall (as measured by the Charlson index) did not predict complications of surgery for 431 patients with stage I-III colorectal cancer, but complications were more common among those with certain conditions particularly chronic respiratory disease and deep vein thrombosis at diagnosis (Lemmens, Janssen-Heijnen et al. 2007).

In contrast, other studies have reported higher rates of complications among cancer patients with comorbidity (Rieker, Hammer et al. 2002; Hall, Jani et al. 2005; Kobayashi, Miura et al. 2011; Lee, Cheung et al. 2011). In their review of the literature relating to the impact of comorbidity on chemotherapy use for solid tumours, Lee et al (2011) reported that among the 10 studies that reported on tolerability of chemotherapy, five reported a higher rate of grade 3 or 4 toxicity among those with comorbidity, but there were no differences in hospitalisation rates or overall complications at 1 year (Lee, Cheung et al. 2011). Hall et al found that prostate cancer patients with diabetes and peripheral vascular disease were more likely to suffer from post treatment impotence and other complications compared to those without these conditions (Hall, Jani et al. 2005). Rieker et al examined the outcomes of 531 colorectal cancer patients in a single German hospital (Rieker, Hammer et al. 2002). They found post-operative complications were higher for those with Charlson scores greater than 2 compared to 0 (OR 2.18; 1.50-3.16), and post-operative transfusions in particular were higher (OR 1.56; 1.07-2.28).

In summary, while there is evidence that some cancer patients with comorbidity may be at increased risk of post-therapeutic complications; this is not a consistent finding. The lack of demonstrable differences in treatment tolerability in many studies between those with and without comorbidity suggests the possibility that the large differences in treatment offer and receipt between these groups may not always be justifiable from the point of view of treatment toxicity and complications.

# Impact of comorbidity on outcomes from cancer

## *Survival*

Comorbidity has been found to have an adverse impact on survival from cancer in every cancer site investigated including breast (Charlson, Pompei et al. 1987; Fleming, Rastogi et al. 1999; Lash, Thwin et al. 2003; Nagel, Wedding et al. 2004; Tammemagi, Nerenz et al. 2005; Cronin-Fenton, Norgaard et al. 2007; Ahern, Lash et al. 2009; Patnaik, Byers et al. 2011), colorectal (Baldwin, Dobie et al. 2005; Lemmens, Janssen-Heijnen et al. 2005; Gross, McAvay et al. 2006; Iversen, Norgaard et al. 2009; Sarfati, Hill et al. 2009; Roxburgh, Platt et al. 2011; Sarfati, Tan et al. 2011; Dasgupta, Youlden et al. 2013), prostate (Albertsen, Fryback et al. 1996; Hall, Jani et al. 2005; Boulos, Groome et al. 2006; Lund, Borre et al. 2008; Daskivich, Sadetsky et al. 2010; Albertsen, Moore et al. 2011; Groome, Rohland et al. 2011), lung (Tammemagi, Neslund-Dudas et al. 2003; Colinet, Jacot et al. 2005; Blanco, Toste et al. 2008; Gronberg, Sundstrom et al. 2010), cervical (Brewer, Borman et al. 2011), ovarian (Tetsche, Dethlefsen et al. 2008), head and neck (Piccirillo and Vlahiotis 2006; Castro, Dedivitis et al. 2007; Yung and Piccirillo 2008), renal (Berger, Megwalu et al. 2008; Kutikov, Egleston et al. 2012), bladder (Koppie, Serio et al. 2008; Megwalu, Vlahiotis et al. 2008), melanoma (Grann, Froslev et al. 2013) and haematological cancers (Kobayashi, Miura et al. 2011). The magnitude of the association is variable depending on how comorbidity is measured, whether all-cause or cancer-specific survival is measured, the cancer site studied, and the population included. Regardless, comorbidity has a major impact on prognosis. In fact, some studies have suggested that the presence of comorbidity has as much prognostic significance as stage of cancer at diagnosis (Albertsen, Moore et al. 2011; Patnaik, Byers et al. 2011). Patnaik et al 2011 found that those with Stage I breast cancer and comorbidity had similar survival to those with stage II cancer with comorbidity. Albertsen (2011) found similar findings in relation to prostate cancer.

Despite the large body of literature examining the associations between comorbidity and cancer survival, and the, at times, inconsistent findings, there are some clear patterns that emerge from the data.

*The impact of comorbidity tends to increase with increasing levels of comorbidity, although not necessarily in a linear fashion (Extermann 2000; Boulos, Groome et al. 2006). The most common way of assessing the role of comorbidity is to categorise comorbidity into (often) two or three categories and compare each with a 'no comorbidity' category. The typical pattern is for ratio measures of association (risk ratios, odds ratios or hazard ratios) to be in the range of 1-2.5 for each category of comorbidity compared with the lowest category. The ratio measures of association tend to be at the lower end of this range and remain relatively stable at lower levels of comorbidity and only increase at higher levels. When multiple categories of comorbidity are assessed in this way, very high levels of comorbidity are often associated with considerably higher risk of death compared with no comorbidity, with ratio estimates sometimes extending to ratio measures of 4-5 or beyond (Extermann 2000). In a population-based study from the Netherlands, Janssen-Heijnen et al (2005) reported the effect of three levels of Charlson index scores for patients with a range of cancer types (Janssen-Heijnen, Houterman et al. 2005). Their most severe category was very broad and included all patients who had a Charlson index score of 2 or more. They found that compared with a score of 0, those with a score of 1, or 2+ had increased risk of 5-year mortality for most cancer types (e.g. for scores 1 and 2+ compared to 0 respectively colon: HR=1.2 (1.1-1.3) & 1.4 (1.2-1.5); rectum HR=1.3 (1.1-1.5) & 1.6 (1.4-1.9); breast HR=1.3 (1.2-1.5) & 1.4 (1.3-1.5); and localised prostate HR=1.2 (1.03-1.4) & 1.9 (1.6-2.2)). Piccirillo et al (2003) reported on data from more than 8000 patients with comorbidity measured using ACE-27, and divided into more differentiating categories of none, mild, moderate and severe comorbidity (Piccirillo, Costas et al. 2003). Having adjusted for age, sex, ethnicity and stage, they found increasing risk of death with increasing comorbidity across cancer sites (e.g. relative to none, for all sites combined mild HR=1.1 (0.9-1.2), moderate 1.3 (1.1-1.5) and severe 1.9 (1.7-2.2); for prostate cancer (n=1545), HR=1.1, 2.9 and 6.6 respectively; breast (n=1378, HR=1.4, 2.7, 4.3 respectively); CRC (n=280, HR= 1.2, 1.7, 2.2 respectively) and gynaecological cancers (n=685, HR= 0.7, 1.1 and 2.0 respectively). They reported a lower gradient for cancers of the lung and head and neck (1.6 and 1.4 respectively for severe comorbidity category).*

*The impact of comorbidity is greater for total or non-cancer survival than cancer-specific survival, but is demonstrable for all measures of survival e.g.(Albertsen, Fryback et al. 1996; Sarfati, Tan et al. 2011; Land, Dalton et al. 2012). For example, Albertsen (1996) reported cumulative total mortality, non-cancer mortality, and cancer mortality for a cohort of men with prostate cancer stratified by Charlson index scores*

(0, 1, 2 and 3). They found that while comorbidity was associated with a higher risk of death in all three cases, the association was considerably stronger for all-cause and non-cancer deaths.

*The (relative) impact of comorbidity tends to be greater for cancers with better prognosis* (Piccirillo, Costas et al. 2003; Piccirillo, Tierney et al. 2004; Read, Tierney et al. 2004; Kendal 2008). This is because those with cancer associated with a high mortality rate will be more likely to succumb to their cancer regardless of other concomitant disease compared to patients with a less severe prognosis. For example, Piccirillo et al (2004) found that when they compared hazard ratios for mortality among those with severe comorbidity to none, these varied from a high of 9.2 for prostate cancer to 1.5 for lung cancer (Piccirillo, Tierney et al. 2004). In general, more indolent cancers were associated with a higher relative impact of comorbidity compared with more aggressive cancers. Similarly, the impact of comorbidity is greater for less than more advanced cancer for similar reasons (Satariano and Ragland 1994).

When individual conditions are investigated, *higher severity conditions such as congestive heart failure, chronic respiratory disease, diabetes with complications, severe renal or liver disease not surprisingly have a greater impact than lower severity conditions* (Fleming, Rastogi et al. 1999; Fleming, Pearce et al. 2003; Baldwin, Klabunde et al. 2006; Gross, Guo et al. 2006; Sarfati, Hill et al. 2009; Brewer, Borman et al. 2011; Groome, Rohland et al. 2011; Sarfati, Tan et al. 2011). Less obviously, some less severe conditions (such as hypertension and angina) are often found to be associated with better cancer survival (Elixhauser, Steiner et al. 1998; Fleming, Pearce et al. 2003; Baldwin, Klabunde et al. 2006; Sarfati, Tan et al. 2011). This finding is likely to be due to a type of information bias where those who have major, potentially life-threatening conditions are less likely to have conditions that are common and less serious recorded. As a result, those that do have these latter conditions, paradoxically, tend to be healthier than those with other comorbidities, and as a result have better outcomes.

There are several reasons why comorbidity impacts survival. The most obvious is the direct, independent impact of concomitant disease on non-cancer mortality. This difference in mortality would be observed in any population where those with comorbidity were compared to those without, all else being equal. This mechanism will affect measures of non-cancer and all-cause survival. Cancer-specific survival is also usually found to be reduced among those with comorbidity. One possible explanation

for this is that it is due to artefact where those with cancer who die of unrelated comorbid conditions are incorrectly categorised as dying from their cancer (Sarfati, Blakely et al. 2010). This is difficult to entirely discount, and is likely to play a role in the excess cancer-specific mortality observed among cancer patients. However, it is unlikely to entirely account for the associations observed. As detailed above, there is consistent evidence that those with comorbidity receive less active treatment than those without, and this impacts their survival probabilities. Those with comorbidity may also suffer higher levels of toxicity to cancer treatments which may also detrimentally impact their cancer-specific survival (Lee, Cheung et al. 2011). A third mechanism, also discussed above, is through a direct impact of comorbidity on cancer progression. For example, Meyerhardt et al investigated the prognosis of patients with and without diabetes within an RCT for adjuvant therapy for stage IIb and III colon cancer in which treatment protocols were strictly standardised (Meyerhardt, Catalano et al. 2003). They found that those with diabetes had 21% increased risk of recurrence even after adjusting for a range of other factors. The authors concluded that this higher risk of recurrence was due to the hyperinsulinaemia of diabetes resulting in more rapid tumour progression. Consistent with this, in their study of 17,712 cancer patients, Piccirillo et al found that the likelihood of developing a recurrence of cancer increased with increasing level of comorbidity (HR 1.18 for mild; 1.37 for moderate and 1.54 for severe relative to none adjusted for extent of disease and treatment) (Piccirillo, Tierney et al. 2004).

## ***Quality of life***

Non-cancer based studies find that comorbidity is associated with poorer quality of life (Fortin, Lapointe et al. 2004; Fortin, Bravo et al. 2006; Mukherjee, Ou et al. 2011; McDaid, Hanly et al. 2013), and the impact varies with type of comorbid condition (Sprangers, de Regt et al. 2000). There are fewer studies that specifically investigate the impact of comorbidity on the quality of life of cancer patients. In a cohort of patients with advanced non-small cell lung cancer, Gronberg et al found that all patients had poor quality of life and that this did not vary much by comorbidity status (Gronberg, Sundstrom et al. 2010). In contrast, studies of patients with early stage prostate cancer have suggested that those with comorbidity have lower quality of life throughout the diagnosis and treatment period, but that all patients report a similar magnitude of reduction of quality of life over that period (Litwin, Greenfield et al. 2007; Daskivich, van de Poll-Franse et al. 2010).

## ***Cost of care***

The cost of care of patients with comorbidity is high in general, both for the patients themselves, and for the health system. (Schoenberg, Kim et al. 2007; Schaink, Kuluski et al. 2012; Tinetti, Fried et al. 2012). Comorbidity is likely to affect the cost of care for cancer patients specifically, although there are few studies that have investigated this specifically. However, Taplan (1995) studied patients with colon, breast and colon cancer and found that comorbidity was associated with higher health system costs for all three sites (Taplin, Barlow et al. 1995).

## **Impact of comorbidity on inequalities in cancer care and outcomes**

While disparities in health care can occur across many axes including gender, socioeconomic position, geography, and sexual orientation, in the New Zealand context, ethnicity-related inequities are the largest and most persistent (Robson and Harris 2007; Robson, Purdie et al. 2010). Māori have a higher prevalence of comorbidity, and are more likely to have multiple, complex comorbidity than non-Māori (Stevens, Stevens et al. 2008; Hill, Sarfati et al. 2010). For example, among patients with colon cancer, only 23% of Māori had no recorded comorbidity compared with 37% of non-Māori (adjusted for age) (Hill, Sarfati et al. 2010). Māori were found to have two-and-a-half times the risk of diabetes, heart failure, respiratory disease and renal disease than non-Māori, and 80% more likely to have three or more comorbid conditions (Hill, Sarfati et al. 2010). There are also well-documented disparities in cancer survival between Māori and non-Māori in New Zealand (Curtis, Wright et al. 2005; Jeffreys, Stevanovic et al. 2005; Robson, Purdie et al. 2006; Stevens, Stevens et al. 2008; Brewer, Pearce et al. 2009; Hill, Sarfati et al. 2010; Priest, Sadler et al. 2010). Late-stage diagnosis contributes to cancer survival disparities between Māori and non-Māori but is unlikely to explain the majority of ethnic survival disparities, and there is clear evidence that factors occurring in the secondary and tertiary care services within New Zealand are likely to be important (Jeffreys, Stevanovic et al. 2005; Robson, Purdie et al. 2006; Hill, Sarfati et al. 2010; Hill, Sarfati et al. 2010).

Comorbidity has been shown to be in part responsible for ethnic disparities in cancer survival, for example, the study by Hill et al showed that a third of the disparity in colon cancer survival between Māori and non-Māori New Zealanders was due to comorbidity (Hill, Sarfati et al. 2010) Similarly, Sheppard et al found that comorbidity was the most important factor in explaining the three-times poorer survival among First Nations women with breast cancer in Canada compared with non-Indigenous women (Sheppard, Chiarelli et al. 2011). Even for a given level of comorbidity, comorbidity may affect some groups of patients differently to others. For example, in Australia, Indigenous cancer patients with diabetes had an overall survival disadvantage compared to Indigenous cancer patients without diabetes with an all-cause Hazard Ratio (HR) = 1.4 (95% CI 1.1-1.8) adjusted for age, sex and cancer site (Martin, Coory et al. 2009). Fewer non-Indigenous cancer patients had diabetes, and those that had diabetes showed no differences in survival compared to their counterparts without diabetes. One explanation for this finding is that the health system tends to work better for ethnic majority compared with ethnic minority patients, so that when there is additional patient complexity due to comorbidity, the system safety nets work better for the former than the latter.

In the US, the evidence relating to the impact of comorbidities on ethnic/racial inequalities in outcomes is somewhat inconsistent. Several authors have found that comorbidity partially or completely explains such disparities (Tammemagi, Nerenz et al. 2005; Allard and Maxwell 2009; Braithwaite, Tammemagi et al. 2009; Holmes, Chan et al. 2009; Putt, Long et al. 2009; Yang, Cheung et al. 2010; Cook, Nelson et al. 2013), while others have concluded that comorbidity may not be important in this regard (Curtis, Quale et al. 2008; Coker, Eggleston et al. 2009; Hines, Shanmugam et al. 2009).

## Summary

Comorbidity is common among cancer patients primarily because cancer patients tend to be older, and cancer shares many risk factors with other medical conditions. The exact prevalence of comorbidity among cancer patients is difficult to determine and varies depending on the measure of comorbidity used, the population studied and the cancer site(s) under investigation. There are contrasting hypotheses relating to the role of comorbidity on the diagnosis of cancer; earlier diagnosis occurs because those with comorbidity experience increased medical surveillance generally, alternatively delayed diagnosis occurs because health professionals and patients are distracted by

their concomitant diseases so symptoms of cancer go unnoticed. These hypotheses are not mutually exclusive and both are likely to exert an influence which will vary depending on specific circumstances. Comorbidity has a clear adverse effect on cancer survival and cost of care. It is also likely to negatively impact the quality of life of cancer patients. Finally, evidence suggests that comorbidity exacerbates inequalities in cancer outcomes for some groups.



# Chapter 4. Measuring comorbidity:

## Review of comorbidity indices

*If you cannot measure it you cannot control it. ~John Grebe*

### List of abbreviations used in this Chapter:

ACE-27	Adult Comorbidity Evaluation-27
ACG	Adjusted Clinical Groups
ASA	American Society of Anesthesiologists
CCI	Charlson Comorbidity Index
CDS	Chronic Disease Score
CIRS	Cumulative Illness Rating Scale
DCG	Diagnostic Cost Group
ICED	Index of Coexistent Disease
KFI	Kaplan-Feinstein Index
MACSS	Multipurpose Australian Comorbidity Scoring System
NCI	National Cancer Institute
SCI	Simplified Comorbidity Index
TIBI	Total Illness Burden Index
WUHNCI	Washington University Head and Neck Comorbidity Index

Chapters 2 and 3 outline the significance of comorbidity for health services, clinicians and patients. Comorbidity is clearly an important potential variable in epidemiological and clinical studies. However, the underlying construct of comorbidity is difficult, if not impossible, to measure. This is partly due to the limitations of data but also to the complexity of this underlying entity.

For this reason and despite the importance of comorbidity, there is little consensus about the best approach to measuring it. The difficulties in measuring comorbidity arise from several factors:

- *The definition and importance of comorbidity depends on the definition of the primary condition.* For example, different concomitant conditions are likely to be important in terms of their impact on outcomes for patients with breast cancer compared to those with congestive heart failure. For this reason, a number of authors have suggested that disease-specific indices are preferable to general ones (van den Akker, Buntinx et al. 2001; de Groot, Beckerman et al. 2003; Grunau, Sheps et al. 2006).
- *Defining what a comorbid condition is can be difficult* (Schneeweiss and Maclure 2000; Bonavita and De Simone 2008; Valderas, Starfield et al. 2009). For example conditions may be defined as specific entities such as angina, peripheral vascular disease or previous myocardial infarction, or may be aggregated to a group of related conditions such as 'cardiovascular disease'. Even when conditions are clearly defined, the importance of them is likely to vary depending on other factors such as the timing and severity of conditions (Preen, Holman et al. 2004).
- *Understanding the combined effects of multiple conditions is also difficult.* Conditions may or may not have a synergistic effect on each other, and if such an effect is present it may be additive or multiplicative. Gross et al found the effects of combinations of comorbidities on survival among cancer patients were complex and difficult to predict (Gross, Guo et al. 2006).
- *The best approach to measuring comorbidity may also be affected by the outcome that is being investigated* (Byles, D'Este et al. 2005; Preen, Holman et al. 2006). For example Preen et al found that focusing on conditions present at current admission or the year previously was most effective for assessing the impact of comorbidity on mortality while reviewing a five-year lookback period for comorbidity was better for assessing readmission rates (Preen, Holman et al. 2006).

This chapter reviews approaches to measuring comorbidity in the context of cancer. It summarises each method, indicates the context in which each has been used, and assesses the validity of each approach. Each is presented chronologically according to the date of the first publication relating to the specified approach, with the exception of using individual conditions as a measure of comorbidity which is briefly addressed first.

# Review of approaches to measuring comorbidity

## *Methods*

A Medline search was carried out for the period 1948 to 2010, using the search terms 'Cancer' or 'neoplasms' and 'comorbidity' or 'multimorbidity' or 'concomitant disease', limited to those written in English. All abstracts were reviewed by the author, and relevant articles were obtained. Articles that described methods to measure comorbidity as a confounding, mediating or explanatory variable in the context of cancer outcomes (survival, treatment receipt, recurrence) were obtained. Original articles and articles that detailed subsequent development or validation of these methods were also obtained.

Data relating to each index or measure were collected in relation to:

1. **A general description of the measure or index.** This included the original purpose of the index or measure, a description of the process through which comorbid conditions were identified, whether severity was accounted for, and whether and how conditions were combined to form an index, whether the index or measure provided ordinal or continuous scores and the usual distribution of scores (if relevant).
2. **Experience with cancer patient populations.** This is a brief description of how each measure or index has been used to assess the role of comorbidity in the context of cancer. The focus here is particularly on how each measure has been used (for example, to assess the role of comorbidity in receipt of treatment and/or survival) and whether each measure has been used for cancer in general, or for one or more sites specifically.
3. **Content and face validity.** Both these measures relate to the degree to which a measure actually evaluates the construct that it purports to measure (Streiner and Norman 2008). Content validity assesses the extent to which a measure includes all relevant items and face validity assesses the extent to which the measure makes sense, given what is known about the construct and the factors used to measure it. These are qualitative assessments which include the degree to which the measure is relevant to cancer, whether all important conditions are included and how these conditions have been selected, whether

other important factors are included such as severity of conditions and whether the measure can be 'individualised' for specific study purposes.

4. **Criterion and Construct validity.** Both of these measures relate to the extent to which an index or measure performs in the expected way (Streiner and Norman 2008).

a. *Criterion validity* is the extent to which a measure correlates with some other measure of the construct under study. Criterion validity can be either concurrent or predictive.

i. **Concurrent validity** refers to the degree to which the measure correlates with another measure taken at the same time. In relation to comorbidity, this will usually be another validated measure of comorbidity. Concurrent validity is most commonly measured using the **Spearman or Pearson correlation coefficient** ( $r$ ) in this context. These give a measure of the degree to which the index of interest changes with a change in a related construct measured at the same time (often a previously validated index of comorbidity). Correlation coefficients range between -1 (perfect negative correlation) and +1 (perfect positive correlation). A correlation coefficient of 0 indicates no correlation between the two measures. Correlation coefficients over 0.40 may be considered to indicate moderate correlation, and those exceeding 0.75 to indicate high correlation (de Groot, Beckerman et al. 2003).

ii. **Predictive validity** is the extent to which the measure is able to predict future outcomes of interest such as cancer survival or receipt of treatment. There are a number of methods used to assess predictive ability including relative risks, hazard ratios and odds ratios, proportion of variance explained (PVE or  $r^2$ ), the area under receiver operating characteristic curve (ROC) and 'c'. **Relative risk, hazard ratios** and **odds ratios** all give a ratio measure of the outcome (in terms of risks or rates, hazards or odds respectively) for those with comorbidity as measured by the specified index or measure compared to those without comorbidity. The **PVE** or  $r^2$  give a measure of how much of the outcome (e.g. cancer-specific or all-cause mortality) is explained by the specified variable (comorbidity measure). **Receiver operating curves** compare the sensitivity of a measure (i.e the

extent to which an index can identify all those with the outcome in question), against '1-specificity' which is the rate of 'false positives' or the proportion of individuals that are predicted to have the outcome by the measure, but who in fact do not have the outcome. The **c-statistic** measures how well a set of predictor variables predicts the outcome of interest. The model considers all possible pairs of patients where at least one has the outcome of interest, and gives the proportion of pairs where the individual with the outcome is correctly predicted as such. It is identical to the area under a ROC for a binary variable. A c-statistic can range from 0.5 to 1.0 with 0.5 indicating random predictions, and 1.0 being perfect predictions. Evidence supporting the predictive validity of an index is provided where models are significantly improved by including the index under study.

- b. *Construct validity* is the extent to which the measure in question performs in the expected manner in relation to hypotheses of associations with other related traits. For example, we expect comorbidity to increase with age, and to be correlated with physical functioning. Therefore any index or measure of comorbidity should be correlated to or associated with each of these.

- 5. **Reliability** is "*the extent to which repeated measurements of a stable phenomenon by different people at different times and places get similar results*" (Hall, Groome et al. 2006). Interrater reliability assesses the extent to which different abstractors obtain the same scores for the same patients. It depends on the simplicity, clarity and ease of use of the scale, as well as the quality of the data and training of the abstractors. Interrater reliability can be reported as percentage of agreement between abstractors, Spearman's correlation coefficient or a kappa (k) statistic. Where there are more than two abstractors/raters an interclass correlation coefficient (ICC) is used (Streiner and Norman 2008). The ICC is the same as the kappa statistic if only two raters are used. Both the k statistic and ICC range between 0 and 1. Reliability coefficients are considered to be fair to moderate when they exceed 0.40 and moderate to good when they exceed 0.75 (de Groot, Beckerman et al. 2003).
- 6. **Feasibility** includes the simplicity, cost, time and effort required to use the measure.

## ***Results of review***

2975 abstracts were identified that related to comorbidity and cancer, in which 21 separate approaches to measuring comorbidity were identified.

Table 5 summarises the key characteristics of these approaches, specifically the first relevant paper in which each measure or index appears, the population characteristics in which each was developed, the sources of data used, and the method for item generation for each approach.

Table 6 summarises the scoring approaches for each measure of comorbidity including the number of items, the severity scale, the score range (if relevant), the variable type and the distribution of each index or measure.

Following these tables is a summary of each approach.

**Table 5: Summary of sources of data for development of measures of comorbidity**

Index name.....	Author (year)	Purpose	Population developed	Initial data sources used	Alternative data sources	Item generation
CIRS	Linn 1968	Measure of physical impairment.	?	Clinical notes data	No	Judgement
KFI	Kaplan and Feinstein 1974	Measure of comorbidity among diabetic patients.	188 men with diabetes.	Clinical notes data	No	Judgement
Charlson	Charlson 1987	To develop a 'prognostic taxonomy' for comorbid conditions.	608 general medical patients	Clinical notes data	Administrative data, Patient questionnaire	Empirical
DCGs	Ash 1989	To predict resource use in HMOs.	Medicare patients	Administrative data	N/A	Empirical
ACGs	Weiner 1991	To predict resource use in HMOs.	16,000 HMO enrollees	Administrative data	No	Empirical
CDS/Rx-Risk	Von Korff 1992 Clark 1995	To predict resource use in HMOs.	122,911 enrollees in a Health Maintenance Organization.	Pharmaceutical data	No	Judgement and Empirical
ICED	Greenfield 1993	To measure impact of comorbidity and physical functioning.	356 patients undergoing total hip replacement	Clinical notes data	No	Judgement
Satariano	Satariano 1994	To assess comorbidity in breast cancer patients.	936 breast cancer patients.	Clinical notes data	Administrative data	Judgement and Empirical
TIBI/ TIBI-CaP	Greenfield 1995 Litwin 2007	To measure total burden of disease.	1,738 general patients and 2894 prostate cancer patients	Patient symptom report	No	Judgement and Empirical
NIA/NCI Collaborative study	Yancik 1996	To investigate comorbidity burden among older cancer patients.	7600 cancer patients	Clinical notes data	No	Empirical
Elixhauser	Elixhauser 1998	To measure comorbidity using administrative data.	1,779,167 adult acute care hospital patients	Administrative data	No	Judgement and Empirical

<b>Index name</b>	<b>Author (year)</b>	<b>Purpose</b>	<b>Population developed</b>	<b>Initial data sources used</b>	<b>Alternative data sources</b>	<b>Item generation</b>
Comprehensive Prognostic Index	Fleming 1999	To develop site specific measures of comorbidity for breast and prostate cancers.	848 breast cancer patients	Administrative data	No	Judgement and Empirical
NCI comorbidity Index	Klabunde 2000 and 2007	To measure comorbidity among cancer patients using administrative data.	14,429 prostate and 7472 breast cancer patients	Administrative data.	No	Judgement and Empirical
ASA	Reid 2001	To assess acute operative risk.	Surgical patients	Clinical notes data	May be obtained from administrative data	N/A
Alcohol-tobacco related comorbidities index	Reid 2002	To assess comorbidity among patients with head and neck cancers.	9386 head and neck cancer patients	Administrative data	No	Known associations with smoking/ alcohol.
Washington University head and neck comorbidity index	Piccirillo 2002	To assess comorbidity among patients with head and neck cancers.	1094 head and neck cancer patients	Clinical notes data	Administrative data	Empirical
ACE-27	Picirillo 2003	To assess comorbidity among cancer patients.	11,906 cancer patients	Clinical notes data	Administrative data	Judgement
Tammemagi	Tammemagi 2003 and 2005	To assess comorbidity among breast and lung cancer patients.	1155 lung and 906 breast cancer patients.	Administrative data.	No	Empirical
MACSS	Holman 2005	To develop a generalised measure of comorbidity.	1,069,770 hospital patients	Administrative data	No	Empirical
SCI	Colinet 2005	To assess comorbidity among patients with lung cancer.	735 patients with lung cancer.	Clinical notes data	No	Judgement
Elixhauser	van Walraven 2009	To combine Elixhauser conditions into index.	228,565 adult acute care hospital patients	Administrative data	No	Judgement and Empirical

**Table 6: Scoring approaches for measures of comorbidity.**

Index name	System or condition based	Items	Severity	Scoring method	Score range	Distribution
CIRS	System	13 or 14 systems	0-4, based on clinical judgment	Summative	0 – 56	Normal (skewed to right)
KFI	System	12 systems	1—3, based on severity of most severe condition	Highest score of single item	1 - 3	Uniform
Charlson	Condition	17 conditions (in 19 categories)	1-6; based on impact on 1-yr mortality (RR)	Sum of weighted conditions	0 - 33	Skewed to right
DCGs	Condition	118 condition categories	Incorporated into condition categories on the basis of resource consumption.	Variable	N/A	N/A
ACGs	Condition	93 mutually exclusive ACGs.	Incorporated into ACGs based on impact on resource use.	Variable	N/A	N/A
CDS/Rx-Risk	Condition	Variable	Based on association with resource use.	Sum of weights	0 - 50+	Skewed to right
ICED	System	14 systems 10 functional	0-4 for comorbidity and 0-2 for function	Combined highest scores of two dimensions	0 - 3	Uniform
Satariano	Condition	7 conditions	Unweighted.	Condition count	0-7	Not specified
TIBI/ TIBI-CaP	System	15/ 11 sub-dimensions	Weighted by clinicians and empirically	Sum of weighted sub-dimension scores	-21 - 77 and 0 - 23	Skewed to right
NIA/NCI Collaborative study	Condition	24 major categories of conditions	Unweighted.	N/A	N/A	N/A
Elixhauser	Condition	30 conditions	Conditions included individually	N/A	N/A	N/A

<b>Index name</b>	<b>System or condition based</b>	<b>Items</b>	<b>Severity</b>	<b>Scoring method</b>	<b>Score range</b>	<b>Distribution</b>
Comprehensive Prognostic Index	Condition	11 categories with 34 subcategories	Based on impact on 1-yr mortality (RR)	Multiplicative	0 -14.8	Skewed to right
NCI comorbidity Index	Condition	12 conditions (in 14 categories)	Based on impact on 2-yr non-cancer mortality ( $\beta$ )	Summing $\beta$ coefficients	Various	Skewed to right
ASA	Overall health status	N/A	N/A	Overall assessment of health status	1 - 6	Skewed to right
Alcohol-tobacco related comorbidities index	Condition	11 conditions	Unweighted	Simple count	0 -11	Skewed to right
Washington University head and neck comorbidity index	Condition	7 conditions	Based on impact on 5-yr mortality ( $\beta$ )	Summing $\beta$ coefficients	0 -15	Skewed to right
ACE-27	Condition	27 conditions	1-3, based on severity of most severe condition	Highest score of single item	1 - 3	Uniform
Tammemagi	Condition	19 and 77 for lung and breast respectively.	Unweighted.	Condition count	0 -19 and 0 - 77	Skewed to right
MACSS	Condition	102 conditions	Conditions included individually	N/A	N/A	N/A
SCI	Condition	7 comorbidity categories	Based on impact on mortality ( $\beta$ )	Summing $\beta$ coefficients	0 - 20	Not specified
Elixhauser	Condition	21 conditions	Based on impact on in-hospital mortality ( $\beta$ )	Summing $\beta$ coefficients	-19 - 89	Skewed to right

# ***Individual conditions or counts of conditions***

## **General description**

The simplest approach to measuring comorbidity is to measure the prevalence of individual conditions, and to either include them separately in models or to simply combine them by summing the total number of conditions. The total count of conditions depends on how conditions are defined, and which are included in the count.

The effect of individual specific comorbid conditions has also been assessed in cancer patient populations. The most commonly assessed single condition in this context is diabetes mellitus which is generally found to have a negative impact on outcomes from cancer (Meyerhardt, Catalano et al. 2003; Gross, Guo et al. 2006; Polednak 2006; Martin, Coory et al. 2009; Sarfati, Tan et al. 2011).

Where authors have identified conditions using an **explicit** process in the context of cancer and these are then treated independently or combined as an 'unweighted' index (or simple count), these are assessed separately in this review (e.g. Tammemagi and Santorini approaches).

## **Experience with cancer patient populations**

Individual comorbid conditions and counts have been used in a number of cancer – related studies, including those relating to cancer in general and to specific sites such as breast, prostate, colorectum, lung, and head and neck cancers (Melfi, Holleman et al. 1995; Newschaffer, Penberthy et al. 1996; Mandelblatt, Bierman et al. 2001; Valery, Coory et al. 2006; Klabunde, Legler et al. 2007; Zeber, Copeland et al. 2008; Sarfati, Hill et al. 2009; Sarfati, Tan et al. 2011).

## **Content and face validity**

The validity of this approach varies with different studies. Where conditions are added together in a simple unweighted index, the implicit assumption is made that all conditions are equally important in their relationship to outcomes.

## **Criterion validity**

**Concurrent.** Comorbidity counts tend to be correlated with other measures of comorbidity where such comparisons are made (Mandelblatt, Bierman et al. 2001).

**Predictive.** Results are variable depending on how individual conditions are treated. Generally higher comorbidity counts are related to lower receipt of treatment and/or poorer outcomes (Newschaffer, Penberthy et al. 1996; Mandelblatt, Bierman et al. 2001; Gross, Guo et al. 2006; Gross, McAvay et al. 2007; Klabunde, Legler et al. 2007; Zeber, Copeland et al. 2008; Sarfati, Hill et al. 2009).

### **Reliability**

Depends on specific approach that has been used.

### **Feasibility**

This approach is simple and easy to use.

## **Early approaches to measuring comorbidity (pre 1980s)**

### ***Cumulative Illness Rating Scale (CIRS)***

#### **General description**

The cumulative illness rating scale (CIRS) is a measure of physical impairment based on assessment of organ dysfunction. (Linn, Linn et al. 1968) Each of 13 independent organ areas (cardiac; vascular; respiratory; ear, nose and throat; upper GI; lower GI; liver; renal; other genitourinary; musculoskeletal; neurological; endocrine/ metabolic and psychiatric ) are rated according to severity of organ dysfunction on a Likert scale (0-none; 1- mild, 2- moderate, 3-severe, 4-extremely severe). A single illness may impact on more than one organ system and can therefore be counted more than once. For example, a stroke may impair neurological, vascular and musculoskeletal systems. Scores can be kept separate for each organ system or summed to give a total score. Information for calculation of a CIRS score is collected by clinical review with the developers of the index commenting that assessment for the CIRS should be '*based on an adequate and complete medical examination and health history*'. CIRS was developed as a measure of 'physical impairment' for research purposes, not comorbidity per se, but it has been subsequently used for that purpose in a number of studies.(Parmelee, Thuras et al. 1995; Hall, Rochon et al. 2002; Fortin, Bravo et al.

2005; Boulos, Groome et al. 2006; Fortin, Bravo et al. 2006; Castro, Dedititis et al. 2007; Nagaratnam and Gayagay 2007). No information was given on how the organ based scales were developed in the original article, but presumably this was done on the basis of clinical experience.

CIRS was modified by Miller et al to form CIRS-G which was specifically created to be used in geriatric populations (Miller, Paradis et al. 1992). The changes were relatively minor, with some additional sub-categories within organ systems, and obesity and smoking status added. Subsequent minor modifications have been made for geriatric psychiatric populations and for use with acute conditions (Parmelee, Thuras et al. 1995; Mistry, Gokhman et al. 2004).

## **Experience with cancer patient populations**

CIRS has been used to identify the negative impact of comorbidity on cancer survival in general (Wedding, Roehrig et al. 2007; Wedding, Rohrig et al. 2007), and for a number of specific cancers including laryngeal cancer (Hall, Rochon et al. 2002; Castro, Dedititis et al. 2007), prostate cancer (Boulos, Groome et al. 2006), and colorectal cancer (Munro and Bentley 2004).

## **Content and face validity**

CIRS is an organ-based system, so collectively the index is likely to include at least some information on all important comorbid conditions. However, it was not developed specifically for cancer, and so does not differentiate conditions that are more or less likely to impact on cancer outcomes. It includes a measure of severity within each organ system, and can be used either as an organ-specific measure of poor health, or an overall measure. Other scoring systems can also be used, for example the 'Illness Severity Scale' is based on an average of all the CIRS items, while the 'Co-morbidity Index', is a count of the number of items with moderate or severe impairment (Nagaratnam and Gayagay 2007). The overall total impairment score assumes that each organ system has an equal impact on the individual, so while there is a measure of severity within each organ system, there is no attempt to measure the potentially differential impact of dysfunction in the different systems. The scoring system also assumes that the effect of dysfunction in multiple organ systems is additive. Much of the research using CIRS has focused on the geriatric population.

## **Criterion validity**

### **Concurrent**

CIRS scores based on medical notes review were found to be closely correlated with those based on autopsy which is considered gold standard, and supports (concurrent) criterion validity (Conwell, Forbes et al. 1993). CIRS has also been found to be moderately correlated with other measures of comorbidity including the CCI, KFI and ICED (Hall, Rochon et al. 2002; Munro and Bentley 2004).

### **Predictive**

CIRS has been found to be associated with higher risk of mortality, readmission, and poorer cancer and non-cancer survival in a number of studies. (Linn, Linn et al. 1968; Hall, Rochon et al. 2002; Munro and Bentley 2004; Boulos, Groome et al. 2006; Castro, Dedivitis et al. 2007; Wedding, Rohrig et al. 2007; Salvi, Miller et al. 2008). In one small study that compared the performance of comorbidity indices in predicting all-cause mortality among 90 patients with laryngeal cancer, only CIRS was found to be an independent risk factor (Castro, Dedivitis et al. 2007).

## **Construct validity**

CIRS has been found to be associated with other relevant constructs such as age, health related quality of life, ADL and IADL scores, WHO performance status, global ratings of medical burden from clinicians, number of medications taken, abnormal laboratory findings, and length of stay in hospital (Miller, Paradis et al. 1992; Parmelee, Thuras et al. 1995; Munro and Bentley 2004; Fortin, Bravo et al. 2005; Fortin, Bravo et al. 2006; Wedding, Roehrig et al. 2007; Britt, Harrison et al. 2008; Salvi, Miller et al. 2008).

## **Reliability**

In the original article, the authors found a high level of consistency between raters (Kendall's  $W=0.83-0.91$ ). Subsequent work has confirmed moderate to high levels of inter and intra-rater reliability (generally with ICC in the range of 0.61-0.85) (Miller, Paradis et al. 1992; Extermann 2000; Hudon, Fortin et al. 2005; Boulos, Groome et al. 2006; Hall, Groome et al. 2006; Salvi, Miller et al. 2008).

## **Feasibility**

Rating patients using the CIRS index requires access to clinical notes and training for abstractors. Generally using CIRS is considered less easy than using CCI (Extermann

2000), although in one study of five comorbidity indices CIRS was rated as second best for ease of use (and better than CCI) (Boulos, Groome et al. 2006). Manuals are available to aid abstraction (Salvi, Miller et al. 2008).

## ***Kaplan-Feinstein Index (KFI)***

### **General description**

Kaplan and Feinstein (Kaplan and Feinstein 1974) were particularly interested in the role of comorbidity among adult diabetic patients. Their aim was to “*develop a scheme of taxonomy for classifying co-morbid ailments, and to assess the prognostic value of the classifications*” in part to allow them to more accurately assess complications of diabetes that were not pre-existing at the time of diagnosis. Their index was developed using data from 188 men diagnosed with diabetes mellitus between 1959 and 1962 from a single veterans’ hospital in the United States. Both baseline and follow up data were collected from medical records. Data on comorbidities were collected at baseline, and changes in pre-existing conditions as well as development of new ones were collected for five years or until death.

They classified comorbid conditions as being either ‘vascular’ or ‘non-vascular’, the former considered potentially related to diabetes. As a measure of severity, they classified each condition as being ‘cogent’ if it might be expected to adversely affect the individual’s life expectancy, or ‘non-cogent’ if the condition could be controlled, had no direct effects on vital organs or was related to a single episode in the past. Cogent conditions were further classified according to their severity with grade 1 being slight decompensation of vital systems, and grade 3 being recent full decompensation of vital systems, or chronic conditions that threatened life.

The analysis was carried out in a categorical manner, so that individuals were variously categorised as having cogent or non-cogent comorbidity; vascular or non-vascular cogent conditions, and according to the highest grade of any single condition.

### **Experience with cancer patient populations**

The KFI has been used in a number of studies, both by itself and as a comparison to other indices including in relation to breast (Newschaffer, Bush et al. 1997), head and neck (Hall, Rochon et al. 2002) and prostate cancer (Boulos, Groome et al. 2006).

## **Content and face validity**

This index was constructed to investigate the complications of diabetes, so cancer was not the focus. It does include a measure of severity, but is highly simplified with only three ordinal categories. It provides explicit criteria for both conditions and severity, but it is not clear whether all relevant conditions for cancer are included in the index for example, diabetes and dementia were not included. The scoring system assumes that a severe rating in any system is equivalent, and that two moderate ratings in different systems have a combined effect equivalent to a single severe rating.

## **Criterion validity**

### **Concurrent**

A number of studies have compared the use of KFI with other indices used concurrently, however none specifically measure the correlation with KFI (Charlson, Pompei et al. 1987; Newschaffer, Bush et al. 1997; Hall, Rochon et al. 2002; Boulos, Groome et al. 2006; Castro, Dedivitis et al. 2007).

### **Predictive**

The authors found that cogent comorbidity was associated with higher 5-year mortality than non-cogent, and vascular cogent comorbidity associated with higher mortality than non-vascular. They also found a clear gradient of higher mortality among those with comorbid conditions of higher severity grade (7%, 28%, 42% and 69% 5-year fatality rate for grade 0-4 severity respectively;  $p$  for trend  $< 0.005$ ). In respect of cancer, Newschaffer et al (Newschaffer, Bush et al. 1997) found that unlike the Charlson and Satiriano indices, KFI scores were poor predictors of survival for breast cancer patients and did not improve the ability of models to predict survival over baseline models that did not include measures of comorbidity. Similarly Castro et al found that KFI was not an independent predictor of all-cause mortality among 90 laryngeal patients (Castro, Dedivitis et al. 2007). In contrast, Hall et al (Hall, Rochon et al. 2002) compared KFI with Charlson, ICED and CIRS and found the KFI performed best in terms of predicting survival. Boulos et al (Boulos, Groome et al. 2006) found that KFI predicted non-prostate cancer related mortality among a group of men with prostate cancer, and accounted for a statistically significant proportion of the variance in non-prostate cancer death.

## **Construct validity**

There is minimal evidence relating to the construct validity of the KFI. Waite et al did not find KFI to be related to readmission rates among 79 patients discharged from VA hospitals in the US. They also found no association between other measures of comorbidity (CCI and ICED) and readmission rates. (Waite, Oddone et al. 1994).

## **Reliability**

Newschaffer et al (Waite, Oddone et al. 1994; Newschaffer, Bush et al. 1997) found high levels of interrater reliability ( $k=0.82$ ,  $p<0.001$ ; and ICC 0.83 respectively). Hall et al (Hall, Groome et al. 2006) found a somewhat lower (but still acceptable) ICC of 0.59 (0.0.44-0.72).

## **Feasibility**

Waite reported that it took abstractors a mean of 8.9 min per set of notes to abstract data to calculate a KFI score. This compared with the Charlson Index (5.9 mins) and the Index of Coexistent Disease (ICED; 9.5 mins)(Waite, Oddone et al. 1994).

# **Developments during 1980s**

## ***Charlson Comorbidity Index (CCI)***

### **General description**

The Charlson Index is easily the most cited comorbidity index in the literature. It was developed in 1987 by Charlson and colleagues (Charlson, Pompei et al. 1987). Their aim was to '*develop a prognostic taxonomy for comorbid conditions which singly or in combination might alter the risk of short term mortality for patients enrolled in longitudinal studies*'. They were explicit about building on the work of Kaplan and Feinstein by identifying a list of comorbid conditions empirically rather than through consensus criteria. The comorbidity index was developed from a cohort of 604 general medical patients admitted during a one month period at a single New York hospital in 1984. At the time of admission, the number and severity of all comorbid conditions were recorded by the admitting doctor, and an overall assessment of severity of illness was made (not ill, mildly ill, moderately ill, severely ill or moribund). Patients (93%) were followed up for one year, and the association of each comorbid condition with one

year mortality was calculated. Charlson et al wanted to assess the combined effect of comorbid conditions. They first used a simple count of conditions, but were concerned about the assumption that all conditions had equivalent impact on mortality. To account for this, they developed a weighted index with the weights being equivalent to the (rounded) adjusted relative risks for mortality for each condition, with a maximum weight of 6. Conditions with relative risks less than 1.2 were excluded from the index. The authors found this weighted index was superior in predicting one year survival to a simple count of conditions.

Algorithms have been developed by several authors to allow administrative data to be used to calculate individual Charlson scores (Deyo, Cherkin et al. 1992; Romano, Roos et al. 1993; D'Hoore, Bouckaert et al. 1996; Quan, Sundararajan et al. 2005). Studies that have attempted to validate the Charlson index using administrative data have found that it performs reasonably well (Malenka, McLerran et al. 1994; Kieszak, Flanders et al. 1999; Klabunde, Legler et al. 2007; Sarfati, Hill et al. 2010; Quan, Li et al. 2011). More recently questionnaires have been developed to allow the calculation of Charlson scores using patients' self-report (Susser, McCusker et al. 2008). Other studies have used the Charlson approach, but re-weighted the index specifically for the outcome under study (e.g. (Cleves, Sanchez et al. 1997; van Doorn, Bogardus et al. 2001; Martins and Blais 2006). The Charlson Index has been used as the basis for other comorbidity indices, most notably the NCI Comorbidity index which uses the same conditions, but includes data from both inpatient and outpatient administrative records, and uses the beta coefficients (rather than the relative risk) of the association of each condition with one-year mortality to assign weights (the NCI index is described in more detail later).

## **Experience with cancer patient populations**

The Charlson is the most widely used comorbidity index in cancer-related studies and has been used in just about every setting, with every cancer including breast (Charlson, Pompei et al. 1987; Newschaffer, Bush et al. 1998; Ahern, Lash et al. 2009), lung (Blanco, Toste et al. 2008; Stevens, Stevens et al. 2008), colorectal (Rieker, Hammer et al. 2002; Munro and Bentley 2004; Lemmens, Janssen-Heijnen et al. 2005; Cronin, Harlan et al. 2006; Iversen, Norgaard et al. 2009; Sarfati, Hill et al. 2009), urological cancers (Miller, Taub et al. 2003; Singh and O'Brien 2004; Nuttall, van der Meulen et al. 2006), cervical (Brewer, Borman et al. 2011), head and neck (Hall, Rochon et al. 2002; Paleri and Wight 2002; Reid, Alberg et al. 2002) and haematological cancers (Sorrer, Maris et al. 2005).

## Content and face validity

The Charlson Index was not specifically developed for use among cancer patients, but was validated by the authors using a cohort of patients with breast cancer. While it is the most commonly used index, it is not without its problems. It includes some conditions that have not been shown to have an impact on survival among patients with cancer (e.g. peptic ulcer disease), it may exclude some that do have such an impact (e.g. non-cerebrovascular neurological conditions), it assumes that the impact of multiple conditions is additive on a relative risk scale, and it assumes that the prognostic importance of a given comorbid condition is the same regardless of the primary condition (Charlson 1993; Deyo 1993; Romano, Roos et al. 1993; Romano, Roos et al. 1993).

## Criterion validity

**Concurrent.** Charlson scores have been shown to be correlated with physician ratings of poor health and a range of other measures of comorbidity including KFI, CIRS, ICED, Satariano, ACE-27, NCI combined index, Washington University Head and Neck Comorbidity Index and ASA score, (Charlson, Pompei et al. 1987; Silliman and Lash 1999; Reid, Alberg et al. 2001; Hall, Rochon et al. 2002; Paleri and Wight 2002; Munro and Bentley 2004; Piccirillo, Tierney et al. 2004).

**Predictive.** Charlson et al validated their new index using a cohort of 685 women with breast cancer treated at a single hospital between 1962 and 1969. Age and comorbidity as measured by the Charlson Comorbidity Score were the only two independent predictors of comorbid death, with a relative risk of each increasing level of comorbidity index of 2.3 (1.9-2.8) . Subsequently the Charlson index has been found to predict cancer-specific and all-cause mortality in a large number of cancer-related settings (Newschaffer, Bush et al. 1997; Hall, Rochon et al. 2002; Reid, Alberg et al. 2002; Munro and Bentley 2004; Singh and O'Brien 2004; Boulos, Groome et al. 2006; Cronin, Harlan et al. 2006; Stevens, Stevens et al. 2008; Hines, Chatla et al. 2009; Iversen, Norgaard et al. 2009; Sarfati, Hill et al. 2009; Brewer, Borman et al. 2011). The predictive validity of the Charlson index appears to be somewhat less clear and consistent with shorter follow-up times, for example in studies that investigate in-hospital death, rather than 1-year mortality (Pompei, Charlson et al. 1991; Melfi, Holleman et al. 1995; Cleves, Sanchez et al. 1997; Soares, Salluh et al. 2005).

## **Construct Validity**

Charlson index has been found to be related to increasing age, length of stay, functional status and life expectancy, all of which support construct validity (D'Hoore, Bouckaert et al. 1996; Coebergh, Janssen-Heijnen et al. 1998; Extermann, Overcash et al. 1998; Mandelblatt, Bierman et al. 2001; Sarfati, Tan et al. 2011).

## **Reliability**

Generally the reliability of the Charlson Index (using medical notes) has been found to be good with ICCs or k statistics ranging from 0.67 – 0.93 (Waite, Oddone et al. 1994; Newschaffer, Bush et al. 1997; Kiefe, Funkhouser et al. 1998; Extermann 2000; Hall, Groome et al. 2006).

## **Feasibility**

The Charlson index is relatively easy to use in the context of medical notes (Extermann 2000). Waite et al found that collecting data for the Charlson index was considerably quicker than for either the KFI or ICED (5.9, 8.9, and 9.5 mins respectively) (Waite, Oddone et al. 1994). In contrast Boulos et al reported that data abstractors rated the Charlson Index least easy to use compared with ICED, KFI and CIRS in their study of 269 patients with prostate cancer (Boulos, Groome et al. 2006). When administrative data are used, algorithms are available to apply to the data, making data collection straightforward.

## ***Diagnostic Cost Group/ Hierarchical Condition Categories (DCG/HCC)***

### **General description**

The DCG system was developed by researchers at Harvard University as a risk adjustment system based on resource use (Ash, Porell et al. 1989). The system has been refined over time (Ellis, Pope et al. 1996). On the basis of inpatient and outpatient data, patients are classified into 'DxGroups' that are similar in terms of resource use, and are clinically-related. These are then condensed into 118 condition categories (CCs), which are further collapsed into 30 aggregated condition categories. An individual may be included in several CCs, so related CCs are organised into hierarchies, and only the highest ranked CC is selected to avoid double counting. The DCG system has largely been used in studies that predict resource use, or compare

the performance of health care providers with different case mixes (Duckett 2000; Rosen, Loveland et al. 2001).

## **Experience with cancer patient populations**

The only study identified that explicitly used DCGs as a measure of comorbidity among cancer patients was a study by Baldwin et al of colon cancer patients in which they compared its performance with other measures of comorbidity (Baldwin, Klabunde et al. 2006).

## **Content and face validity**

The process for allocating patients into DCGs is entirely based on resource consumption, and is not specifically designed to measure comorbidity in the context of cancer.

## **Criterion validity**

**Concurrent.** Not reported (in the context of cancer patient populations).

**Predictive.** Baldwin et al used four measures of comorbidity (NCI Comorbidity Index, Elixhauser approach; DCG system and ACG system) to assess the impact of comorbidity on colon cancer receipt of treatment and survival (Baldwin, Klabunde et al. 2006). They found all four measures were associated with lower receipt of definitive treatment and poorer non-cancer survival, and none clearly out-performed the others.

## **Construct Validity**

Not reported in the context of cancer patient populations.

## **Reliability**

Reliability is not relevant because data are extracted in a standardised way from electronically stored records.

## **Feasibility**

Specialised software is available to group patients into DCGs.

# Progress during the 1990s

## *Adjusted Clinical Groups (ACG) System*

### **General description**

The ACG system was described in Chapter 2. Briefly this is a system that was developed at John Hopkins University to categorise individuals into groups with similar health resource use expectations. It was developed using data from four Health Maintenance Organisations in the United States, relating to 160,000 individuals (Weiner, Starfield et al. 1991). The current system works by grouping ICD-9 diagnoses identified from administrative data sources on the basis of disease or condition characteristics such as expected duration, severity and speciality care involvement of each condition into ADGs (Ambulatory Diagnostic Groups) (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991). Patients can be included in multiple ADGs, which are then further divided into Adjusted Clinical Groups (ACGs,) based on factors such as age, sex, presence of specific ADGs, and number of ADGs. Some are further subdivided resulting in 102 final categories each including individuals that would be expected to experience a similar pattern of resource use (Weiner, Starfield et al. 1991).

This system has been used in a number of settings primarily for health care management purposes including setting capitation rates and profiling the efficiency of health care organisations and clinicians (Starfield, Weiner et al. 1991; Weiner, Starfield et al. 1991; Fowles, Weiner et al. 1996; Greene, Barlow et al. 1996; Tucker, Weiner et al. 1996; Orueta, Lopez-De-Munain et al. 1999; Reid, MacWilliam et al. 2001; Duckett and Agius 2002; Perkins, Kroenke et al. 2004; Chang and Weiner 2010).

### **Experience with cancer patient populations**

ACGs have not been used extensively as a measure of comorbidity among cancer patients in epidemiological or clinical studies, although they have been used in studies to investigate variations in care and outcomes for cancer patients treated in different hospitals (McArdle and Hole 2002; Caldon, Walters et al. 2005; Talsma, Reedijk et al. 2011). Baldwin et al (Baldwin, Klabunde et al. 2006) included ACGs as one of their measures of comorbidity in a study of colon cancer patients.

## **Content and face validity**

The original grouping of ADG categories was based on clinical criteria related to resource use (Weiner, Starfield et al. 1991). These clusters were then empirically tested e.g. using correlation coefficients and factor analysis to ensure statistically distinct entities. The splitting into the smaller ACGs was also done using empirical methods which aimed to identify groups of enrolees with the lowest possible within-group variation in resource consumption. The processes in these groupings are not, therefore specifically related either to comorbidity or to cancer, but to resource consumption.

## **Criterion validity**

**Concurrent.** Not reported (in the context of cancer patient populations).

**Predictive.** The ACG system performed in a similar way as the other four indices included in Baldwin et al's study of treatment receipt and outcomes among patients with colon cancer (Baldwin, Klabunde et al. 2006).

## **Construct Validity**

Not reported in the context of cancer patient populations.

## **Reliability**

Reliability is not relevant because data are extracted in a standardised way from electronically stored records.

## **Feasibility**

Specialised software is available to group patients into ACGs.

# ***Chronic Disease Score (CDS) and RxRisk***

## **General description**

This approach uses population-based pharmaceutical data to measure the chronic disease status of a population (Von Korff, Wagner et al. 1992). The CDS was developed using data was from a database held by a large Health Maintenance Organisation in the United States. A multidisciplinary group of clinicians and researchers identified chronic conditions and medications that would be likely to

contribute to chronic disease burden. A score was assigned on each pattern of medication use based on the impact of the condition for which the medication was (likely to be) prescribed; and for cardiac and respiratory disease, a higher score was assigned if more than one class of drug was used for its management. A CDS for each individual was calculated by summing the scores assigned for each class of medications using data over a one-year period.

A later paper by Clark et al (Clark, Von Korff et al. 1995) refined the CDS for use with empirically derived weights, and with a wider range of medications than the original index. The weights were derived for medications by assessing the associations between each medication class and specific cost and health service utilisation outcomes (total cost of care, outpatient costs and primary care visits) using data from a random half of an enrolled population of a Health Maintenance Organisation. Weights were age group and sex specific within each medication class.

Fishman and colleagues (Fishman, Goodman et al. 2003) further modified the CDS, and re-named it the RxRisk Model. Their purpose was to use this model as a case-mix model to predict health care costs, and so they compared its performance to those of the Ambulatory Clinical Groups (ACG) and Hierarchical Coexisting Conditions (HCC) diagnosis-based case-mix instruments. Fishman et al expanded the index to include paediatric related medications, they reviewed the categories of conditions for which specific drugs were dispensed, and removed medications for which there was a large degree of inconsistency in prescribing practices particularly drugs related to treatment for pain and inflammation. Development of the RxRisk index is on-going and is largely focused on its ability to predict health care costs in the managed care environment of the US (Sloan, Sales et al. 2003; Johnson, El-Serag et al. 2006), although has also recently been used in Australia (Lu, Barratt et al. 2011).

## **Experience with cancer patient populations**

The CDS and RxRisk scores have not been used extensively among cancer populations. CDS scores were used (with other measures of comorbidity) in studies relating to patients with head and neck, and prostate cancer (Hall, Rochon et al. 2002; Boulos, Groome et al. 2006). The CDS has also been used to adjust for comorbidity in a study of cancer outcomes among patients with diabetes (Bowker, Majumdar et al. 2006; Bowker, Yasui et al. 2010), and in a cost of illness study relating to cervical cancer (Helms and Melnikow 1999).

## **Content and face validity**

The original CDS was developed largely on the basis of clinical expertise, but the later refinements meant that scores were developed on an empiric basis. Only conditions for which regular medications are prescribed will be identified by the CDS, and the CDS will be subject to provider variation in prescribing habits and utilisation bias in that only prescriptions that are filled will be identified. Medication-based indices may address some of the concerns about using administrative databases such as inaccurate recording of diagnoses, and may be more likely to identify conditions managed in the outpatient system. They are based on the assumption that medications are being used for the purpose for which they are usually prescribed. The current scoring system assumes that the effect of multiple medications is additive.

## **Criterion validity**

### **Concurrent**

Concurrent validity was assessed at the time of the original CDS development by comparing CDS scores with physician-rated disease severity scores, and self-rated health status for individual patients (Von Korff, Wagner et al. 1992). The Pearson correlation of CDS with physicians' ratings of severity of physical disease (well, mild, moderate, severe) was moderate ( $r=0.46-0.57$ ). CDS was not well correlated with self-rated health status ( $r=0.23$ ). The correlation between specific diagnoses made on the basis of the RxRisk score and from ICD-9 diagnostic classifications was also variable depending on the condition (Sloan, Sales et al. 2003). More recently, the Rx-Risk index was found to correlate poorly with the Charlson comorbidity index (Lu, Barratt et al. 2011).

### **Predictive validity**

Among cancer patient populations, results are mixed. In their study of 655 head and neck cancer patients, Hall et al found that while CIRS, KFI and ICED scores were all strongly related to survival, CDS scores were not (Hall, Rochon et al. 2002). CDS was removed from subsequent analysis for this reason. In contrast, Boulos et al found that CDS was better than CIRS, ICED, KFI, or CCI in distinguishing groups with different survival probabilities (Boulos, Groome et al. 2006). CDS also had the biggest partial PVE estimate in predicting non-cancer mortality (11.3% compared with 3.8%-9% for other indices)(Boulos, Groome et al. 2006).

## **Construct Validity**

Construct validity is supported by the associations of CDS with measures of psychological impairment, chronic pain status, functional disability and age. CDS scores were moderately associated with age ( $r=0.37$ ) and number of ambulatory visits ( $r=0.42$ ) (Von Korff, Wagner et al. 1992; Johnson, Hornbrook et al. 1994).

## **Reliability**

Reliability is generally not relevant because data are extracted in a standardised way from electronically stored records. Boulos et al found that there was 87% agreement between medications identified through chart review and those identified through CDS (Boulos, Groome et al. 2006).

## **Feasibility**

The CDS is based on electronically stored data, and therefore is considerably less time consuming than the indices requiring manual review of data.

# ***Index of Coexistent Disease (ICED)***

## **General description**

The Index of Coexistent Disease combines two dimensions; a measure of comorbid disease severity and a measure of functional impairment (Greenfield, Apolone et al. 1993). The index is a modified version of an earlier (unnamed) comorbidity index that had been used to assess the role of comorbidity in the receipt of treatment among older patients with breast or prostate cancers (Greenfield, Blanco et al. 1987; Bennett, Greenfield et al. 1991). The earlier index included three dimensions: 1) a measure of severity of comorbid conditions, 2) a measure of acute exacerbations of these conditions and 3) a measure of functional impairment. However, the index was later modified to exclude the acute aspect of comorbid conditions (Greenfield, Apolone et al. 1993). The severity of comorbidity is assessed for each of 14 organ systems (organic heart disease; ischemic heart disease; primary arrhythmias; congestive heart failure; hypertension; cerebrovascular accident; peripheral vascular disease; diabetes mellitus; respiratory problems; malignancies; hepatobiliary disease; renal disease; arthritis; and gastro-intestinal disease) which are rated on a five-point scale ranging from no co-existent disease to severe uncontrolled disease based on explicit criteria. The degree of physical impairment due to these and other conditions within 10 functional areas

(circulation, respiration, neurological, mental status, urinary, fecal, feeding, ambulation, transfer, vision hearing and speech) are graded on a three point scale from no impairment to severe/serious impairment. Individuals are then classified according to the highest grade for any of the categories in each of the comorbidity and functional impairment dimensions. Finally, these two dimensions are combined into a four-point ordinal scale indicating no, mild, moderate or severe coexistent disease as per the Table below (Imamura, McKinnon et al. 1997). Data are required from clinical notes (ideally including nursing, medical, and laboratory findings).

**Table 7: Scoring system for the Index of Coexistent Disease (OECD)**

<b>Highest comorbidity severity score (0-3)</b>	<b>Highest functional status score (0-2)</b>	<b>ICED level (0-3)</b>
0	0	0
0	1	0
1	0	1
2	0	1
1	1	2
2	1	2
3	(Any)	3
Any	2	3

## **Experience with cancer patient populations**

The ICED (or its immediate precursor) has been used for assessment of role of comorbidity in treatment and survival for breast (Greenfield, Blanco et al. 1987; Mandelblatt, Bierman et al. 2001), prostate (Bennett, Greenfield et al. 1991; Albertsen, Fryback et al. 1996; Krousel-Wood, Abdoh et al. 1996) and head and neck cancers (Hall, Rochon et al. 2002; Castro, Dedivitis et al. 2007).

## **Content and face validity**

The ICED combines elements of comorbidity and functional status. All relevant items are likely to be included, and a measure of severity is included for each item within the index, with explicit criteria specified. Like the KFI there are major simplifying assumptions made in the scoring system, with a variety of comorbidity and functional status score combinations being treated as equivalent (see Table above). Some authors argue that given that comorbidity and functional status are distinct constructs,,

they should not be combined (Extermann 2000; Lash, Mor et al. 2007) and it is not clear whether the method used to combine the two scores is optimal or even appropriate.

## **Criterion validity**

### **Concurrent**

The ICED was compared to the American Society of Anesthesiologists' Physical Status (ASA) score concurrently, and found to be weakly associated with the index overall ( $r=0.27$ ), but the comorbidity aspect of this index was more strongly correlated (Spearman  $r=0.40$ ) than the functional impairment aspect (Spearman  $r=0.22$ ) (Greenfield, Apolone et al. 1993). It has been also shown to be significantly correlated with CCI, KFI and CIRS (Mandelblatt, Bierman et al. 2001; Hall, Rochon et al. 2002).

### **Predictive**

ICED has been found to be associated with higher all-cause mortality among patients with head and neck cancer. For example, compared to those with no comorbidity, those with a high score had three times higher risk of mortality ( $HR=3.17$ ; 2.13-4.47) (Hall, Rochon et al. 2002). ICED has also been shown to be (slightly) more effective at predicting non-cancer death or all-cause mortality among prostate cancer patients than CIRS, KFI or CCI (Albertsen, Fryback et al. 1996; Boulos, Groome et al. 2006), and more strongly associated with treatment received for early breast cancer than CCI (Mandelblatt, Bierman et al. 2001).

## **Construct validity**

ICED has been found to be related to functional status as measured by ADLs (Greenfield, Apolone et al. 1993).

## **Reliability**

Greenfield et al found a reasonable percentage of agreement between all four raters in their study of 30 breast cancer patients with 56.7% agreement in the functional status score, 73.3% in the comorbidity severity score and 66.7% overall (Greenfield, Blanco et al. 1987). Inter-rater reliability has subsequently generally been found to be moderate or high with  $k$  or ICC scores ranging from 0.57-0.80 (Waite, Oddone et al. 1994; Krousel-Wood, Abdoh et al. 1996; Imamura, McKinnon et al. 1997; Hall, Groome et al. 2006).

## **Feasibility**

The ICED comes with a manual, and requires notes review. Several problems with interpreting the instructions for rating individuals using ICED have been reported (Imamura, McKinnon et al. 1997). Abstracting data for ICED took longer than either the CCI or KFI (9.5 mins compared with 5.9 and 8.9 mins respectively) in one study of 526 patients from VA hospitals in the US (Waite, Oddone et al. 1994).

## ***Satariano approach***

### **General description**

Satariano et al (Satariano and Ragland 1994) considered the impact of comorbidity on breast cancer survival. They studied 1011 women with invasive breast cancer followed up for three years post-diagnosis. They reviewed medical notes from the time of diagnosis until six months subsequently and abstracted data on eight pre-specified conditions (hypertension, myocardial infarction, other types of heart disease, diabetes, arthritis, respiratory disease, stroke and other forms of cancer), as well as noting other comorbid conditions. They specified whether the diagnosis of each condition was made before, at the time of or subsequent to diagnosis of breast cancer. They found that only 3.9% of diagnoses occurred after the diagnosis of breast cancer. They identified 18 comorbid conditions. Of these 7 (myocardial infarction, other types of heart disease, diabetes, other forms of cancer, and respiratory, gallbladder and liver conditions) were found to be associated with all-cause mortality, breast cancer mortality or mortality from other causes after adjustment for age, stage and other comorbid conditions. These seven were combined in a simple unweighted index based on the number of conditions present. The Satariano index has also been modified for use with administrative data (Newschaffer, Bush et al. 1997), and used in combination with measures of performance, functional status, depression and cognitive status in the Comprehensive Geriatric Assessment tool (Repetto, Fratino et al. 2002). A subset of the identified conditions that predict functional status have also been used in a study to assess the role of comorbidity in stage at diagnosis of breast cancer (Vaeth, Satariano et al. 2000).

### **Experience with cancer patient populations**

This has been used for patients with breast cancer patients (Satariano and Ragland 1994; Newschaffer, Bush et al. 1997; Silliman and Lash 1999) and has subsequently

been used for colon cancer patients where it was compared with the Charlson, NCI and ACE-27 indices (Hines, Chatla et al. 2009).

## **Content and face validity**

This is a simple site-specific index that has not been widely used since its development. The conditions included are likely to be those of most importance to breast cancer outcomes, but the index is calculated simply by summing the number of conditions present, which assumes that all have an equal impact on outcomes.

## **Criterion validity**

**Concurrent.** The Satariano index correlated with the CCI in one study of 303 women with early breast cancer (correlation coefficient=0.68;  $p<0.001$ ) (Silliman and Lash 1999).

**Predictive.** Satariano et al found that comorbidity as measured by this index was strongly associated with increased risk of all-cause mortality, and non-breast cancer mortality (Satariano and Ragland 1994). Subsequently higher Satariano index scores were found to be associated with poorer colon cancer survival whether medical records, administrative data or both were used (Newschaffer, Bush et al. 1997). Silliman et al found that neither the Satariano nor the Charlson index predicted receipt of treatment or all-cause mortality among 303 breast cancer patients (Silliman and Lash 1999).

## **Construct Validity**

Higher Satariano comorbidity scores are associated with increasing age, lower receipt of treatment and lower physical functioning (Satariano and Ragland 1994; Silliman and Lash 1999).

## **Reliability**

A subset of notes was re-abstracted and reviewed in the original paper (Satariano and Ragland 1994). While a formal assessment of reliability was not carried out, they found that there were inconsistencies in less than 5% of cases. Newschaffer et al found that the Satariano index had an excellent inter-rater reliability with a kappa score of 0.955 ( $p<0.001$ ) (Newschaffer, Bush et al. 1997).

## **Feasibility**

This index was developed using notes review, which requires time and training. However the index itself is very simple, and has been subsequently successfully used with administrative data (Newschaffer, Bush et al. 1997).

## ***Total Illness Burden Index (TIBI)***

### **General description**

The focus of this index was to develop a measure of case-mix for use in comparisons between hospitals, treatments or health care organisations (Greenfield, Sullivan et al. 1995). It is based on patient report of symptoms and was designed to be a measure of impact on poor health on functional status and quality of life outcomes, not mortality or costs of care. It is, therefore, not strictly speaking a measure of comorbidity, but a measure of impact of illness burden on patients. However, it has been used in the context of (prostate) cancer as a proxy measure of comorbidity so is included here. Data for the index development was collected from 1738 patients with diabetes mellitus. The index was developed in three phases. In the first phase, physicians identified items that could be included in a patient-response questionnaire which would allow the identification of the most common diseases and conditions within each body system. For example, to identify and assess the severity of chronic obstructive airways disease, questions were asked about diagnoses of emphysema, chronic bronchitis and asthma; history of pneumonia, bronchitis with antibiotics and flu with coughing; and symptoms of sleeping on extra pillows, sputum production and shortness of breath. In the second phase, physicians classified patient responses according to severity on an ordinal scale (three or four levels) for each of 15 different sub-dimensions. For example, a patient with shortness of breath at rest, cough with heavy sputum and continuous wheeze would rate at the most severe end of the spectrum within the respiratory sub-dimension (Litwin, Greenfield et al. 2007). Finally, in phase three, the clinically based severity scales were tested empirically. Each scale was then validated against appropriate criterion variables such as functional status and disability days.

A summary measure was constructed by combining the 15 severity scales in a two-stage process. First physicians ranked each condition (or sub-dimension) as having minimal, moderate or severe impact on functional status. For example hearing loss, hypertension and incontinence were defined as having minimal negative impact, while

chronic pulmonary disease, congestive heart failure and renal disease were classified as having a severe impact on functional status (Greenfield, Sullivan et al. 1995). Each scale was then individually empirically tested against functional outcomes such as the physical functioning scale of the short-form 36 (SF-36). Where the clinical and the empirical rankings did not agree, clinical assessment was given precedent. Weights were applied to each scale with a weight of 3 for those conditions classified as severe, 2 for moderate and no weights for minimal. The summary measure was calculated by summing the individual condition (or sub-dimension) severity scores, having weighted them by the condition weights.

TIBI has subsequently been adapted specifically for use among men with prostate cancer (Stier, Greenfield et al. 1999; Litwin, Greenfield et al. 2007). In this instrument (TIBI-CaP) 84 items are included in 11 sub-dimensions for which severity scores are calculated based on patient symptom report. The sub-dimensions are also weighted according to greatest expected clinical impact on the patient.

## **Experience with cancer patient populations**

TIBI has not been widely used with cancer populations, but has been validated in populations with prostate cancer (Stier, Greenfield et al. 1999; Litwin, Greenfield et al. 2007; Daskivich, Sadetsky et al. 2010). A subset of TIBI (the cardiopulmonary index) has been used to assess patient outcomes among breast cancer patients (Silliman and Lash 1999; Mandelblatt, Bierman et al. 2001).

## **Content and face validity**

This index was designed to investigate the impact of illness on physical functioning. The conditions that it weights highly are likely to be those with a large impact on physical functioning, and these may differ from conditions that impact treatment choice or survival from cancer. The complete index has not been validated for cancer patient populations other than prostate cancer.

## **Criterion validity**

**Concurrent.** The cardiopulmonary aspect of TIBI has been shown to be significantly associated with other concurrent measures of comorbidity (Mandelblatt, Bierman et al. 2001). It was more closely correlated with the Charlson and Satariano indices calculated from patient interview, than from medical records review (correlation

coefficient = 0.45-53; both  $p < 0.001$  from notes review; and 0.73-0.75;  $p < 0.001$  from patient interview ) (Silliman and Lash 1999).

**Predictive.** TIBI-CaP scores were found to be related to non-cancer mortality after adjustment for sociodemographic factors (Litwin, Greenfield et al. 2007; Daskivich, Sadetsky et al. 2010). For example those with the highest TIBI\_CaP scores were 13 times more likely to die than those with the lowest (HR=13.1; 95% CI=6.3-27.4 for TIBI-CaP score  $\geq 12$  compared with score 0-2) (Litwin, Greenfield et al. 2007).

## **Construct Validity**

The global TIBI severity scale was negatively correlated with physical function and role physical scales of the SF-36 ( $r = -0.55$ ,  $p < 0.001$  and  $r = -0.54$ ,  $p < 0.001$  respectively), and positively correlated with disability days and use of health services (Greenfield, Sullivan et al. 1995). High TIBI-CaP scores were associated with low physical functioning scores on the SF-36 (Litwin, Greenfield et al. 2007), and poorer health related quality of life (Daskivich, van de Poll-Franse et al. 2010).

## **Reliability**

Not reported.

## **Feasibility**

This index requires data from patient interview. It has been estimated that the TIBI-CaP can be completed by a patient within about 15 minutes (Greenfield, Sullivan et al. 1995; Daskivich, Sadetsky et al. 2010).

# ***NIA/NCI Collaborative Study: Yancik***

## **General description**

Yancik and colleagues (Yancik, Havlik et al. 1996) reported on the NIA/NCI Collaborative Study on Comorbidity and Cancer (NIA/NCI SEER study). This was a collaboration between the National Institutes of Aging (NIA) and the National Cancer Institute (NCI) with the SEER program to investigate the comorbidity burden of older people with cancer and to assess the extent to which these conditions affect diagnosis, treatment and survival from cancer. The total sample consisted of more than 7600 people, aged 65 years or older, with diagnosed cancers of breast, cervix, ovary,

prostate, colon, stomach and bladder. They used data from six areas within the SEER program relating to incident cancers linked to standardised data on comorbidity abstracted from medical notes by trained registrars. The comorbidity data abstraction form consisted of 24 major categories of conditions, some of which were divided into subcategories. Data on comorbidity were collected from the period four months prior to diagnosis until diagnosis, and each condition was coded according to severity, with these categories collapsed into two based on whether or not the patient was receiving active management for the specified condition. A group of high severity conditions was specified in later papers also (including chronic obstructive pulmonary disease, diabetes requiring insulin, high severity heart disease, previous malignant cancer and renal failure) (Yancik, Wesley et al. 2001). Conditions were treated separately in most descriptive and multivariable analyses, but were combined as a simple count in some (Yancik, Wesley et al. 2001). Hines et al also used this index as a simple count and compared this to CCI and ACE-27 in a cohort of patients with colon cancer (Hines, Chatla et al. 2009).

## **Experience with cancer patient populations**

This index was developed among, and for use with, older cancer patients including those with cancers of breast, cervix, ovary, prostate, colon, stomach and bladder (Yancik, Havlik et al. 1996; Yancik, Wesley et al. 2001; Hines, Chatla et al. 2009).

## **Content and face validity**

This system was developed specifically for cancer patients using a range of sites, and therefore it is likely that all (or most) of the important conditions have been included. However, the only method used to combine the index is as a simple count which makes the assumption that all conditions are equally important to cancer outcomes.

## **Criterion validity**

**Concurrent.** Not reported.

**Predictive.** Patients with comorbidity were less likely to receive aggressive treatment and had poorer survival compared with other patients (Yancik, Havlik et al. 1996; Yancik, Wesley et al. 2001). Similarly, the number of NIA/NCI index conditions predicted cancer-specific and all-cause mortality among colon cancer patients e.g. those with 6+ conditions had nearly double the risk of all-cause death than those with fewer than 6 conditions (HR=1.83; 1.29-2.61)(Hines, Chatla et al. 2009).

## **Construct Validity**

The number of NIA/NCI conditions increased with age (Yancik, Wesley et al. 2001)

## **Reliability**

Not reported.

## **Feasibility**

This work was based on excellent data which included review of medical notes. While it would not be difficult to use this list of comorbidities as the basis for an administrative index, this has not yet been done (nor validated). Furthermore, the conditions were not combined into a single index limiting its usefulness in some situations.

## ***Elixhauser (comorbidity count and index)***

### **General description**

Elixhauser and colleagues (Elixhauser, Steiner et al. 1998) focused on developing a measure of comorbidity using administrative data. They *“used a large administrative data set to develop and test comorbidity measures that can be used to control for a broad array of patients’ underlying, pre-existing conditions in many types of studies”*. In effect, the main focus of this work was to identify those pre-existing conditions recorded in administrative data that had an effect on major short term patient outcomes (cost of care, length of hospital stay and in-hospital mortality). Using administrative data, Elixhauser et al first excluded the primary reason for hospitalisation and only included secondary conditions that were not related to the DRG of the primary condition. Second, they excluded diagnoses that could have been due to complications of treatment (e.g. pneumonia, pleural effusion, urinary tract infections, cardiac arrest, cardiogenic shock, respiratory failure). Finally, they excluded unimportant comorbidities or conditions that were likely to have a trivial impact on resource use or outcomes (e.g. inguinal hernia, benign prostatic hypertrophy, diverticulosis). They developed an initial list of comorbid conditions through a review of relevant literature and examining the list of conditions included in ICD-9-CM. Conditions were then excluded either if they were infrequent or statistically unrelated to length of stay, total charges or in-hospital mortality. Some conditions were sub-classified further, and others were grouped if sufficiently similar. There was a final list of 30 comorbidities included. This final list of comorbid conditions was tested to assess the impact of each

condition on cost and length of stay, and in-hospital mortality. There was no attempt made to combine these conditions into a summary index, except as a simple comorbidity count. This initial list of comorbidities described by Elixhauser et al (Elixhauser, Steiner et al. 1998) was tested using hospital discharge data collected on an adult population drawn from acute care inpatients in California in 1992.

Van Walraven et al (van Walraven, Austin et al. 2009) modified the Elixhauser system to allow it to be expressed as a summary score. These authors argued that head-to-head comparisons with the Charlson index had found the Elixhauser approach to be superior, but the fact no summary measure was available for the Elixhauser approach was a distinct disadvantage. To address this they applied weights to the comorbid conditions previously identified by Elixhauser, using the regression coefficients from the independent association of each with in-hospital death. The regression coefficients were divided by the coefficient of the variable that had the smallest absolute parameter estimate, and then rounded to the nearest whole number. This meant that each parameter estimate was translated into units which are relative to the 'weakest' variable in the model, so that a variable assigned 2 points is around twice as strong as that of a variable with 1 point. The total score for each patient was simply the sum of all the points assigned to each condition for that patient.

## **Experience with cancer patient populations**

The original Elixhauser index has been used in a number of cancer related studies including breast (Elixhauser, Steiner et al. 1998), cervical (Brewer, Borman et al. 2011), colon (Baldwin, Klabunde et al. 2006), and prostate cancers (Putt, Long et al. 2009). The modified Elixhauser index has not yet been used in any cancer patient populations.

## **Content and face validity**

Individual items were selected using prior research and clinical expertise, and the importance of each condition on multiple endpoints was assessed using standard statistical methods. It is likely that all major comorbidities were identified for short-term outcomes among general inpatients, but these were not specifically those that may have an impact in cancer outcomes. In the original system individual comorbidities were retained rather than a summary score calculated, which means it was not possible to estimate an overall measure of an individual's comorbidity status. Furthermore, because there was no weighting system used, it was difficult to estimate

the relative importance of the individual conditions. However, these latter two issues have been adequately addressed in the recent work by van Walraven (van Walraven, Austin et al. 2009).

## **Criterion Validity**

### **Concurrent**

There is no specific evidence of concurrent validity, although the summary score outperformed the Charlson index in predicting in-hospital death.

### **Predictive**

Among cancer patients, the Elixhauser system has been found to be associated with lower receipt of treatments for cancer and worse cancer-specific, non-cancer related and all-cause survival (Baldwin, Klabunde et al. 2006; Putt, Long et al. 2009; Brewer, Borman et al. 2011).

## **Construct Validity**

The Elixhauser index was positively associated with age, hospital length of stay and use of medical and intensive care services (van Walraven, Austin et al. 2009).

## **Reliability**

Reliability is generally not relevant because, within a given study, data are extracted in a standardised way from electronically stored records. However, it is of note that different coding algorithms exist, and these differences may have a small impact on the way in which the Elixhauser system performs (Quan, Sundararajan et al. 2005).

## **Feasibility**

The Elixhauser system is relatively straight forward with coding algorithms available for identifying the relevant conditions from administrative data. The weighting of conditions and construction of the summary index would also be straight forward if the weights from van Walraven (van Walraven, Austin et al. 2009) were used, but would require some effort if population-specific weights were required. The summary index has yet to be used or validated in other populations.

# ***Fleming (Comprehensive Prognostic Index)***

## **General description**

Fleming et al (Fleming, Rastogi et al. 1999) first developed a 'Comprehensive Prognostic Index' which combined comorbidity, stage and age to predict survival among a cohort of patients with breast cancer. Their aim was to produce a disease-specific index which outperformed more general indices such as the Charlson Index. This index was developed using data from 848 breast cancer patients aged 67 or older in 1993 from Kentucky in the US. The study population was divided into training and testing samples. Comorbidity data were collected for up to two years prior to diagnosis from Medicare claims data, and conditions were divided into 34 categories. Conditions with a prevalence less than 1% or greater than 50% were excluded, leaving 28 categories. The association of each comorbid category with one year mortality was assessed, and those with a hazard ratio greater than 1.2 (n=12) were included in a multivariable model which included two and three-way interaction terms for multiple comorbidities with (a combined) prevalence of at least 2%. They calculated multiplicative and additive indices for each of all-cause and breast cancer specific mortality. The multiplicative indices were calculated by multiplying together the relative risk for each comorbidity category, and by the interaction term of combinations of comorbidities if it was significant. This means that a patient with a score of 2 had twice the chance of dying in the first year post-diagnosis than a patient with a score of 1. The additive index was calculated by summing the log-hazard ratios. Scores of less than 1 on this scale suggest that the particular combination of comorbid conditions had a protective effect on survival. The multiplicative index was used to develop the full comprehensive prognostic index which included age and stage.

In a later article, Fleming et al (Fleming, Pearce et al. 2003) used a similar approach to develop a prostate cancer specific index among 2,931 black men using data from the SEER program in five states in the US linked to Medicare data. Twenty-seven categories of comorbidities were selected on the basis of prevalence, previous work by Charlson and Fleming, and clinical expertise. A multiplicative index was calculated as previously, and either used as a continuous variable in models or categorised for Kaplan-Meier estimations. Additional weighting was given for each additional diagnosis within a given comorbidity category. The index was assessed using five different modelling approaches which variably included the individual conditions, and two, three

and four way interactions. The model with only statistically significant two-way interactions was found to perform best.

## **Experience with cancer patient populations**

The approach described by Fleming et al has been used for patients with breast cancer, and prostate cancer (Fleming, Rastogi et al. 1999; Fleming, Pearce et al. 2003).

## **Content and face validity**

The strength of this index is that the authors underwent a stringent process of comorbidity selection, and explicitly investigated the role of common combinations of comorbidity. Weights were empirically calculated, and combined. The index was separately specified in terms of comorbid conditions and their respective weights for each of the two cancers, so has a high level of internal validity for these specific cancer populations. In the earlier paper, the authors combined measures of comorbidity with age and stage which is possibly less useful if the focus of an investigation is the effect of comorbidity specifically. In the later paper, these other factors were kept separate. However, it is not easy to generalise this index to other populations with cancer, because the weights were cancer (and, in the case of prostate cancer, ethnicity) specific.

## **Criterion and Construct validity**

**Predictive.** The authors found that both the breast and the prostate cancer-specific indices predicted one year mortality well (Fleming, Rastogi et al. 1999; Fleming, Pearce et al. 2003). For example, the original index compared predicted with observed one year mortality using the multiplicative index, and found observed survival was within 95% confidence interval of the predicted survival except in the highest comorbidity category (Fleming, Rastogi et al. 1999).

## **Reliability**

Reliability is not relevant because data are extracted in a standardised way from electronically stored records.

## **Feasibility**

This approach is based on electronically stored data, and therefore is considerably less time consuming than the indices requiring manual review of data. However, because

this index is disease specific, it would potentially have to be re-calculated and validated for every additional cancer, and possibly for other non-Black men for prostate cancer (Fleming, Pearce et al. 2003).

## **Recent attempts to measure comorbidity**

### ***NCI (combined) Comorbidity Index***

#### **General description**

This extension of the Charlson index uses empirically derived weights based on the  $\beta$  coefficients (rather than hazard ratios) and eliminates the 'arbitrary threshold' of HR=1.2 to include conditions used in the original index (Klabunde, Potosky et al. 2000). The new index was developed and tested in cohorts of patients aged over 65 years with breast and prostate cancer identified through the SEER registries during 1992 and 1993. The cohorts were randomly split in half with the first used to develop the index, the second to validate it. Comorbid conditions included in the Charlson index were identified during the 12 months prior to diagnosis, excluding the month of diagnosis to avoid the identification of complications, or conditions arising as a result of the cancer or its treatment. Other cancer-related comorbid conditions identified in the Charlson Index were also excluded (solid tumours, leukaemia and lymphoma conditions). Conditions were identified from physician claims (outpatient) data as well as inpatient hospital data. Codes that only appeared once in physician claims data, and did not appear in inpatient data, or conditions that appeared more than once in physician claims data within a 30-day period but did not appear again were excluded to avoid the inclusion of conditions that may have been considered and ruled out in an outpatient setting.

To develop weights, the inpatient and physician claims data were treated separately, and models were developed for the two patient cohorts separately. Cox proportional hazards models were constructed with two-year non-cancer mortality as outcome and age, and each individual condition included with an indicator for the source of data (with in and out patient sources being mutually exclusive). Estimated coefficients were used as weights rather than the adjusted hazard ratios (including negative coefficients).

Initially three indices were constructed; Inpatient Claims Index (which included only data from inpatient admissions), the Physician Claims Index (which included conditions found in physicians claims but not inpatient records) and the Charlson index (using the Charlson method to estimate study specific weights).

Subsequently, the same authors extended this work to combine conditions, identified in either inpatient or outpatient sources in a single combined index, and to identify site-specific weights for a wider range of cancers (Klabunde, Legler et al. 2007).

## **Experience with cancer patient populations**

This index was developed and validated among breast and prostate cancer patients, and further validated among patients with colorectal and lung cancer (Klabunde, Potosky et al. 2000; Klabunde, Legler et al. 2007).

## **Content and face validity**

The index has used conditions identified by Charlson which means that it is unlikely that all relevant conditions are included. However, the weights for included conditions are cancer-specific and no arbitrary cut off has been pre-defined. This means that the weights have been optimised for the cancer in question, at least in relation to non-cancer death. The scores are calculated by adding the beta coefficients which assumes that conditions have a multiplicative effect on each other.

## **Criterion validity**

**Concurrent.** The authors compared their index to the Charlson index, and found that their models generally performed better than the usual Charlson approach in predicting two year non-cancer mortality (Klabunde, Potosky et al. 2000; Klabunde, Legler et al. 2007). However, they excluded conditions from the Charlson index that did not have a HR of 1.2 for non-cancer death within their specific cancer cohorts. This meant that several conditions were excluded from their Charlson score calculations (for example, for the prostate cancer cohort only eight conditions were included in the Charlson score), which may have negatively impacted on the performance of the Charlson index in this study.

**Predictive.** To assess the ability of each index to predict mortality, the authors constructed models that included age, stage and sex and 2-year non cancer mortality as outcome, and then included each of the indices in turn. All indices significantly

improved model fit, but for all cancer sites the combined NCI indices showed greatest improvement in fit (Klabunde, Legler et al. 2007).

## **Construct Validity**

No evidence presented on this in these papers.

## **Reliability**

Reliability is not relevant because data were extracted in a standardised way from electronically stored records.

## **Feasibility**

The NCI Comorbidity Index is relatively straight forward given that administrative data are used. For cancers sites that have not been included to date, site specific weighting would take some effort if required. The summary index has yet to be used or validated in other populations.

# ***American Society of Anesthesiologists' class (ASA)***

## **General description**

The American Society of Anesthesiologists' (ASA) classification was developed as a pre-operative summary measure of risk of perioperative complications (Reid, Alberg et al. 2001). The ASA classification is widely used clinically and is not commonly used as a general measure of comorbidity in the context of cancer. The ASA classification is assigned (usually) by the attending anaesthetist on the basis of a structured review of the patient's physical status. The ASA score ranges from 1 to 6 (1 - healthy, 2- mild systemic disease, 3- severe systemic disease, 4- severe systemic disease that is a constant threat to life, 5- moribund and 6 - brain dead).

## **Experience with cancer patient populations**

The ASA classification has been used as a method of measuring comorbidity in patients with head and neck, prostate, bladder and breast cancer (Reid, Alberg et al. 2001; Froehner, Koch et al. 2003; Lash, Thwin et al. 2003; Froehner, Koch et al. 2005; Prout, Wesley et al. 2005; Kanatas, Gorton et al. 2010).

## **Content and face validity**

This is a useful measure of acute outcomes in the surgical setting, however has not been developed for the purpose of measuring comorbidity in a cancer cohort (Reid, Alberg et al. 2001).

## **Criterion validity**

**Concurrent.** ASA class has been found to be moderately correlated with Charlson index (Spearman correlation coefficient=0.36,  $p < 0.001$ ) (Reid, MacWilliam et al. 2001).

**Predictive.** ASA class has been associated with all-cause mortality among patients with head and neck cancers in some (Nicolai, Redaelli de Zinis et al. 1997; Reid, Alberg et al. 2001) but not all studies (Kanas, Gorton et al. 2010). For example, in a cohort of 388 such patients, those grouped into ASA categories 3 and 4 had twice the likelihood of dying from any cause than those in categories 1 and 2 after adjusting for age, stage, sex, ethnicity, site, date of diagnosis, treatment, marital status, alcohol and tobacco use (HR= 2.0; 95% CI 1.38-2.89) (Reid, Alberg et al. 2001). Similarly higher ASA scores were associated with poorer all-cause and non-cancer mortality among men with early prostate cancer (Froehner, Koch et al. 2003; Froehner, Koch et al. 2005).

## **Construct Validity**

Not reported in cancer patient populations.

## **Reliability**

The reliability of the assignment of ASA score has been questioned, but some evidence suggests that the reliability of this measure can be considerably improved with minimal training (Reid, Alberg et al. 2001).

## **Feasibility**

The ASA classification is collected routinely for many surgical patients. It is simple and quick to do, but in administrative data will depend on the patient undergoing a surgical procedure.

# ***Alcohol-tobacco related comorbidities index***

## **General description**

This index identifies comorbid conditions that are strongly related to alcohol use and smoking (Reid, Alberg et al. 2002). It was developed for use specifically with patients diagnosed with head and neck cancers because these cancers tend to be associated with high exposure to these agents. The index is a simple count of up to eleven conditions associated with alcohol or tobacco use (chronic pulmonary disease, hypertension, lung cancer, alcoholic gastritis, bladder cancer, alcoholic cardiomyopathy, cardiovascular disease, pancreatitis, peripheral vascular disease, oesophageal cancer, alcoholic cirrhosis), with no attempt made to weight conditions for seriousness (Reid, Alberg et al. 2002).

## **Experience with cancer patient populations**

This index was specifically developed for use with patients with cancer of the head and neck (Reid, Alberg et al. 2002).

## **Content and face validity**

This index included only conditions that were related to alcohol and tobacco use, so is likely to have excluded some important conditions. All conditions were assumed to have the same impact on survival.

## **Criterion validity**

**Concurrent.** This index has been found to be poorly correlated with the Charlson index (Spearman correlation coefficient = 0.24,  $p < 0.001$ )

**Predictive.** The alcohol-tobacco related comorbidity index was associated with all-cause mortality among patients with head and neck cancer (HR=1.49, 95% CI=1.32-1.68), but the pattern of increasing mortality was not linear with increasing scores (Reid, Alberg et al. 2002). In contrast, Castro et al did not find that this index was associated with all-cause survival after adjusting for confounders, but their study included only 90 patients with laryngeal cancer (Castro, Dedivitis et al. 2007).

## **Construct Validity**

Not reported.

## **Reliability**

Reliability is not relevant because data are extracted in a standardised way from electronically stored records.

## **Feasibility**

This is a simple and easy to use index.

# ***Washington University head and neck comorbidity index (WUHNCI)***

## **General description**

This index was also developed specifically for use in patients with head and neck cancer (Piccirillo, Lacy et al. 2002). Data were collected on 132 conditions. Those that were found to have a prevalence of <1% in the study population (1094 patients with head and neck cancer) were excluded. All conditions that were found to be independently associated with 5 year mortality with a p value<0.1 after adjusting for age, sex, ethnicity, stage and symptom severity were included in the index. These were congestive heart failure, cardiac arrhythmia, peripheral vascular disease, pulmonary disease, renal disease, other cancer uncontrolled and other cancer controlled. Conditions were weighted according to the magnitude of the parameter estimate from the multivariable model (Piccirillo, Lacy et al. 2002).

## **Experience with cancer patient populations**

This index was specifically designed for use with patients with head and neck cancer.

## **Content and face validity**

It is likely that most conditions that are strongly related to survival among head and neck patients within this population were identified. However, validation outside this population has not occurred. Appropriate weighting of conditions was applied.

## **Criterion validity**

**Concurrent.** Not reported.

**Predictive.** Survival was negatively associated with comorbidity as measured by the WUHNCI (Piccirillo, Lacy et al. 2002). The c-statistic for the model that included age, sex, stage, symptom severity, ethnicity and the index was 0.754. The model that included the seven conditions as individual variables had a c statistic of 0.756 suggesting that the weighted index was capturing almost all of the prognostic information of the individual conditions.. Sanabria et al also found an association between high score on WUHNCI and higher overall mortality (HR= 1.65; 1.12-2.44) (Sanabria, Carvalho et al. 2008). In contrast, Castro et al did not find an association between this index and mortality in their small study of 90 laryngeal cancer patients (Castro, Dedivitis et al. 2007).

### **Construct Validity**

Not reported.

### **Reliability**

This was not formally reported, but the authors stated that only minor differences were seen between the three physician data extractors.

### **Feasibility**

This index can be used either with clinical notes or administrative data. It is relatively simple to use.

## ***Adult comorbidity evaluation-27 (ACE-27)***

### **General description**

Piccirillo et al modified the Kaplan-Feinstein Index first into the Modified Medical Comorbidity Instrument and then into the Adult Comorbidity Evaluation-27 (ACE-27) index (Piccirillo 2000; Piccirillo, Costas et al. 2003; Piccirillo, Tierney et al. 2004). The purpose was specifically to assess comorbidity in the context of cancer. Cancer registry personnel were trained to collect comorbidity data, and define it according to ACE-27 protocols (Johnston, Piccirillo et al. 2001). Particular attention was paid to differentiating comorbid conditions from those that might be related to the primary disease, or to progression of the cancer or adverse effects of treatment. Twenty-seven conditions were identified based on previous research and clinical judgement. These were conditions that occurred reasonably frequently and were considered to have a

negative impact on prognosis (Piccirillo, Tierney et al. 2004). ACE-27 therefore included several conditions that were not part of the KFI (e.g. diabetes, dementia and HIV/AIDS) (Johnston, Piccirillo et al. 2001).

The ACE-27 was initially assessed using all newly diagnosed patients diagnosed in one of six hospitals between 1999 and 2002 for whom ACE-27 data were available (n=11,906) (Piccirillo, Costas et al. 2003). The ACE-27 system grades specific comorbid conditions into three grades according to severity in the same way as the KFI. Once all an individual's comorbid conditions are identified and classified, an overall ranking is assigned based on the severity of the single most severe condition, except where there were two or more conditions in different body systems that have a grade 2 (moderate) severity, in which case the overall score is grade 3 (severe).

More recently, work has been done to convert the ACE-27 into a claims-based index using ICD codes to differentiate the severity of individual conditions (Fleming, Sabatino et al. 2011).

## **Experience with cancer patient populations**

Piccirillo et al assessed ACE-27 among 17712 patients admitted for prostate, respiratory tract, breast, digestive system, gynaecological, urinary or head and neck cancers at a single academic cancer specialist centre (Piccirillo, Tierney et al. 2004). In this population 45.5% had no comorbidity, 29.8% had mild, 17.3% moderate and 7.4% severe. ACE-27 has also been used successfully in a number of other cancer-related studies (Read, Tierney et al. 2004; Soares, Salluh et al. 2005; Berger, Megwalu et al. 2008; Megwalu, Vlahiotis et al. 2008; Sanabria, Carvalho et al. 2008; Yung and Piccirillo 2008; Hines, Chatla et al. 2009; Fleming, Sabatino et al. 2011).

## **Content and face validity**

This index was developed specifically to evaluate the role of comorbidity in the context of cancer. Consideration was therefore given to ensure that all relevant conditions were included. However, identification of these conditions was based on previous research on comorbidity which did not necessarily focus on cancer, and on clinical experience of one of the authors. Like the KFI from which it was developed there are clear criteria for the inclusion of conditions, and their severity. However there are some

highly simplifying assumptions made regarding both the equivalence of severity ratings across conditions, and the effect of multiple conditions.

## **Criterion validity**

### **Concurrent**

Among 20 head and neck patients, the ACE-27 was found to be significantly correlated with CCI (Spearman's coefficient =0.75) and ASA score (0.58) (Paleri and Wight 2002).

### **Predictive**

A number of studies have shown an association between higher ACE-27 grades and poorer all-cause and cancer-specific survival (Piccirillo, Costas et al. 2003; Piccirillo, Tierney et al. 2004; Read, Tierney et al. 2004; Soares, Salluh et al. 2005; Berger, Megwalu et al. 2008; Megwalu, Vlahiotis et al. 2008; Yung and Piccirillo 2008; Hines, Chatla et al. 2009). In the earliest of these papers, Piccirillo et al found that there was a relationship between severity of comorbidity based on ACE-27 and higher all-cause mortality (Piccirillo, Costas et al. 2003). For all cancers combined, hazard ratios increased with increasing severity having been adjusted for age, sex, ethnicity and stage of tumour (HR for mild 1.1 (0.9-1.2); moderate 1.3 (1.1-1.5) and severe 1.9 (1.7-2.2) compared with patients with no comorbidity. Gradients were also seen for each individual cancer type, with adjusted HRs for those with severe comorbidity compared with none varying by site from a low of 1.6 (1.2-2.1) for lung cancer to a high of 7.6 (3.5-16.5) for prostate cancer (Piccirillo, Costas et al. 2003). The addition of comorbidity data significantly improved the prognostic ability of all models for all sites (after adjustment for age, sex, ethnicity and stage) with c-statistics in the final models varying from 0.71 for lung cancer to 0.89 for prostate cancer (Piccirillo, Costas et al. 2003). Subsequent work by the same authors also supports the predictive validity of ACE-27 (Piccirillo, Tierney et al. 2004; Read, Tierney et al. 2004; Berger, Megwalu et al. 2008; Megwalu, Vlahiotis et al. 2008; Yung and Piccirillo 2008).

## **Construct Validity**

ACE-27 was found to not be strongly related to functional status (Extermann, Overcash et al. 1998).

## **Reliability**

Johnston et al found that the inter-rater reliability of the cancer registrars ranged from 88% to 100%, registrars achieved high levels of sensitivity and specificity (80-100%)

and kappa scores ranging from 0.68-1.0 with most >0.8 (Johnston, Piccirillo et al. 2001).

## **Feasibility**

Like the KFI (from which it was adapted) the ACE-27 requires special collection of comorbidity data. Registrars require special training taking a full day to complete to ensure the quality of the comorbidity data. Once training is completed, the authors found that the time required to obtain these data was minimal with the mean additional time for registrars to abstract comorbidity data estimated to be 2.1 mins (Johnston, Piccirillo et al. 2001). However, other studies have reported the time taken is longer, averaging 16.8 mins per person in a cohort of patients with head and neck cancers (Paleri and Wight 2002). Recent work involving the use of claims data to measure ACE-27 is promising (Fleming, Sabatino et al. 2011).

## ***Tammemagi approach***

### **General description**

Tammemagi and colleagues (Tammemagi, Neslund-Dudas et al. 2003) carried out a study to investigate the effect of comorbidity on lung cancer survival, and to assess the extent to which these effects were mediated by differences in receipt of treatments. They identified subjects using data from the Henry Ford Health System Tumor Registry. Data on clinicopathological and treatment factors relating to each patient were abstracted from detailed computerised medical records. Data on comorbidities were classified using a system developed by the US Department of Health and Human Services in which ICD 9 diseases are collapsed into 259 homogenous groups, of which 56 categories were considered in this study. It is not clear whether only comorbidities present at the time of diagnosis were included, or whether another period was used. The hazard ratios for each of these was calculated for one-year mortality both unadjusted and adjusted for age, sex, smoking status, histology and stage. Conditions for which there were hazard ratios of 1.2 in any of these models were further investigated by including other comorbid conditions and variables relating to cancer treatments in models. The proportion of the excess hazard for each condition that was due to other comorbidities and/or differences in treatment receipt was assessed, with a shift in HR of 15% or more considered important. Adjusted R<sup>2</sup> statistics were used to assess the proportion of survival variation that was explained in each of the models.

There were 841 deaths in the population studied (72.8% of total population). The authors identified 19 conditions which predicted survival among lung cancer patients. Of these, several conditions appeared to have an effect on survival independent of other conditions or on receipt of treatment (asthma, tuberculosis, previous metastatic cancer, osteoporosis, pulmonary fibrosis/interstitial disease, and neurological disease). The effect of other conditions seemed to be explained to a large degree by non-receipt of treatments (congestive heart failure and COPD), and/ or at least in part, by their relationship with other comorbid conditions (e.g. HIV/AIDS, gastrointestinal bleeding, thyroid/glandular disease, connective tissue/musculoskeletal disease and electrolyte/mineral imbalance). The authors combined comorbidities by using a simple count.

Subsequently, Tammemagi et al applied a similar approach to a cohort of 906 breast cancer patients (Tammemagi, Nerenz et al. 2005). In this later study, data on comorbidities were abstracted from medical records for the three years prior to diagnosis and up until first treatment, or until six months post-diagnosis if no treatment was given. In this study 77 conditions were classified as adverse and included in further analysis. Like the previous study, Tammemagi et al assessed the role of both individual conditions and conditions combined using a simple count.

## **Experience with cancer patient populations**

This approach was developed for cancer populations, and has been used to estimate the impact of comorbidity among patients with breast and lung cancers (Tammemagi, Neslund-Dudas et al. 2003; Tammemagi, Nerenz et al. 2005).

## **Content and face validity**

The authors of this approach have gone to considerable effort to identify all relevant conditions. They have done this separately for the two cancer types. They have kept the conditions separately or combined them in a simple count, which assumes that all relevant conditions are equally important

## **Criterion validity**

**Concurrent.** The conditions identified by Tammemagi accounted for more of the survival variation than either a simple comorbidity count, or the Charlson index score. In their second paper, they also found that their comorbidity count correlated

reasonably well with Charlson score ( $r^2=0.47$ ,  $p<0.001$ )(Tammemagi, Nerenz et al. 2005).

**Predictive.** In the original paper, the 19 comorbidities that had been found to predict survival collectively explained 6.1% of the survival variation in addition to stage. This compares to the Charlson index and comorbidity counts which explained 2.0% and 2.5% respectively (Tammemagi, Neslund-Dudas et al. 2003). In the second paper, the predictive ability of the study specific comorbidity count was better than that of the Charlson score for both all-cause and competing causes of death (e.g Cox model c-statistic for 5-level comorbidity variable was 0.70 for study comorbidity count and 0.65 for Charlson score for competing causes mortality)(Tammemagi, Nerenz et al. 2005).

### **Construct Validity**

The Tammemagi comorbidity index was found to be related to increasing age, and smoking status (Tammemagi, Neslund-Dudas et al. 2004).

### **Reliability**

Reliability is not relevant because data were extracted in a standardised way from electronically stored records.

### **Feasibility**

This system would require considerable work to identify relevant conditions for each cancer, however once that was done, it would be relatively easy to apply.

## ***Multipurpose Australian Comorbidity Scoring System (MACSS)***

### **General description**

The Multipurpose Australian Comorbidity Scoring System (MACSS) was designed to *'develop a new and improved comorbidity scoring system, encompassing all comorbid conditions having any effect of practical importance on mortality, readmission, or length of stay outcomes in medical, procedural, or psychiatric patients.'* (Holman, Preen et al. 2005) The authors used linked administrative health data from Western Australia on a

population-based cohort of over a million individuals admitted to hospital in 1989-1996, and included obstetric, paediatric and psychiatric subgroups.

All conditions recorded on the index admission or any admissions in the 12 month prior were identified, and included in the analysis if they were among the most frequent 100 comorbid conditions in any of the clinical subgroups, or if it had been identified in either the Charlson or Elixhauser systems. Complication codes were excluded. Patients were followed up for 30-day readmission rates, index length of stay, and one-year mortality. Conditions were initially included as separate variables, and analyses were conducted for each of the clinical subgroups. Models were adjusted for age, gender, ethnicity and an index of relative socioeconomic disadvantage. Conditions with a relative risk greater than or equal to 1.1 for one year mortality, or 30-day readmission, or an average length of stay difference of greater than or equal to 0.5 days were selected for inclusion in MACSS. Some conditions were then combined or further stratified to derive a final list based on clinical experience. A hierarchical approach was added so that additional terms were added for each ICD-9\_CM chapter. The effect relating to the presence of any condition within a specified chapter was accounted for first, and then the additional effect of each individual condition within the chapter added subsequently. Conditions were not included if they came from the same ICD-9\_CM chapter as the principal diagnosis, or if it was considered to be a complication of the principal diagnosis. The final MACSS included 102 conditions. All 102 conditions were then included in models relating to five heterogeneous populations, and the performance of MACSS was compared to that of the Charlson index in predicting one-year mortality, readmission rates, and length of hospital stay. No attempt was made to summarise MACSS into a single summary measure of comorbidity.

Further work by the same authors incorporated measures of comorbidity recency, duration and severity to the MACSS system (Preen, Holman et al. 2004). Recency was defined as a measure of how current a particular condition is with the understanding that those that are more current are likely to have a greater impact on post-hospitalisation outcomes. Recency was defined as the number of days between the date of index admission, and the most recent discharge with the specified comorbidity recorded within the study period. The duration of each condition was measured as the number of days between the first admission date preceding the index admission where a specified condition had been recorded, and the last discharge date that included that condition. Severity was estimated using the cumulative length of stay

preceding the index discharge for which the specified comorbidity was included. These three variables were included for each comorbidity diagnostic chapters for each patient.

## **Experience with cancer patient populations**

MACSS has not been used extensively for cancer patients, but was used in a cohort of patients who had undergone mastectomy for breast cancer (Holman, Preen et al. 2005).

## **Content and face validity**

The authors of this work state that “*Arguably, our study has gone to the greatest lengths to date in endeavouring to identify an optimal list of conditions for inclusion in a comorbidity index.*” Whilst this may well be true, the aim of this index was to develop an instrument that is useful for general patients, and not specifically for cancer patients. Over a third of their derivation cohort had been admitted for obstetric, paediatric or psychiatric conditions. It may be that the comorbid conditions that are most relevant for these populations are different to those for cancer patients. No attempt was made to summarise it into a single index.

## **Criterion validity**

### **Concurrent**

There is no specific evidence of concurrent validity, although MACSS out-performed the Charlson index in predicting in-hospital death, readmission and length of hospital stay.

### **Predictive.**

To assess the validity of MACSS, five specific subgroups of patients were selected (patients admitted for asthma, acute myocardial infarction or major depressive disorder, and patients undergoing mastectomy for breast cancer or TURP for benign prostatic hypertrophy)(Holman, Preen et al. 2005). The authors compared the performance of MACSS with that of Charlson comorbidity index. MACSS outperformed the CCI, demonstrated with lower deviance, larger areas under the ROC curve and higher  $R^2$  statistics, with slightly better performance if measures of duration, recency and severity were also included for each condition. However it is of note that the authors required large datasets to assess the performance of MACSS (given the very large number of variables that were included in the models).

## **Construct Validity**

Comorbidity as measured by MACSS was less prevalent in patients undergoing procedures as expected.

## **Reliability**

Reliability is not relevant because data were extracted in a standardised way from electronically stored records.

## **Feasibility**

MACSS uses electronic records so extracting the data is not overly burdensome. However, there are 102 comorbidities included in this index, which means that the entire index can only be used in the context of very large sample sizes which may often not be feasible in the context of cancer. This is particularly so if variables relating to recency, duration and severity of each condition are added or if there is interest in investigating the role of interactions between variables.

# ***Simplified Comorbidity Index***

## **General description**

The Simplified Comorbidity Index (Colinet, Jacot et al. 2005) was developed to determine whether it improved the prediction of prognosis for non-small-cell lung cancer patients in general, and compared to the Charlson comorbidity index. The index was developed using data from 735 consecutive patients from a network of cancer centres in France treated between 1998 and 2003 who underwent full clinical assessment. Individual conditions were grouped into categories of cardiovascular, respiratory, and neoplastic comorbidity, renal insufficiency, diabetes mellitus, alcoholism and tobacco consumption. The association of each of these with mortality was assessed in multivariable models. The beta coefficients were determined and used to assign weights (rounded to the nearest whole number). The comorbid conditions with the greatest impact on mortality were tobacco consumption (weight of 7), diabetes mellitus (weight of 5) and renal insufficiency (weight of 4). The remaining conditions had a weight of 1. Whilst not explicitly stated, the final score appeared to be the sum of the weights.

## **Experience with cancer patient populations**

This index was designed for application to patients with small-cell lung cancer.

## **Content and face validity**

The process for identifying comorbid conditions was appropriate for lung cancer patients, and it is likely that all major relevant comorbid conditions were identified. The index accounts for the relative severity of different conditions, but like the Charlson index, it seems to assume that the combination of conditions increases risk in an additive fashion, and that no interaction exists between conditions.

## **Criterion validity**

### **Concurrent**

The Simplified Comorbidity Index was validated in a population of patients with non-small-cell lung cancer (n=136) diagnosed in 2003 and 2004 who were not included in the development population. There was statistical (weak) concordance between the Charlson and Simplified Comorbidity Index (k coefficient of reliability=0.288;  $p < 0.00001$ ).

### **Predictive.**

Survival was adversely affected with increasing Charlson and SCI scores, but the latter discriminated better between those who survived and those who did not. In multivariate models that included demographic, detailed disease variables, and measures of physiological dysfunction (e.g. full blood count, serum fibrinogen, calcium, and sodium levels), the SCI was as important as stage in predicting survival. However, some methodological details were missing, and it was hard to determine the exact meaning of the key results. For example, the hazard ratio for SCS for (presumably) mortality is given as 1.36 (1.09-1.69), but it is not clear whether the HR is measuring one unit change in SCS, or a categorised version of the score. The negative impact of comorbidity on survival was confirmed by the same authors in a later study (Jacot, Colinet et al. 2008).

## **Construct Validity**

No information was provided on construct validity.

## **Reliability**

No information was provided on the reliability of the index.

## **Feasibility**

This index is relatively simple, but requires data extracted from patient notes, and has only been validated among patients with non-small cell lung cancer, so it is unclear how it would perform for other cancers.

# **Summary and conclusions**

This chapter provided a review of methods used to measure comorbidity in the context of cancer-related epidemiological studies. While all these approaches aim to measure the same underlying construct, they vary in terms of the purpose for which the measures were developed, whether they are based on individual conditions or organ systems and the type and detail of data required for their estimation. Additionally, they vary in their ease of use and complexity of design. The following summarises the key findings relating to the content and face validity, criterion validity, reliability and feasibility of these measures of comorbidity.

## ***Content and face validity***

Authors have used varying approaches to identify relevant conditions based on clinical experience or literature in the area (e.g. CIRS, KFI, ICED, ACE-27), empirical analysis (e.g., Charlson, NIA/NCI Collaborative study, MACSS, Tammemagi) or both (e.g. Satariano, Elixhauser, CPI, NCI Comorbidity Index) (Table 5). All indices are likely to capture some elements of comorbidity important to cancer patients. Individual condition counts and weighted indices include a highly variable number of conditions (ranging from 7 to 102). Some conditions are included almost universally such as cardiac, respiratory, liver and renal conditions, and diabetes; others less so. For example, alcohol abuse, obesity, drug abuse, angina, osteoporosis, non-diabetes endocrine disorders and tuberculosis are included in several indices but not others. The Charlson and Satariano measures include none of these conditions, and only MACSS includes all of them. The extent to which this is important is likely to depend on the primary condition under study, and the study questions to be addressed.

The content validity of organ-based measures (such as CIRS, ICED and ACE-27) depends on the validity of the criteria used to categorise individuals into severity categories for each organ system (Table 6). These criteria should ideally be explicit

and kept up-to-date with medical knowledge, and thus the criteria of ACE-27, which were also designed relatively recently and with a cancer focus may have higher content validity than those of KFI and CIRS (Hall 2006). The CDS approach using pharmaceutical data will only identify conditions for which regular medications are prescribed, and will be subject to utilisation bias and provider variation in prescribing habits. However medication-based indices may address some of the concerns about using administrative databases such as inaccurate recording of diagnoses, and may be more likely to identify conditions managed in the outpatient system. The process for allocating patients into DCGs or ACGs is entirely based on resource consumption, and is not specifically designed to measure comorbidity in the context of cancer. Similarly, ASA grade is a useful measure of acute outcomes in the surgical setting, but has not been developed for the purpose of measuring comorbidity in a cancer cohort.

Another key component of content and face validity relates to the extent to which severity of conditions are combined (if relevant) into a single measure of comorbidity (Table 6). Where conditions are added together in a simple unweighted index, the implicit assumption is made that all conditions are equally important in their relationship to outcomes, which is unlikely to be true. Organ or systems-based approaches tend to use highly simplified scoring systems. For example, KFI and ACE-27 assume that a 'severe' rating in any body system is equivalent, and that two 'moderate' ratings in different systems have a combined effect equivalent to a single 'severe' rating.

Weighted systems are designed to account for the fact that different conditions are likely to have different impacts on outcomes. The Charlson index is the prototype for all subsequent weighted indices. It assumes that the impact of multiple conditions is additive, that the prognostic importance of a given comorbid condition is the same as it was when the index was developed and is constant regardless of the primary condition. Subsequent indices have dealt with these issues to a greater or lesser extent. For example, some authors have used coefficients calculated for specific cancer sites as weights rather than adjusted hazard ratios and some have explicitly investigated the role of common combinations of conditions (Fleming, Rastogi et al. 1999; Fleming, Pearce et al. 2003).

## ***Criterion validity***

There is at least some evidence to support the predictive ability of all measures reviewed here (Table 8). The strength of this evidence varies, but six measures

(CIRS,CCI, ICED, Elixhauser, NCI Combined and ACE-27) have particularly strong evidence of predictive ability in the context of cancer patient outcomes. Table 8 summarises the findings of 26 papers that have compared the performance of the various measures of comorbidity. There is little consistency between the findings, which depend on various factors including the size of the study population and the type of cancer studied, the way the indices were categorised and the outcome measures used.

In terms of concurrent validity, measures of comorbidity tend to be correlated with each other, although the strength of that correlation is highly variable. All measures of comorbidity mismeasure the underlying construct of comorbidity to some extent, so the degree of correlation between two measures is more related to how closely they relate methodologically than whether one or the other more accurately captures the construct.

## ***Reliability***

Reliability is most relevant for indices that use data abstracted from medical records or from patients themselves. The reliability of measures tends to depend on the simplicity, clarity and ease of use of the scale, as well as the quality of the data and training of the abstractors. Studies examining the reliability of data collected for CIRS, CCI, ICED, and ACE-27 have all found moderate to high levels of interrater reliability. No data were available on the reliability of TIBI, NIA/NCI Collaborative Study Index or the Simplified Comorbidity Index. Interrater reliability is less relevant for the remaining measures because they use administrative data abstracted in a standard manner. However data obtained from administrative databases is likely to be less accurate and complete than data collected specifically to measure comorbidity.

## ***Feasibility***

Indices that require access to clinical notes and training for abstractors are more time-consuming to use. Whilst measures based on administrative data do not require primary data collection, these databases are often large and unwieldy, and require expertise to manage them. Indices with large numbers of individual variables (e.g. MACSS with 102 variables) require large datasets to be statistically feasible.

**Table 8: Table of articles comparing predictive validity of measures of comorbidity in the context of cancer**

Author/ year	Indices reviewed	Population	Endpoints	Predictive validity	Conclusion
Charlson 1987	CCI, KFI	685 pts with breast cancer	Non-cancer mortality	Both differentiated groups on basis of survival, and variance explained was similar.	Both good.
Albertsen 1996	CCI, KFI, ICED	451 pts with prostate cancer	All-cause survival	All associated with all-cause mortality. ICED marginally more so than others.	ICED marginally better at predicting ACS in this cohort.
Newschaffer 1997	CCI, KFI, Satariano	404 pts with breast cancer	All-cause survival	All predicted survival. Results given as HR for medical records, claims data and both for one unit change. For Charlson these were 1.48; 1.53 and 1.50 respectively. For Satariano: 1.44, 1.28 and 1.40 respectively. For KFI 1.15; 1.08 and 1.14 respectively.	Charlson performed best. Notes and claims had similar predictive abilities for CCI only.
Extermann 1998	CCI, CIRS-G	203 elderly pts with cancer	Functional status	There was little or no relationship between comorbidity measures and functional status. Correlation between Charlson and CIRS-G was fair.	Both reliable tools for older cancer patients.
Silliman 1999	CCI, TIBI, Satariano	303 pts with breast cancer	ACS, receipt of definitive treatment, physical functioning.	None predicted receipt of definitive treatment or mortality. All predicted physical functioning.	No comment.
Reid 2001	CCI, ASA	388 pts with head and neck cancer	All-cause survival	Both predicted all-cause mortality but ASA performed better than CCI.	Concluded that ASA class was at least comparable to CCI if not better.
Mandelblatt 2001	CCI, ICED, TIBI, condition count	718 pts with breast cancer	Treatment receipt Functional status	Comorbidity count and ICED were significantly associated with treatments received after adjustment for age and stage. CCI and TIBI were not.	Final choice of measure depends on goals of analysis.
Piccirillo 2002	KFI, WUHNI	1094 pts with head and neck cancer	All-cause survival	Both predicted mortality WUHNCI performed significantly better than KFI.	WUHNCI outperformed general measure of comorbidity in this population.
Reid 2002	CCI, Satariano, ATI	9386 pts with head and neck cancer	All-cause survival	Both predicted mortality to similar degree (HR=1.53 for Charlson and 1.49 for ATI).	Similar performance but preferred CCI b/c standardised in other populations

Author/ year	Indices reviewed	Population	Endpoints	Predictive validity	Conclusion
Hall 2002	CCI, KFI, CIRS, ICED, CDS	655 pts with head and neck cancer	All-cause survival	CDS did not predict survival. Only KFI produced non-overlapping survival curves. For most of least comorbidity: HR CIRS 2.18 (1.31-3.63); KFI: 3.03 (2.12-4.33); CCI 2.82 (1.77-4.48) ICED: 3.17 (2.13-4.72).	KFI overall best, but not much difference.
Lash 2003	CCI, ICED, ASA	830 pts with breast cancer	Receipt of definitive treatment and discussion or receipt of tamoxifen.	All findings were in expected direction and of similar magnitude across measures of comorbidity.	Recommends combining indices using multiple informants approach.
Froehner 2003	CCI, ASA	444 pts with localised cancer	All-cause survival, non-cancer survival	Both predicted both outcomes. Crude analyses presented only. Dose response evident.	Concluded that ASA class was slightly better than CCI
Piccirillo 2004	CCI, WUHNI, NCI combined	7131 pts with head and neck cancer	All-cause survival	All weakly associated to poorer survival e.g. CCI score 4+ assoc with HR 1.26 (1.17-1.36); and WUHNCI score 4+ HR=1.32 (1.19-1.46) compared with scores of 0.	Weak association with survival for all indices. None clearly outperformed others.
Munro and Bentley 2004	CCI, CIRS	483 pts with colorectal cancer.	All-cause and cancer-specific survival	Charlson more strongly associated with both all-cause and cancer-specific survival than CIRS e.g. CCI HR 1.44 (1.17-1.79) for overall survival and 1.33 (1.06-1.68) for cause specific compared with CIRS 1.09 (1.04-1.14) and 1.06 (1.01-1.11) respectively.	Charlson better than CIRS.
Soares 2005	CCI, ACE-27	772 ICU pts with cancer.	ICU, in-hospital and 6 month mortality rates	ACE-27 associated with 6 month mortality (HR 1.52; 1.06-2.20). Not associated with CCI.	Concluded ACE-27 better in this population.
Holman 2005	CCI, MACS	615 pts with breast cancer	One-year mortality, 30 day readmission and index LoS	MACSS showed better model fit, discrimination and control of confounding compared with CCI	MACSS considerably better than CCI for this population.
Colinet 2005	CCI, SCS	735 pts with lung cancer	All-cause survival	SCS but not CCI was an independent predictor of poor survival	Concluded that SCS was more informative than CCI in this population.

Author/ year	Indices reviewed	Population	Endpoints	Predictive validity	Conclusion
Boulos 2006	CCI, KFI, CIRS, ICED, CDS	269 pts with prostate cancer	% variance explained (PVE) of non-cancer death	CDS, ICED and KFI distinguished groups with different survival probabilities. CIRS and CCI less so. All indices had partial PVE estimates significantly different to zero (in addition to age, PVE=2%). CDS had biggest (11.3%), then ICED (9%), CIRS (7.2%), KFI (4.9%) and CCI (3.8%).	All indices predicted non-cancer mortality. CDS best then CIRS, ICED better than KFI and Charlson.
Baldwin 2006	NCI combined, Elixhauser, ACGs, DCGs	5777 pts with colorectal cancer	Receipt of adjuvant chemotherapy and non-cancer mortality.	All indices suggested that comorbidity was associated with lower receipt of chemotherapy and higher non-cancer mortality. Elixhauser produced best fitting model according to c statistic but AIC measure showed Elixhauser to have poorer fit because of number of covariates.	No index consistently out-performed others.
Castro 2007	CCI, KFI, CIRS, ICED, ACE-27, ATI, WUHNI	90 pts with laryngeal cancer	All-cause survival	Only CIRS remained significant in multivariable model	Only CIRS was independent risk factor.
Klabunde 2007	CCI, NCI combined, comorbidity count	140315 pts with breast, prostate colorectal, lung	Non-cancer mortality	NCI index resulted in better model fit than comorbidity count for all sites. CCI performed least well.	Preferred NCI index.
Sanabria 2008	ACE-27, WUHNI, NIA/NCI index	477 pts with head and neck cancer	All-cause and cancer-specific survival	HR for overall survival were 1.33 (0.94-1.88); 1.72 (1.15-2.58) and 1.65 (1.12-2.44) for NCI, ACE-27 and WUHNI respectively for highest to lowest categories. Cancer specific HRs were closer to the null.	Concluded ACE-27 better (although results do not support their conclusion).
Jacot 2008	CCI, SCS	301 pts with lung cancer	All-cause survival and quality of life	SCS>9, but not CCI was independently associated with poorer survival.	SCS more informative in this population.
Hines 2009	CCI, ACE-27, NIA/NCI index	496 pts with colon cancer	All-cause and cancer-specific survival	All predicted all-cause mortality in multivariable models. Magnitude varied (NIA/NCI 1.83 (1.29-2.61); ACE-27 1.63 (1.24-2.15); CCI 1.46 (1.14-1.88). Similar results for CSS.	Any of these three indices are justifiable.

Author/ year	Indices reviewed	Population	Endpoints	Predictive validity	Conclusion
Sarfati 2009	CCI, comorbidity count	589 pts with colon cancer	All-cause and cancer-specific survival	Both predicted all-cause mortality. CCI score 3+ compared with 0 HR=2.63 (1.82-3.81) and condition count 3+ compared with 0, HR=2.00 (1.41-2.82)	Inclusion of individual conditions optimal for adjustment for comorbidity. CCI better than simple count for index.
Brewer 2011_	CCI, Elixhauser	1,594 pts with cervical cancer	All-cause, cancer specific and non-cancer survival	Both predicted outcomes to similar extent	No comment.

## ***So which index is best?***

Table 9 provides some qualitative criteria to assess each measure of comorbidity in the context of cancer. While the criteria are highly simplified, they provide a basic framework to compare the various approaches. Table 10 provides the assessment of 20 measures of comorbidity in the context of cancer, though it should be noted the outcomes of this assessment may well differ if specific research questions or contexts were considered. For example, if clinical data are already collected, the feasibility of clinical-notes based indices will be scored higher. Similarly, the score for cancer-site specific indices (e.g. WUHNC and SCI indices) are only relevant for studies of the site specified.

There is some evidence to support the predictive validity of all approaches. For all indices, where these criteria were relevant and data could be found, there was at least moderate evidence for concurrent validity and reliability. There was more variability in the remaining three criteria: experience with cancer patients, content and/or face validity, and feasibility. There were three administrative-based approaches (DCGs, ACGs and MACSS) that have not generally been used in the context of cancer patients, so there is relatively little evidence on their validity in this particular context and these approaches tended to rate lower on content and face validity also. Other indices that rated lower on this criterion were those developed for purposes other than assessing the impact of comorbidity on patient outcome. For example, DCGs, ACGs and Rx-Risk were all developed as predictors of resource use, ASA was developed to predict acute perioperative risk and TIBI was primarily developed as a measure of case-mix.

Some indices that scored highly on all other criteria scored low on the feasibility criterion, for example, CIRS, ICED and ACE-27. Whilst these are all good measures of comorbidity, they all require special collection of data, and therefore may not be available at a population level. The recent work underway to develop a claims-based version of ACE-27 will, if further validated, improve the feasibility of this measure (Fleming, Sabatino et al. 2011).

Eight indices scored at least moderately well on all criteria. These were CCI, Satariano, Elixhauser and Tammemagi approaches, Fleming's Comprehensive Prognostic Index, NCI (combined) Comorbidity Index, Alcohol-Tobacco Related Comorbidities Index and the Washington University Head and Neck Comorbidity Index. Several of these have been developed specifically for one or two cancer sites (Satariano, Tammemagi approaches, Fleming's Comprehensive Prognostic Index, Alcohol-tobacco related comorbidities index and the Washington University head and neck comorbidity index), leaving only three indices with generally good properties (CCI, Elixhauser approach and NCI Index). Neither the Charlson Index nor the Elixhauser approach were developed specifically for cancer populations. The NCI index provides weights that are cancer-specific and derived more recently than the other two indices (particularly CCI), but is based on the same conditions used in the Charlson index which may not be those that are most important for cancer populations.

Given the difficulty of identifying a single gold-standard measure of comorbidity, other approaches have been suggested. Lash et al. suggested an approach that combines different sources of data into a single model (Lash, Thwin et al. 2003). This approach uses a latent variable approach, which allows separate logistic regression models for each comorbidity measurement to be merged into single regression equation (Horton, Laird et al. 1999). This allows an overall assessment of the impact of comorbidity on the outcome of interest, and the roles of each individual index. However, Lash et al concluded that "*when a single comorbidity index applies directly to a research question, or such an index can be developed, then that single index should be given preference [over multiple informants approaches]*"(Lash, Thwin et al. 2003).

Currently there is no simple, administrative data-based comorbidity index developed specifically for cancer patients that can be used in multiple cancer sites or for cancer populations generally. The work presented in the next Chapters aims to develop and validate such an index.

**Table 9: Qualitative criteria used to assess measures of comorbidity.**

<b>Criteria</b>	<b>*</b>	<b>**</b>	<b>***</b>	<b>NR</b>
Experience with cancer patients	Not generally used for cancer patients populations.	Used in limited way with cancer patients. One or two sites only.	Used extensively among cancer patient populations.	
Content and face validity	Developed among non-cancer patients. Some relevant items likely to be excluded, and/or unreasonable scoring assumptions made.	Most relevant items likely to be included. Some assumptions may not be reasonable.	All relevant items likely to be included. Reasonable scoring assumptions made. Developed among cancer patient populations.	
Concurrent validity	Evidence against concurrent validity.	Some evidence to support concurrent validity.	Strong evidence to support concurrent validity.	No evidence relating to concurrent validity found.
Predictive validity	Evidence against predictive validity.	Some evidence to support predictive validity.	Strong evidence to support predictive validity.	No evidence relating to predictive validity found.
Reliability	Evidence for poor reliability only.	Evidence for moderate level of reliability.	Evidence for high level of reliability.	No evidence relating to reliability found.

**Table 10: Qualitative assessment of validity of indices in relation to cancer patient populations**

Index name	Experience with cancer patients	Content/ face validity	Concurrent validity	Predictive validity	Reliability <sup>‡</sup>	Feasibility <sup>‡</sup>
Cumulative Illness Rating Scale	***	**	***	***	**	*
Kaplan-Feinstein Index	**	**	***	**	**	*
Charlson comorbidity Index	***	**	***	***	**	***
DCGs	*	*	NR	**	NA <sup>†</sup>	**
ACGs	*	*	NR	**	NA <sup>†</sup>	**
Chronic Disease Score/ Rx-Risk	**	*	**	**	NA <sup>†</sup>	**
Index of Coexistent Disease	**	**	***	***	**	*
Satariano approach	**	**	**	**	***	***
Total Illness Burden Index/ TIBI-CaP	**	*	***	**	NR	*
NIA/NCI Collaborative study	***	**	NR	**	NR	*
Elixhauser approach	***	**	NR	***	NA <sup>†</sup>	***

Index name	Experience with cancer patients	Content/ face validity	Concurrent validity	Predictive validity	Reliability <sup>‡</sup>	Feasibility <sup>‡</sup>
Comprehensive Prognostic Index	**	***	NR	***	NA <sup>†</sup>	**
NCI Comorbidity Index	***	**	**	***	NA <sup>†</sup>	***
ASA	**	*	**	**	**	**
Alcohol-Tobacco Related Comorbidities Index	**	**	**	**	NA <sup>†</sup>	***
Washington University Head and Neck Comorbidity Index	**	***	NR	**	**	***
ACE-27	***	**	***	***	***	*
Tammemagi approach	**	***	**	**	NA <sup>†</sup>	**
Multipurpose Australian Comorbidity Scoring System	*	**	NR	**	NA <sup>†</sup>	**
Simplified Comorbidity Index	**	**	**	**	NR	*

<sup>‡</sup> Reliability assessed when notes review or patient interview carried out.

‡ The most simple approach is assessed e.g. if both notes review and administrative data are potential data sources, the latter will be assessed.

NA<sup>†</sup> Not applicable



# Chapter 5: Methods

*Not everything that counts can be counted, and not everything that can be counted counts. ~Albert Einstein*

## Overview:

The aim of this thesis was to develop and validate a simple cancer-related comorbidity index that could be applied to routine hospitalisation data quickly and easily. The first decision to make was what kind of measure to develop. Organ or system-based approaches such as CIRS (Linn, Linn et al. 1968), KFI (Kaplan and Feinstein 1974), ICD (Greenfield, Apolone et al. 1993), TIBI (Greenfield, Sullivan et al. 1995) and ACE-27 (Piccirillo, Lacy et al. 2002) tend to require data from clinical notes, so are not designed for use with administrative data. Some of these (ICD and TIBI) also conflate functional status with comorbidity. Measures based on clinical judgement (such as ASA) also generally require data from clinical notes, and are also highly simplified proxies of comorbidity. The focus of case-mix approaches such as ACG and DCG measures (Ash, Porell et al. 1989; Starfield, Weiner et al. 1991; Ellis, Pope et al. 1996) is on allocation of resources. These approaches identify particular groupings of conditions and patient characteristics that predict healthcare expenditure, so are not true measures of comorbidity. The final two alternatives are counts of conditions or weighted indices. Both are simple and can be used with administrative data, but weighted indices have the advantage that they incorporate a measure of relative severity between conditions. For these reasons, a weighted index approach was taken in this thesis.

Comorbidity is a 'slippery' concept. The underlying construct is complex, and varies depending on the primary disease and outcome of interest. Despite many and varied attempts to measure it, it is clear that no true gold standard measure exists. This lack of 'measurability' means that there is no well-defined standard against which to compare a new cancer-specific index. For this reason, before a simplified index could be validated, considerable effort was required to develop a measure that was as close to gold standard as possible, which in turn required validation against established comorbidity measures. This 'gold-standard' measure had to be site and outcome specific, use more than one source of comorbidity data, include all important conditions and exclude those that may be complications of the primary disease, consider the

timing of the comorbid condition in relation to the diagnosis of cancer, take account of the severity of conditions and their likely impact on the outcomes of interest, and ideally also consider the impact of clustering of conditions.

This Chapter describes the process of developing and validating multiple site-specific hospitalisation and pharmaceutical-based comorbidity indices with the aim of optimising administrative-based measures of comorbidity in the context of cancer. It then describes how these were used to validate simplified comorbidity indices.

## ***Aims***

The main research aims of this thesis are:

1. To assess how well data on comorbidity are captured in routine databases in New Zealand by comparing detailed comorbidity data extracted from hospital records with routinely collected hospitalisation and pharmaceutical data from the same patients.
2. To develop and validate optimised ('gold standard') measures of comorbidity using routinely collected data for patients with cancer. These measures would be:
  - a. Site- and outcome-specific;
  - b. Use more than one source of data;
  - c. Include all important conditions and exclude those that may be complications of the primary disease;
  - d. take account of the severity of conditions and their likely impact on survival and;
  - e. consider the impact of clustering of conditions.
3. To develop and validate a simplified comorbidity index using routinely collected data on comorbidity; and to compare the performance of this 'user-friendly' index with the comprehensive 'gold-standard' approach.

This chapter is divided into four sections:

1. **Section 1** provides a description of the main **data sources, subjects** included in the development and validation cohorts, and key **covariates** used in the analyses presented in this thesis.
2. **Section 2** describes the measurement of comorbidity using administratively collected **hospitalisation** data. The first part of this section details the initial

- validation** of these data, which was carried out prior to the remainder of the thesis to ascertain whether New Zealand hospitalisation data could be used for the purpose of measuring comorbidity. This early validation exercise compared the routine hospitalisation data with data collected manually from hospital notes (which had been collected as part of an earlier study), and largely compared conditions used in the Charlson index. The second part of this Section describes the process of **optimising the identification** of comorbid conditions from routine hospitalisation data. The final part of this section describes the **development and validation of cancer site-specific hospitalisation-based indices** to be used as part of the gold-standard measure of comorbidity.
3. **Section 3** describes the process of measuring comorbidity using community **pharmaceutical** data. The first part of the Section describes the process of **identifying comorbid** conditions from these data. The second part **compares** conditions identified from these pharmaceutical data with conditions identified from a manual hospital notes review. The final part of the section describes the **development and validation of the Pharmacy-based comorbidity indices** (PBCIs) to be used as part of the gold-standard measure of comorbidity.
  4. **Section 4** describes the development and validation of **simplified administrative data-based comorbidity indices**, and comparison of their performance with the gold standard measures of comorbidity.

All analyses were carried out on SAS (Version 9.2, SAS Institute Inc., Cary, NC).

Ethics approval for this study was granted by the Multiregion Ethics Committee (MEC/10/042/EXP).

# **Section 1: Data sources, subjects and variables used**

This section first describes the key data sources used in this thesis. It then provides detail about the subjects included in the main development and validation cohorts employed in the development of the various measures of comorbidity. Finally it details the main variables used in the analyses presented here.

## ***Data sources***

A number of data sources were used in this thesis including the New Zealand Cancer Registry, National Minimum Dataset, National Mortality data, community pharmaceutical data, and data from a manual review of hospital notes. All data were linked using National Health Index (NHI) numbers.

## **National Health Index (NHI) number**

The NHI is a unique health identifying number that is assigned to all individuals who use health services in New Zealand (Ministry of Health 2009; Ministry of Health 2011). NHI numbers are held on the NHI database along with individuals' address, date of birth, sex, New Zealand resident status, ethnicity and date of death. The NHI number is also included on all health-related records held nationally allowing datasets to be easily linked.

## **New Zealand Cancer registry**

The New Zealand Cancer Registry is a population-based register of all primary cancers diagnosed in New Zealand excluding non-melanoma skin cancers (Ministry of Health 2010). Most new cancer diagnoses are identified from data supplied by pathology laboratories which have been legally required to report all relevant diagnoses to the Cancer Registry since 1994. In addition, a small proportion (<10%) of cancers are identified from hospital discharge forms, death certificates or coroners' reports. The cancer registry therefore provides a theoretically complete register of all new cases of cancer diagnosed over this period. The cancer registry provided data on the site, extent of disease at diagnosis using SEER summary staging (American Joint Committee on Cancer 2009), date of diagnosis and patient demographic characteristics.

## Mortality data

The Mortality database collects information on all deaths occurring in New Zealand (Ministry of Health 2011). The underlying cause of death is recorded according to the International Classification of Diseases system and the WHO Rules and Guidelines for Mortality Coding. Cause of death was coded according to the ICD-10-AM system (Australasian Modification of the International Classification of Diseases System, tenth revision).

## Hospitalisation data

Routine hospitalisation data are held in the **National Minimum Dataset** data (NMDS) (NZ Health Information Service 2005). This includes data from all publically-funded, and some privately-funded hospitalisations in New Zealand. It includes information on the dates of admission, in-patient procedures and diagnoses. These data were largely used for the construction of the hospitalisation-based comorbidity indices, but also for defining date of diagnosis.

Details on primary and secondary diagnoses are provided and coded using ICD-10-AM (World Health Organization 2008). These data are coded onsite in District Health Boards (DHBs) around the country. Trained coders use all available data in the clinical record to identify relevant diagnoses and procedures. The primary source of data is the discharge summary, but this is checked against the entire record including laboratory and radiological reports, clinical letters, medical and nursing notes, and operation records. Where there are inconsistent or ambiguous documentation, coders will contact clinicians to clarify information. Codes are assigned using appropriate coding standards and conventions according to the ICD-10-AM procedures. In most DHBs, coding is done using coding software such as 3M Codefinder™, although ICD-10-AM manuals are also used. Data are then supplied to the Ministry of Health. Data quality is monitored using Performance Indicators for Coding Quality (PICQ) which includes predetermined logic checks at the national level. There are also individual audits carried out at the local level of individual coders (personal communication Tracy Thompsen, Senior Analyst, Classification and Terminology, Ministry of Health).

## Pharmaceutical data

Community pharmaceutical data are collected on all subsidised medications dispensed from community pharmacies nationally. These data were used in the construction of the pharmaceutical-based comorbidity index.

Community pharmaceutical data include all claim and payment information collected from pharmacists for any subsidised dispensed medications (New Zealand Health Information Service 2006). These data have been collected since 1992, but NHI numbers have only been included since 2002. These data are jointly owned by the Ministry of Health and Pharmac (the Governmental organisation that manages the pharmaceutical schedule in New Zealand). Data include identification of the primary active chemical ingredient of each drug as well as the formulation name and identification (form and strength of the medication). Data on medications dispensed by hospital pharmacies or purchased over the counter (at pharmacies) are not held in this database.

## **Hospital notes review**

In order to validate the routinely collected hospitalisation (NMDS) and pharmaceutical data, clinical data on comorbidity obtained through hospital notes review were compared with conditions identified in the administrative data. Two separate data validation exercises were carried out using two separate hospital notes reviews.

### **1. Hospital notes review for validation of NMDS data.**

To validate the comorbidity data from the NMDS (hospitalisation dataset), data from an earlier study (led by Sarfati and Dr Sarah Hill) (Sarfati, Hill et al. 2009; Hill, Sarfati et al. 2010) involving a cohort of colon cancer patients diagnosed between 1996 and 2003 were used. This was done very early in the thesis process to ensure that the routinely held hospitalisation data were valid to use for the construction of a comorbidity index in New Zealand. Because ICD-10 codes were not introduced until 1999 (and some of the patients used in this cohort were diagnosed prior to that time), usual ICD-9 coding practices were used to carry out the validation process. However, the intention was to review the coding and use ICD-10 codes for the remainder of the thesis. The data validation has since been published (Sarfati, Hill et al. 2010). This validation exercise was designed, led and written up by the author of this thesis (Sarfati), however the clinical data were collected by Dr Sarah Hill, and analyses for the validation were carried out by a biostatistician (Gordon Purdie) using an analysis plan developed by Sarfati (see Statement of Participation).

Clinical data on comorbidity obtained through hospital notes review were compared with routinely collected NMDS data for the same cohort. The cohort was made up of patients with first primary colon cancer diagnosed between 1996 and 2003, and notified to the New Zealand Cancer Registry (ICD-10-AM site codes C18-C19 excluding 18.1). All Māori patients meeting the above criteria were included along with an approximately equal number of randomly-sampled non-Māori patients. This was to allow an assessment of survival disparities between Māori and non-Māori patients with colon cancer which was the aim of the original study (Hill, Sarfati et al. 2010).

Clinical data were abstracted directly from patients' hospital medical notes during 2006-07. These were recorded on a standardised form by a physician (Hill) and double-entered into an electronic database. Data were collected on all major comorbid conditions present at the time of diagnosis including all conditions from the Charlson Index, and the following conditions: angina, essential hypertension, cardiac arrhythmias, previous pulmonary embolism, cardiac valvular disease, inflammatory bowel disease, other neurological conditions and major psychiatric conditions (including schizophrenia, bipolar disease, and depressive psychosis).

## **2. Hospital notes review for validation of pharmaceutical data.**

To validate the pharmaceutical data, data from a clinical notes review that was carried out on a subset of the main development cohort used in this thesis (described below) were used. This notes review was part of a larger (Cancer, Care and Comorbidity) study, also led by Sarfati (Chamberlain, Sarfati et al. In press; Gurney, Sarfati et al. In press; Swart, Sarfati et al. in press). All eligible Māori patients diagnosed with rectal (ICD-10 C20), liver (C22) or stomach (C16) cancers and who had been treated in the North Island of New Zealand, along with a randomly sampled equal number of non-Māori patients were included in the notes review. Clinical data were abstracted by a trained oncology nurse from patients' medical records from public hospitals and, where possible, from medical records held by physicians practicing in private using a standardised study pro-forma. Data were double entered into an electronic database. Data were collected on a range of pre-specified chronic conditions, specifically:

- *Cardiovascular disease*: angina, hypertension, previous myocardial infarction, arrhythmias, valvular disease, congestive heart failure, previous pulmonary embolism, peripheral vascular disease and other cardiovascular diseases.

- *Respiratory disease*: mild chronic pulmonary disease; moderate to severe chronic pulmonary disease, other respiratory disease
- *Haematological conditions*: iron deficiency anaemia; other deficiency anaemias; coagulopathies; other haematological diseases.
- *Gastrointestinal conditions*: peptic ulcer disease, gastrointestinal bleeding, inflammatory bowel disease, mild liver disease, moderate/severe liver disease, other gastrointestinal conditions.
- *Neurological conditions*: cerebrovascular disease (stroke/ transient ischaemic attacks), hemiplegia/ paraplegia, dementia, multiple sclerosis, other neurological conditions.
- *Endocrine conditions*: diabetes, diabetes with end organ damage, hypothyroidism, other endocrine conditions.
- *Malignancies*: Leukaemia, lymphoma, solid malignant tumours, metastatic tumours.
- *Mental health conditions*: alcohol dependence/ abuse, other substance dependence/ abuse, major depression, anxiety disorder, bipolar disease, schizophrenia, other major psychiatric conditions.
- *Other conditions*: connective tissues diseases, mild renal disease, moderate/severe renal disease, AIDS, weight loss, and other miscellaneous conditions.

## ***Subjects***

In order to develop and validate comorbidity indices, separate development and validation cohorts were required. The development cohorts were used to initially explore the data and to develop the indices. The validation cohorts provided a population external to that used in the development of the indices to assess index performance.

### **Development cohort**

Because the impact of comorbidity may vary depending on cancer site and underlying prognosis, the development cohort included cancers with different characteristics in relation to these factors. Patients who had been diagnosed with colon (C18-19), rectal (C20), uterine (C54), ovarian (C56), liver (C22), stomach (C16), female breast (C50), kidney (C64) or bladder (C67) cancer between 1 July 2006 and 30 June 2008 were identified from the NZ Cancer Registry. Patients were excluded if they were diagnosed with carcinoma-in-situ, were aged under 25 years at diagnosis, normally resided

outside New Zealand, had a previous diagnosis with the same cancer or were diagnosed at post-mortem.

Eligibility criteria for development cohort:

- Newly diagnosed colon (C18-19), rectal (C20), uterine (C54), ovarian (C56), liver (C22), stomach (C16), female breast (C50), kidney (C64) and bladder (C67) cancers. Carcinoma-in-situ will be excluded.
- Cancers registered between 1 July 2006 and 30 June 2008.
- Aged 25 years or over at diagnosis.
- Normally resident in New Zealand.
- No previous diagnosis of the same cancer.
- Diagnosis made prior to death or post-mortem.

The NZ Cancer Registry data were linked to mortality data, routine hospitalisation data (NMDS) and community pharmaceutical data.

Patients in the development cohort were followed up for mortality until **31 Dec 2009**.

## **Validation cohort**

The validation cohort was defined using the same inclusion and exclusion criteria as the development cohort except that it included patients diagnosed from **1 July 2008 until 31 Dec 2009**; followed up for mortality until **31 Dec 2010**.

## ***Variables used in study analyses***

### **Comorbidity**

Comorbidity was measured in various ways and was the focus of the substantive analyses. Details of the variables involved will be provided in the relevant sections below.

## Demographic variables

**Age** at diagnosis: Calculated from date of birth and date of diagnosis. Because there was a non-linear relationship between age and both all-cause and non-cancer survival, age was generally categorised into four categories; 25-49 yr; 50-64 yr; 65-74 yr and 75+ yr.

**Sex:** Recorded in NHI database: male or female.

**Ethnicity:** Ethnicity was defined as Māori or non-Māori. The Cancer Register uses an 'ever-Māori' approach which classifies an individual as being Māori if they have been identified as Māori on any previous health record (Ministry of Health 2010). An individual's ethnicity is updated when the NHI data are updated which occurs whenever an individual is admitted to hospital or attends an outpatient clinic. For this reason, the ethnicity for a given individual will be the ethnicity at the time the data were extracted from the database, rather than the ethnicity recorded at diagnosis. While the latter would have been preferable, it is not possible to track changes in ethnic classification after diagnosis using NZ Cancer Registry data. Patients whose ethnicity was not recorded in the NZ Cancer Registry were assumed to be non- Māori.

## Cancer-related variables

**Cancer site:** Data on cancer site were obtained from the Cancer Registry for all newly diagnosed patients in the time periods given above. Patients identified with colon (C18-19), rectal (C20), uterine (C54), ovarian (C56), liver (C22), stomach (C16), female breast (C50), kidney (C64) and bladder (C67) cancers were included.

For most analyses these cancer types were collapsed into five site categories: colorectal (colon and rectal); female breast; gynaecological (uterine and ovarian); upper gastrointestinal (liver and stomach) and urological (kidney and bladder).

**Cancer date of diagnosis:** The date of diagnosis recorded on the NZ Cancer Register is the date the cancer is confirmed pathologically so may differ slightly from dates in hospital notes. If a hospital admission had occurred for the specified cancer within three months prior to the NZ Cancer Registry recorded date of diagnosis, or if one of a list of specified cancer-related treatment procedures had occurred within seven days of the NZ Cancer Registry date of diagnosis (if the cancer diagnosis was

not specified) then the earlier of these dates was taken as date of diagnosis. If hospital admissions for the cancer in question were identified more than three months prior to the NZ Cancer Registry recorded date of diagnosis, patients were excluded from the study because it was not possible to rule out the possibility that such an admission was indicative of a previous diagnosis of the same cancer.

<i>Date of Diagnosis</i>	The earliest of: <ul style="list-style-type: none"><li>• Date of diagnosis recorded on the NZ Cancer Register <b>or</b></li><li>• Hospitalisation for specified cancer within three months of date of diagnosis recorded on NZCR <b>or</b></li><li>• Date of relevant cancer-related procedure (without cancer diagnosis specified) within seven days prior to NZCR date of diagnosis.</li></ul>
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**Cancer stage/ extent of disease:** Extent of disease on the Cancer Registry is assigned according to the SEER summary staging system based on any information obtained up to four months after the date of diagnosis (American Joint Committee on Cancer 2009). The SEER system classifies extent of disease as local, regional (regional extension to adjacent tissue or to lymph nodes) or distant. The quality and completeness of extent of disease data tends to be (cancer) site specific (Gurney, Sarfati et al. 2013). Those without stage recorded on the NZ Cancer Registry were included in a separate 'missing' category. While extent of disease and stage of disease at diagnosis are not completely synonymous, these terms are used interchangeably in this thesis.

## **Mortality variables**

Three mortality (and survival) outcomes were used in this study; cancer-specific death, non-cancer death and all-cause death. For this purpose, each death was assigned as either due to cancer or due to other causes. Cancer-specific deaths were all those with an underlying cause of death identified as being caused by any cancer (any ICD 10 'C' code).

If no mortality records were identified for an individual in the follow-up period, that person was assumed to be still living.

## **Section 2: Use of hospitalisation data to measure comorbidity**

This section describes:

1. The methods used in validating New Zealand administrative hospitalisation data for measuring comorbidity. As mentioned previously, this validation exercise was carried out very early in the PhD process to ensure that routinely collected hospitalisation data in New Zealand were adequate to meet the aims of this thesis. For this reason, the cohorts used were not the same as the main study cohorts used for the remainder of the thesis but those from an earlier study (Sarfati, Hill et al. 2009; Hill, Sarfati et al. 2010).
2. The later process (using the main study cohorts) in which important comorbid conditions were identified from routine hospitalisation data and categorised for this study.
3. The approach used to develop and validate site-specific comorbidity indices to be used as part of the optimised 'gold standard' against which the simplified index could be compared.

### ***Validation of comorbidity identified using administrative hospitalisation data***

This validation aimed to assess how well data on comorbidity were captured in the NMDS by comparing detailed comorbidity data extracted by a physician from hospital records of patients diagnosed with colon cancer between 1996 and 2003, with routinely collected hospitalisation data from these same patients (see under Data sources/ Hospital notes review).

NMDS data were obtained from the (then) New Zealand Health Information Service on the cohort specified above. Admission for surgical resection of colon cancer was considered the index admission. Where a patient did not receive surgical resection, the first hospital admission with colon cancer as primary diagnosis was considered the index admission. Those without such an admission were excluded from the validation exercise.

As discussed in the last chapter, one of the problems with using administrative data to assess comorbidity is deciding on an optimal comorbidity ascertainment lookback period. Shorter periods may be more likely to identify currently active health issues, while longer periods may be more likely to identify all important comorbidity (Preen, Holman et al. 2006). Two lookback periods were assessed: 1 and 8 years, 8 years being the longest available time (for NMDS hospitalisation data) for the earliest cancer registrations.

Both the principal and secondary diagnoses fields were used to identify comorbid conditions from the administrative dataset. For the purposes of this validation exercise, the Deyo coding algorithm, (Deyo, Cherkin et al. 1992) which provides a method of translating the Charlson index for use on administrative data using ICD 9 coding, was used. The algorithm was modified to take account of the fact that data were collected on additional conditions to those included in the Charlson Index. These are listed in Table 11. Because it can be difficult to differentiate between pre-existing conditions and complications of treatment, some conditions were only included in the definition of comorbidity if they were listed prior to the index admission.

**Table 11: Diagnostic codes used for mapping in NMDS validation exercise**

Diagnostic category	ICD-9 codes
Myocardial infarction	410.x, 412*
Congestive heart failure	428.x
Peripheral vascular disease	441.x*, 443.9*, 785.4*, V43.4*, procedure 38.48
Cerebrovascular disease	430-437.x, 438*
Dementia	290.x*
Chronic pulmonary disease	490-496*, 500-505*, 506.4*
Connective tissue disease	710.0-710.1*, 710.4*, 714.0-714.2*, 714.81*, 725*
GI ulcer disease	531.x-534.9*
Mild liver disease	571.2*, 571.4*, 571.5*, 571.6x*
Diabetes (mild to moderate)	250.0x-250.3x*, 250.7x*
Hemiplegia or paraplegia	342.x*, 344.1*
Moderate or severe renal disease	582.x*, 583.0-583.7*, 585*, 586*, 588.x*
Diabetes with end organ damage	250.4x-250.6x*

Any malignancy (except colon or rectal) including lymphoma or leukaemia	140.x-152.x*, 155.x-172.0*, 174.x-195.8*, 200.x-208.x*
Moderate or severe liver disease	572.2-572.8*, 456.0-456.21*
Metastatic solid tumour	196.x-199.1
AIDS	042.x-044.x
Angina <sup>‡</sup>	411.1*, 413.0*, 413.1*, 413.9*
Essential hypertension <sup>‡</sup>	401.x
Cardiac arrhythmias <sup>‡</sup>	426.x-427.x
Previous pulmonary embolism <sup>‡</sup>	415.1
Cardiac valve disease <sup>‡</sup>	394.x-397.0*, 424.0-424.3*
Inflammatory bowel disease <sup>‡</sup>	555.x*, 556.x*
Other neurological condition <sup>‡a</sup>	332.x-336.x*, 340.x*, 341.x*, 343.x*, 345.x*, 358.x*, 359.x*
Major psychiatric conditions <sup>‡b</sup> (with psychosis)	295.x*, 296.x*, 298.0*

\* included in definition of a comorbidity if they are listed either in the index or prior hospital discharge; other codes only included if they are recorded prior to index admission

<sup>‡</sup> not included as part of Charlson Comorbidity Index

<sup>a</sup> includes multiple sclerosis, Parkinson's disease, other abnormal movement disorders, epilepsy, spinocerebellar disease, anterior horn disease, other diseases of spinal cord, other demyelinating diseases of CNS, cerebral palsy, myoneural disorders, muscular dystrophies.

<sup>b</sup> includes schizophrenia, bipolar disease and depressive psychosis

## Analysis for the validation exercise

To calculate the maximum comorbidity from all data available, the total number and proportion of patients who were recorded with each condition either in the medical notes review, or in the administrative data combined (separately for 1 and 8 year lookback) were calculated. The proportion of these who had been identified in the notes, the administrative data or both were compared, and p-values calculated using McNemar's test to test whether the number of people with the condition differed significantly between the medical notes and administrative data.

The distribution of Charlson score using medical notes, and administrative data with 1 and 8 year lookback were calculated. The cross-source agreement for each condition as well as for the Charlson score (uncategorised) using the weighted kappa statistic with quadratic (Fleiss-Cohen) weights were compared (Fleiss and Cohen 1973). This statistic equals the intraclass correlation coefficient when comparing two 'observers'

(Streiner and Norman 2008) and provides a measure of reliability that adjusts for agreement that occurs by chance. Scores of <0.40 were used to suggest poor agreement, 0.40 to 0.74 to suggest moderate agreement and 0.75 or higher to suggest very good agreement, although these cut-offs (like any other) are arbitrary (de Groot, Beckerman et al. 2003; Streiner and Norman 2008).

The association of comorbidity and all-cause survival among this cohort was assessed using Cox proportional hazards regression models. A baseline model was fitted that included sex, age, and ethnicity, year of registration, stage, grade and site of disease. The fit of the baseline model was compared to various models that included comorbidity using the likelihood ratio test. For these models comorbidity was measured using Charlson categories or individual conditions. The conditions were selected on the basis that they had been previously shown to be related to survival from colon cancer in this cohort (Sarfati, Hill et al. 2009), and that there were a minimum of 10 cases within the cohort (these conditions were previous myocardial infarction, congestive heart failure, diabetes, chronic respiratory disease, renal disease, cardiac arrhythmias, non-cerebrovascular neurological conditions and peripheral vascular disease). Results from models that included comorbidity measured using data from medical notes and those using administrative data were compared.

Researchers have an interest in knowing how much of the 'true' confounding by comorbidity might be captured when adjusting for a misclassified measure such as that from routine administrative data. This was explored for the putative association of ethnicity with survival, and particularly how much of the association might be due to confounding/ mediation by comorbidity. We know that Māori experience poorer survival from colon cancer than non-Māori, and that some of this association is due to Māori carrying a higher burden of comorbidity than non-Māori (Hill, Sarfati et al. 2010). The hazard ratio for all-cause mortality of Māori compared with non-Māori was calculated having adjusted for sex, age, year of registration, stage, grade and site. Comorbidity was added to the model measured using the individual conditions specified above identified either in the notes, or in the administrative data to assess the extent to which each changed the underlying hazard ratio.

## ***Optimising the identification of comorbid conditions using hospitalisation data***

The results of this first validation exercise (presented in the next Chapter) suggested that it would be reasonable to use routine hospitalisation data to measure comorbidity among patients with cancer in New Zealand. The validation exercise was important to establish the general usefulness of the comorbidity data held within the routine New Zealand hospitalisation datasets but, through necessity, the hospitalisation data that were validated were somewhat historic (1996-2003) and the coding was ICD-9 rather than ICD-10. There was also no effort made to ensure that the coding algorithms used to identify conditions within the routine data were optimal.

The next step in the process was to use more recent hospitalisation data, and to optimise the identification of conditions in the data. The validation exercise had been largely based on the conditions identified as important by Charlson et al (Charlson, Pompei et al. 1987). Conditions were included in this index if they were found to be important in relation to mortality in a relatively small cohort of 559 general medical patients admitted to a single hospital. While the Charlson index has been used extensively to measure comorbidity among cancer patients, there has been little consideration as to whether the conditions that Charlson and colleagues identified in their general medical cohort nearly 30 years ago, are those that are most important for cancer patients today.

The aims of this part of this Section were to 1) optimize the identification of important chronic health conditions in the context of cancer using routinely collected ICD-10 coded data; 2) estimate the prevalence of these conditions among cancer patients within a range of cancer sites, and 3) investigate the impact of individual conditions on outcomes from cancer in terms of survival.

The development cohort was used for this aspect of the work. To reiterate, this consisted of all patients identified in the NZ Cancer Registry with newly diagnosed colon, rectal, breast, ovarian, uterine, stomach, liver, bladder or kidney cancers between 1 July 2006 and 30 June 2008; followed up until 31 Dec 2009.

The aim of this process was to identify all important concurrent chronic conditions among individuals with the specified cancers that were likely to have an impact on

function or length of life. For this reason, conditions that were likely to be acute, self-limiting and/or highly localised were not included. Gender-specific conditions other than co-morbid malignancies were also excluded.

Conditions which might be caused by the primary cancer of interest or its treatment were excluded and for each cancer site, any codes relating to malignancy at that site were omitted. For all patients, malignancies of brain, liver, bone or lung were also excluded because of the possibility that these were metastases due to the primary disease.

There were several steps involved in identifying all relevant conditions. First, all conditions included in the most commonly used (cancer-related) comorbidity indices (Charlson, ACE-27 and Elixhauser indices) were included (Charlson, Pompei et al. 1987; Elixhauser, Steiner et al. 1998; Piccirillo, Costas et al. 2003; Piccirillo, Tierney et al. 2004). Conditions were also included if they were identified in at least two of seven other validated comorbidity indices previously used in the context of cancer (Satariano and Ragland 1994; Yancik, Havlik et al. 1996; Fleming, Rastogi et al. 1999; Fleming, Pearce et al. 2003; Tammemagi, Neslund-Dudas et al. 2003; Colinet, Jacot et al. 2005; Holman, Preen et al. 2005; Tammemagi, Nerenz et al. 2005). A Table showing conditions included in each of these is presented in Appendix 1. Next, three cancer clinicians (two cancer surgeons and a medical oncologist) reviewed the full list of conditions identified above, and a list of conditions included in ICD-10-AM (at the three digit level), and some additional relevant conditions were identified.

The next step was to ensure accurate coding of each condition. The ICD-10 codes used by Quan et al (Quan, Sundararajan et al. 2005) to code conditions included in the Charlson and Elixhauser indices were used initially. These codes were reviewed by the author of this thesis (a physician), a medical oncologist and a data analyst. As a result, some coding categories were amended, for example:

1. Additional conditions were included in some categories, e.g. J98.2-4 (interstitial emphysema, compensatory emphysema and other disorders of the lung) were added to the 'Chronic pulmonary disease' category.
2. Conditions were removed from a specified category, e.g. R56 (convulsions, not elsewhere classified) was removed from 'Other neurological conditions' because convulsions do not necessarily signify a chronic neurological condition.
3. 'Diseases classified elsewhere' were removed from all categories to avoid double counting of conditions.

4. Categories were expanded or changed, e.g. 'Peptic ulcer disease' was expanded to include all significant upper gastrointestinal disease.
5. Some conditions were shifted to new categories, e.g. E10.6 and 10.8 (Type 1 diabetes mellitus with other specified complication and with unspecified complication) were moved from 'Diabetes: uncomplicated' to 'Diabetes: with complications'. Patients who were identified with complicated diabetes were excluded from the uncomplicated diabetes category.
6. E87 (disorders of fluid, electrolyte and acid-base balance), which has been found in a number of studies to be associated with poor outcomes, was removed from Endocrine conditions. This is because this is a vague categorization of a condition which may be acute, and occurs frequently when a patient is unstable medically. It may be therefore more accurately conceived of as an indicator rather than a cause of poor outcome (in this context).

Appendix 2 shows the final list of 50 condition categories, and their ICD-10-AM codes.

For each patient, an index hospitalisation was identified. This was the first admission that occurred at or within four weeks of the date of diagnosis with the index cancer as the primary diagnosis. Where no such admission was identifiable, the date of diagnosis of cancer was used as the index date. A five-year lookback period from the index admission was used to identify chronic conditions. The results of the (earlier) validation exercise suggested that a one-year lookback period for hospitalisation data resulted in a lower yield of comorbid conditions and was less similar to data extracted directly from medical records than the longer period (Sarfati, Hill et al. 2010). A Charlson score was calculated for each patient using the ICD coding algorithm of Quan et al (2005), and patients were categorised into those with scores of 0, 1, 2 and 3+.

Some conditions were only included if they were identified prior to the diagnosis of cancer or index admission to exclude complications of the primary disease or its treatment. In other words, if these conditions were identified only in the index admission of an individual, they were not included as comorbid conditions for that individual, however if they were identified in any admission prior to the index date, they were included. These were myocardial infarction, congestive heart failure, pulmonary embolism, anxiety and behavioural disorders, anaemias, hypertension and cardiac arrhythmias.

Crude and age/sex standardised proportions of sex, age, ethnicity, stage and Charlson score categories were calculated for each cancer site group, and for all sites combined. The survival impact of individual conditions was estimated using Cox proportional regression models for each site category, and for all sites combined for all-cause and non-cancer mortality. Cox regression models were fitted to estimate crude hazard ratios, and hazard ratios adjusted for age and stage; or for age, stage and site (for all cancers combined). For non-cancer mortality, those who died of cancer causes were censored on the date of death. For all analyses, those who were alive at the end of follow up were censored at that time.

The proportionality assumption was tested visually using Kaplan Meier curves, and by checking for interactions between each variable in the age and stage adjusted models with log (survival time). If a covariate was significantly associated with time (or log (time) in this case), this indicated that the proportionality criterion had been violated (Therneau and Grambsch 2000). In most cases, the proportionality assumption was met. The most common violation was for stage in the all-cause mortality models. The impact of this was assessed by re-running the models stratified by stage. Stratifying by stage means that stage is not included in the model as a covariate itself, but is adjusted for by stratification, with the different underlying hazard ratios estimated for each stage pooled according to the proportion of patients within each stage group (a type of standardisation) (Kleinbaum and Klein 2012). This approach resulted in a negligible effect on the estimated hazard ratios for the comorbid conditions, so the results of the unstratified models are presented here.

## ***Developing hospitalisation-based comorbidity indices***

The final step in this Section was to develop and validate site-specific hospitalisation comorbidity indices. To reiterate, the purpose of these indices were to act as 'gold standard' indices. As such, these measures ideally needed to: be site specific, include all important conditions and exclude those that are complications of care or of the primary disease, take account of the severity of each condition and consider the impact of clustering of conditions. These factors were addressed as follows:

1. The indices were based on **specific site** groups: colorectal; breast; gynaecological (ovary and uterine); upper gastrointestinal (liver and stomach); and urological (kidney and bladder).

2. There was an extensive process to ensure **all important conditions** were identified, as detailed above. All conditions with a (site-specific) prevalence of >0.5% were included in the final indices and are shown in Chapter 7: 'Results'. Conditions that may have been **complications** of the primary disease or its treatment were excluded if they were identified only at the time of diagnosis, but included if they were identified prior to diagnosis.
3. The **relative severity** of conditions was accounted for by weighting each condition by its impact on non-cancer death (see below). Non-cancer mortality was chosen as the outcome of interest because both cancer and all-cause mortality are heavily influenced by the prognosis of the cancer itself and therefore will be less sensitive to the impacts of other conditions particularly when the cancer prognosis is poor (Fleming, Rastogi et al. 1999; Klabunde, Potosky et al. 2000; Klabunde, Warren et al. 2002; Fleming, Pearce et al. 2003).
4. The impact of **clustering of the conditions** was assessed by evaluating versions of the indices that incorporated interactions between common conditions. The performance of indices that were constructed using weights from models that simply adjusted for age, sex and stage, were compared to those that additionally adjusted for all other conditions; or for all other conditions plus all two-way interactions between conditions that were independently associated with non-cancer mortality and where the prevalence of the interaction was greater than 0.5%. Details of this process are provided in Appendix 4, but the inclusion of weights from the more complex models had little impact on index performance, so the final indices reported here do not include them.

## Determining weights for conditions

For each condition, parameter estimates from the site-specific age- and stage-adjusted models using non-cancer mortality as the outcome were used as weights in the comorbidity indices. Where there were fewer than five non-cancer deaths within a particular site among patients with a given comorbid condition, the parameter estimates from the all-site model for that condition were substituted, adjusted for the mean parameter estimates of the conditions that had been included for the specified site as in the formula below:

$$w_x = (m^{ss} \times w^{as})/m^{as}$$

Where  $w$  =substituted weight for condition  $x$ ;  $m^{SS}$  = mean site specific parameter estimates for all (non-substituted) conditions included in that site;  $w^{AS}$  = all-site condition weight for condition  $x$ ;  $m^{AS}$  =mean parameter estimate for (site specific non- substituted) conditions from all-sites models.

For example, for breast cancer it was not possible to calculate a weight for major psychiatric disorders because only four women with both breast cancer and a major psychiatric condition died of non-cancer causes in the follow-up period. In this case, the mean parameter estimate for conditions with sufficient non-cancer deaths to allow the calculation of site-specific weights in the breast cancer cohort ( $m^{SS}$ ) was 0.845. The mean parameter estimate for these same conditions from the all-site model ( $m^{AS}$ ) was 0.814, and the parameter estimate for major psychiatric disorders from the all-site model ( $w^{AS}$ ) was 0.786. In other words, 0.845 and 0.814 are measures of the impact of (a common set of) major conditions on non-cancer mortality for those with breast cancer and all (included) cancer sites respectively. The substituted weight for major psychiatric conditions is scaled to account for the difference in impact of conditions on breast cancer compared with all-sites generally (using the aforementioned measures of impact of chronic conditions generally on these two groups of patients). The substituted weight was therefore  $(0.845 \times 0.786) / 0.814 = 0.816$ .

The index scores were calculated for each patient by adding together all parameter estimates (i.e. the log hazard ratios) for all comorbid conditions recorded for that patient. These scores are henceforth referred to as C3 index scores (because they were developed by the author as part of the Cancer, Care and Comorbidity or C3 studies). Scores were treated as continuous except for some descriptive analyses where they were categorised into four categories: 0 (raw scores  $\leq 0$ ); 1 (raw scores  $>0$  and  $\leq 1$ ); 2 (raw scores  $>1$  and  $\leq 2$ ); 3 ( raw scores  $>2$ ).

Charlson index scores were calculated using the coding by Quan et al (Quan, Sundararajan et al. 2005) and the weights specified by Charlson et al (Charlson, Pompei et al. 1987) excluding cancer-related codes for all sites.

For colorectal and breast cancers NCI (site specific) indices were also calculated using the weights specified by Klabunde et al (Klabunde, Legler et al. 2007). Site-specific weights were not provided for our other cancer sites of interest. For the Charlson and NCI indices congestive heart failure and myocardial infarction were only included if they were recorded prior to the index admission. For each of these indices the score was

calculated by summing the weights of conditions that were present for a given individual. Scores were treated as continuous except for some descriptive analyses where they were categorised into scores of 0, 1, 2 and 3+.

## ***Validation of hospitalisation-based indices***

In order to test for **concurrent validity**, Spearman's rank correlation coefficient was calculated to compare the C3 indices with the Charlson index in both the *development* and *validation* cohorts. The Spearman's rank correlation measures the strength of association between two ranked variables. It measures the extent to which when one variable, in this case, the Charlson index score, increases or decreases, so does the other (C3 index score). A correlation coefficient can range between -1 and 1, with 0 indicating no relationship between the variables, and -1 and 1 indicating a perfect negative and positive correlation of ranked values respectively. In this case, the Charlson index is itself not a perfect measure of comorbidity, so for this reason a correlation in the range of 0.4-0.8 was considered optimal (Streiner and Norman 2008). If the correlation coefficients were greater than 0.8, the implication would be that the new measure is essentially measuring the underlying construct in the same way as the comparison measure (in this case, the Charlson index), and therefore adds little. Assuming that the Charlson index is accurately measuring the underlying construct of comorbidity to some degree, if the correlation coefficient is <0.4, this would suggest that the new C3 measure may not be accurately measuring this construct.

The ability of each comorbidity index to **discriminate** between those who died and those who did not in the *validation cohort* was compared using a rank correlation measure of goodness of fit, *c*, which is the proportion of pairs of observations that are concordant, allowing for tied observations (Hosmer and Lemeshow 2000). This is the equivalent of calculating a Receiver Operating Curve (ROC) for the outcome (died/ did not die) based on the predicted probabilities from the logistic regression models. Two sets of logistic regression models were fitted for each site; one for 1-year all-cause mortality and the other for 1-year non-cancer mortality. Within each of these sets, *c*-statistics for baseline models which included age, stage and sex (for relevant cancer sites) were calculated, then re-calculated after the addition of the site-specific C3; NCI or Charlson indices. *C*-statistics for models that included each measure of comorbidity were compared to the baseline models and to each other. Confidence intervals for the *c*-index were calculated using bootstrap estimation processes: for each cancer site, the

c-index was calculated in each of 10,000 bootstrap samples (sampled with replacement from the original site-specific dataset, using PROC SURVEYSELECT) for both outcomes and for each of the models.

The same 10,000 bootstrap samples were used for all models for each cancer site, to allow estimation of differences in model performance between the comorbidity indices. Differences between the models were calculated within each bootstrap sample, and the empirical distribution of differences was used to calculate the median difference and 95% confidence interval. The reported c-indices in the results represent the median of the bootstrapped c-indices, with an empirical 95% confidence interval (i.e. the 2.5th and 97.5th percentile of the bootstrapped c-indices). The differences in c-indices by comorbidity measure were also calculated in this manner. In some bootstrap samples, particularly for non-cancer deaths, the logistic regression model failed to converge (due to quasi-complete separation, driven by small absolute numbers of deaths appearing in a particular bootstrap sample). Medians and confidence intervals were calculated based only on bootstrap iterations that successfully converged. The bootstrapping was carried out by Dr James Stanley (biostatistician) at the request of the author (see under Statement of Participation).

Finally, to assess for **goodness of fit** in the *validation cohort*, baseline logistic regression models of one-year (non-cancer and all-cause) mortality which included age, sex and stage were compared with models that included each of the measures of comorbidity, using the Akaike information criterion (AIC). The AIC uses the log likelihood and number of parameters in each model to assess model fit. The absolute value of the AIC is not relevant but lower suggests a better model, with an absolute difference of 10 between competing models being considered potentially important (Hosmer and Lemeshow 2000).

# **Section 3: Use of community pharmaceutical data to measure comorbidity**

Community pharmaceutical data are collected on all subsidised medications dispensed from community pharmacies nationally. Data similar to these have been used to calculate the CDS/RxRisk indices in US and Australia (Von Korff, Wagner et al. 1992; Clark, Von Korff et al. 1995; Fishman, Goodman et al. 2003; Lu, Barratt et al. 2011), but New Zealand data have not been previously used for this purpose. This section describes:

1. The identification of important comorbid conditions from community pharmaceutical data.
2. The validation of NZ pharmaceutical data for the purpose of developing a comorbidity index.
3. The approach used to develop and validate pharmaceutical-based comorbidity indices to be used as part of the optimised 'gold standard' against which the simplified index could be compared.

## ***Identification of comorbid conditions from Pharmaceutical database***

Each medication in the pharmaceutical database is categorised into three hierarchical levels based on their primary indication for use with increasing detail provided at each level. For example, Omeprazole (medication to treat peptic ulcers) was categorised in 'Alimentary Tract and Metabolism' (level 1), and sub-classified into 'Antiulcerants' (level 2) and then 'Proton Pump Inhibitors' (level 3). Level 3 categories were used to identify the condition for which each medication was most likely to be used.

In order to summarise all possible conditions into a feasible summary, the list of conditions included in a previously validated medication-based comorbidity index, RxRisk (Sloan, Sales et al. 2003; Johnson, El-Serag et al. 2006) was used. This initial

list of 45 conditions was amended with input from cancer clinicians and an oncology pharmacist, as follows:

1. Conditions were excluded if they were likely to be acute, self-limiting and/or likely to relate to highly localised conditions. For example, pain and inflammation, and allergies were excluded.
2. Other categories were excluded because they required non-pharmaceutical data that were not available e.g. data on colostomies and urostomies were not included in the Pharmac/ Ministry of Health pharmaceutical database, but were required to identify some conditions in the RxRisk score so were excluded.
3. Some categories were re-grouped. For example, in the original list there were five categories related to cardiovascular disease/ hypertension. These were 1) Arrhythmias, 2) CHF/Hypertension; 3) Hypertension; 4) IHD/Angina and 5) IHD/Hypertension. Because of the considerable overlap between these categories and the medications used for them, these were simplified into 1) Arrhythmias; 2) CHF; 3) IHD/Hypertension; and 4) IHD/Angina.
4. Some additional categories were added: Anaemia, Peripheral Vascular Disease, Rheumatoid Arthritis, and Multiple Sclerosis.

The final list of conditions and the drug classes included are provided in Appendix 3. All medications dispensed for individuals in the period starting twelve months prior to the date of diagnosis, and finishing three months prior to the date of diagnosis were identified. A shorter period than the hospitalisation data was used because the quality of the pharmaceutical data had improved substantially by the beginning of 2006 (with over 90% of data including NHIs), so a longer lookback period was not possible for the earliest patients in the development cohorts. Most prescriptions are filled for a three month period, therefore twelve months was considered sufficient to identify relevant medications prescribed for current active conditions in most cases. Medications in the three months prior to diagnosis were avoided to ensure medications dispensed for the treatment of the cancer or its complications were not included. Medications for conditions that might be caused by the cancer were excluded, specifically medications for anaemia for those with colorectal or upper gastrointestinal cancers, and medications for gastric acid disorders from those with upper gastrointestinal cancers.

The prevalence of each condition for each site and for all cancers combined was calculated. Conditions were excluded from further analysis where the prevalence was <0.5% in the all-site cohort, or there were fewer than five non-cancer deaths over the

entire cohort during the follow-up period. The final list of 19 conditions and their relevant drug classes are included in Appendix 3.

To assess the impact of each condition on survival, Cox proportional hazards models of all-cause and non-cancer mortality were fitted for each condition within each site group, and for all cancers combined. Crude models, and models adjusted for age and stage were fitted for each site, and for age, stage and site for all sites combined. For non-cancer mortality, patients who died from cancer causes were censored at that date. In all cases, those who were alive at the end of follow up were censored at this time. The proportionality assumption was tested visually using Kaplan Meier curves, and by checking for interactions between each variable in the age and stage adjusted models with  $\log(\text{survival time})$ .

## ***Comparison of pharmaceutical data with hospital notes review data***

Community-dispensed medications are most commonly prescribed in the primary care context, and therefore ideally these data would be validated against primary care data. However data from primary care services were not available. It is possible to compare conditions identified from community pharmaceutical data to those identified through hospital notes review in the same way as was done for administratively collected hospitalisation data. While it is reasonable to expect that diagnoses recorded on routine collected hospitalisation data are the same or similar to the ones found using manual hospital notes review, the same is not necessarily true of comorbidities identified through pharmaceutical data. These are likely to differ from conditions identified in hospital notes review for several reasons. Some conditions may not require specific medication but be recorded in hospital notes (such as renal disease), other conditions may be treated with medication but not be considered of sufficient severity or longevity to be recorded in hospital notes (for example, low dose antidepressants or anxiolytics prescribed for acutely stressful life events may not result in a diagnosis of depression or anxiety disorder). Not all individuals with a specific complaint will require medication (for example some patients with diabetes or hypertension manage their condition with lifestyle modification), and some medications may be used for more than one condition (for example, some medications can be used for hypertension and angina).

Despite these differences, it is reasonable to assume there should be some correlation between conditions identified through hospital note review, and those identified through use of community pharmaceutical data. It may also be helpful to understand the extent to which these data sources vary in their ability to identify specific conditions, noting that neither approach can be considered gold standard. However, for the reasons given here, I have referred to this process as a data ‘comparison’ rather than data ‘validation’.

In order to carry out this comparison, data from the three cohorts of patients for which we had hospital notes review data available were combined (see under Data sources, subjects and variables used/Hospital notes review). There was a total of 719 patients (194 rectal, 336 stomach and 189 liver cancer patients), and ten conditions which were recorded in both data sources (Table 12).

**Table 12: Categories of comorbid conditions from clinical notes and PBCI categories**

Clinical notes	PBCI category	Comments
Angina	IHD/angina	Some medications in IHD/hypertension also relevant.
Hypertension	IHD/hypertension	Some medications in IHD/angina also relevant.
Arrhythmias	Arrhythmias	Some medications in other IHD categories may also be relevant.
CHF	CHF	
Any respiratory disease	Reactive respiratory disease	Not exact match
Peptic ulcer disease	Peptic ulcer disease	Likely to be underestimate in hospitalisation data.
Diabetes	Diabetes	
Anxiety disorder	Anxiety	Likely to be underestimate in hospital data.
Depression	Depression	Overlap with other mental health categories esp anxiety.
Bipolar + schizophrenia + other major psychiatric disorder	Antipsychotics	Pharmaceutical data will only identify those on recent medication, therefore likely to underestimate lifetime prevalence.

## Analysis for the comparison exercise

P-values were calculated using McNemar’s test to test whether the number of people with the condition differed significantly between the medical notes and the pharmaceutical data. The cross-source agreement was measured for each condition using kappa statistics. This provides a measure of ‘reliability’ which adjusts for

agreement between the two sources that occurs by chance. For the reasons given above, high kappa scores were not expected for several of the conditions, but in general scores  $<0.40$  were considered to show poor agreement,  $0.40-0.74$  moderate agreement and  $0.75$  or higher to suggest very good agreement.

## ***Developing pharmaceutical-based comorbidity indices***

As for the hospitalisation-based indices, the aim was to develop comorbidity indices that combined the impact of multiple conditions into a single measure, this time using conditions identified from the pharmaceutical database. This was for two reasons: 1) the usefulness of pharmaceutical data for measuring comorbidity in the context of cancer could be directly assessed, and 2) developing pharmaceutical measures meant that the two sources of data for assessing comorbidity could potentially be used together to produce a 'gold-standard' measure of comorbidity.

As for the hospitalisation-based indices, conditions were first weighted according to their impact on non-cancer mortality. For all conditions, except for anaemia and gastric acid disorders, all-cancer sites combined were used for the estimation of weights because using site-specific weights made very little difference to the results. For estimating anaemia and gastric acid disorder weights, patients with upper gastrointestinal or colorectal cancers were excluded because these medications may reflect symptoms relating to early (undiagnosed) cancer.

The parameter estimates (i.e. the log hazard ratios) from the Cox regression models for non-cancer mortality adjusted for age, stage and site were used as weights for each condition in the pharmaceutical-based comorbidity index. The index scores were calculated for each patient by summing all the weights for all comorbid condition recorded for that patient. The index was referred to as the PBCI (Pharmaceutical-based Comorbidity Index) score, and these were treated as continuous in subsequent analyses.

## ***Validation of pharmaceutical-based comorbidity indices***

In order to test for **concurrent** validity, the Spearman's rank correlation coefficient was calculated to compare the PBCI with the Charlson Index in the *development* cohort. Because the Charlson index itself is not a perfect measure of comorbidity, and is measuring a somewhat different construct (comorbidity recorded in hospitalisation episodes), correlations in the range of 0.4-0.8, indicating moderate correlation, were

considered ideal (Streiner and Norman 2008). However, we might expect estimates at the lower end of that range due to the slightly different data sources and constructs being measured.

Next the performance of models including the different measures of comorbidity was compared using the *validation* cohort to assess the ability of the PBCI to **discriminate** between those who died and those who did not, and to assess model **goodness of fit**. Two sets of logistic regression models were fitted: one for 1-year all-cause deaths and another for 1-year non-cancer deaths. Within each of these sets, the c-statistic and Akaike information criterion (AIC) were calculated for the baseline models, which included age, stage and sex (for relevant cancer sites). These were then re-calculated for each model after the addition of (each of) PBCI, Charlson and C3 indices, and PBCI in combination with each of the other indices. Confidence intervals for the c-index were calculated using bootstrap estimation processes as detailed previously (and also carried out by James Stanley).

To assess whether the PBCI and C3 indices could reasonably be combined in a single model to provide (arguably) the 'gold standard' measure of comorbidity using administrative data the degree of **collinearity** between these indices was assessed. Collinearity is where there are predictors in a model that are very strongly correlated with each other, which results in a reduction in the ability of regression models to estimate reliable regression coefficients. Collinearity is measured using 'variance inflation factors' (VIF), with  $VIF > 10$  commonly being considered problematic (O'Brien 2007; Steyerberg, Vickers et al. 2010). In order to test for collinearity between PBCI and C3, linear regression models for each cancer site in the development cohorts were fitted using survival time as the outcome variable, and continuous variables for age, and all paired combinations of C3, PBCI, and Charlson, as well as all three together. In all cases the VIFs were less than 5 indicating that collinearity was not a major issue for these indices, and that they could, therefore be used simultaneously in single models.

# **Section 4: Development of simplified comorbidity index, and comparison with other indices**

The Charlson comorbidity index is the most popular measure of comorbidity used. One of the reasons for its popularity is likely to be its simplicity. For this reason, one of the aims of this thesis is to develop a single, simple index of comorbidity for use with cancer populations that is based on administrative data. The focus of this section is the hospitalisation data, because this is the most commonly used and most validated source of data to measure comorbidity. This section identifies the process for developing the simplified indices, then provides a comparison of these indices with the Charlson, C3 and PBCI indices.

## ***Development of simplified indices***

It was not clear how much information would be lost by simplifying the indices. For this reason, three alternative simplified indices were developed and assessed. In all cases, conditions that may have been caused by a particular primary cancer were excluded from patients with that cancer as was done for all previous indices (for example, liver and renal disease were excluded from upper GI and urological cohorts respectively):

1. The first (and 'least' simple) was an index in which all 42 conditions used in the C3 indices were included but the weights were now standardised across sites; parameter estimates from the all-site models adjusted for age, site and stage were used. The rationale for this index with simplified non-site specific weighting was that, in theory, the inclusion of important conditions is considerably more important than their specific weighting (Streiner and Norman 2008). For this reason, the use of all-site, rather than site-specific weights would be unlikely to result in the loss of much information, but would be simpler to operationalise.
2. The second index also used all-site weights as above, but excluded conditions that had adjusted (for age, site and stage) hazard ratios less than 1.2 for non-cancer death, or had a prevalence less than 2% in the all-cancer cohort. The rationale for this was that the excluded conditions would either have almost no weight attached to them, or would be sufficiently uncommon that they would be

unlikely to have an effect at the group level. This process reduced the number of included conditions to 19 from the original 50. These were:

- i. Anaemia
  - ii. Angina
  - iii. Cardiac arrhythmia
  - iv. Cardiac valve disease
  - v. Cerebrovascular disease
  - vi. Congestive heart failure
  - vii. Coagulopathies and blood disorders
  - viii. Chronic respiratory disease
  - ix. Diabetes with complications
  - x. Eye disorders with major effect on vision
  - xi. Hypertension
  - xii. Inflammatory bowel disorders
  - xiii. Liver disorders
  - xiv. Metabolic disorders
  - xv. Previous myocardial infarction
  - xvi. Obesity
  - xvii. Other cardiac conditions
  - xviii. Peripheral vascular disease
  - xix. Renal disease
3. The third index included the same conditions as the second index, but the weights were further simplified. Each parameter estimate was divided by the smallest beta coefficient (or the parameter estimate of the condition with the weakest association with non-cancer death), and then rounded to the nearest integer. Of those included, the condition with the weakest association on non-cancer mortality was angina (HR=1.7; 1.3-2.2; parameter estimate=0.51). In this way, a condition with a weight of 2, had (approximately) twice the impact on non-cancer mortality of angina (van Walraven, Austin et al. 2009).

## ***Comparison of simplified indices with other approaches***

Each of the simplified indices was compared with the following:

1. **Charlson Index.** This was to provide a validation index external to the indices developed in this thesis.
2. **Full site-specific C3 indices.** This provided the most detailed measure of comorbidity using hospitalisation data including site-specific weights.
3. **PBCI index.** This provided a measure of comorbidity using an alternative data source, pharmaceuticals.
4. **'Gold standard'** (C3 combined with PBCI). This provided arguably the 'best' measure of comorbidity included here, in that it provided measures that were site specific, included all important conditions, took account of the severity of conditions and their likely impact on the outcome of interest as well as using utilising more than one source of data.

## C-statistics and AICs

The first part of the comparison involved the same validation process detailed above under C3 and PBCI indices. In brief, c-statistics and AICs were calculated from logistic regression models using the validation cohort data fitted for 1-year all-cause, and non-cancer mortality for each site (adjusted for age, sex where relevant and stage) and for all sites combined (adjusted for age, sex, site and stage) with each of the indices included. Confidence intervals for the c-index were calculated using bootstrap estimation processes as detailed previously.

## Discrimination slopes and Integrated Discrimination Improvement (IDI)

The last part of the thesis involved comparing the performance of different approaches to measuring comorbidity. New(er) methods of assessing improvement in model performance in predicting outcomes have been recently suggested (Cook 2007; Pencina, D'Agostino et al. 2008; Steyerberg 2009; Steyerberg, Vickers et al. 2010). **Reclassification tables** and the resulting **net reclassification improvement (NRI)** assess the extent to which alternate models accurately classify individuals according to their risk of outcome (Cook 2007; Pencina, D'Agostino et al. 2008). Ideally, a better model will predict a higher risk category for an individual who ultimately experiences the outcome, and a lower one for an individual who does not. Reclassification tables require that there are *a priori* risk categories into which individuals can be grouped based on the probability of the outcome. For example, clinical prediction models can

be used to categorise patients into coronary heart disease (CHD) risk categories (low, 0-6%; moderate, 6-20% and high >20% 10 year risk of CHD) (Pencina, D'Agostino et al. 2008). The net reclassification improvement assesses the extent to which those who ultimately experienced the outcome move up in the risk categorisation and vice versa for those who did not experience the outcome.

This idea can be extended to one in which no *a priori* categories are necessary, resulting in a measure that has been named the **Integrated Discrimination Improvement (IDI)**. This is a measure of a 'new' model's ability to improve average (integrated) sensitivity without reducing the average (integrated) specificity compared to an 'older' model (Pencina, D'Agostino et al. 2008). In order to calculate an IDI, first the population being assessed is divided into those who experienced the outcome and those who did not. The mean *predicted* probability of the outcome is calculated for each of these from the model parameters, with the obvious expectation that the predicted probability of the outcome should be higher among those who eventually experience the outcome compared with those who do not. The difference between the two mean predicted probabilities of those who did and those who did not experience the outcome is referred to as the **discrimination slope** (Yates 1982). Where two (or more) models are being compared (in this case, to compare the validity difference measures of comorbidity), discrimination slopes can be calculated for each of them. The IDI is the difference between two slopes, for example, one from a 'newer' model, and one from an 'older /comparison' model. If the IDI is positive it shows that the newer model is better at accurately predicting whether individuals will or will not experience the outcome of interest compared with the older model (and vice versa). This process provides a measure jointly of the overall improvement in the sensitivity and the specificity of the model predictions (Pencina, D'Agostino et al. 2008).

First, box and whisker plots of mean *predicted* risk of 1-year all-cause and non-cancer death were calculated for those who did and did not experience these outcomes. Cox regression models were fitted for each site and for all sites combined for the validation cohort. As previously, site-specific models included age, sex (where relevant) and stage, and all-site models included site. Mean predicted risks were calculated for baseline models, and models that included Charlson, C3, PBCI, PBCI and C3 combined, and each of the simplified indices.

For each index, within each site and for both all-cause and non-cancer death, discrimination slopes were calculated by subtracting the mean predicted risk from

those who did not die from those who did die. From these IDIs were calculated for models that included each measure of comorbidity compared with baseline models; each new measure of comorbidity (C3, PBCI, gold standard and the simplified indices) compared with Charlson, and each simplified index compared with 'gold standard' using:

$$IDI = (pred_{died,new} - pred_{not\ died,\ new}) - (pred_{died,old} - pred_{not\ died,\ old})$$

$pred_{died,new}$ : mean predicted risk of 1-year mortality from models including the 'new' index among those who died.

$pred_{not\ died,new}$ : mean predicted risk of 1-year mortality from models including the 'new' index among those who did not die.

$pred_{died,old}$ : mean predicted risk of 1-year mortality from models including the comparison index among those who died.

$pred_{not\ died,old}$ : mean predicted risk of 1-year mortality from models including the comparison index among those who did not die.

Two-tailed p-values were calculated for the IDI (with the null hypothesis being that the difference between the predicted mean risk of one-year mortality of those who did and did not die is equal for the new and comparison index) using an asymptotic test based on pooled standard errors of the mean differences between predicted risks (Pencina, D'Agostino et al. 2008).

## Summary

This work aims:

1. to assess how well data on comorbidity are captured in routine databases in New Zealand by comparing detailed comorbidity data extracted from hospital records with routinely collected hospitalisation and pharmaceutical data from the same patients;
2. to develop and validate an optimised ('gold standard') measure of comorbidity using routinely collected data for patients with cancer; and
3. to develop and validate a simplified comorbidity index using routinely collected data on comorbidity; and to compare the performance of this 'user-friendly' index with the comprehensive 'gold-standard' approach.

In summary, there were three distinct stages of analysis:

1. The first stage involved the measurement of **comorbidity using administratively collected hospitalisation data**. These administrative data were validated against data from manually collected hospital notes from an earlier study. Once the validity of the data had been established, there was an extensive process of optimising the identification of comorbid conditions from these data. Cancer site-specific hospitalisation-based indices (C3 indices) were then developed and validated to be used as part of the gold-standard measure of comorbidity.
2. The second stage involved the measurement of **comorbidity using administratively collected pharmaceutical data**. These data were also compared with manually collected comorbidity data from hospital notes, and pharmacy-based comorbidity indices (PBCIs) were developed and validated.
3. Finally, **simplified versions of the administrative data-based comorbidity indices** were developed and validated. These were compared with the Charlson index as well as the gold standard hospitalisation and pharmaceutical measures of comorbidity developed here.

# Chapter 6: Results

*Although this may seem a paradox, all exact science is dominated by the idea of approximation. When a man tells you that he knows the exact truth about anything, you are safe in inferring that he is an inexact man. ~Bertrand Russell*

## Outline

The results chapter is divided into four sections:

1. Description of the main development and validation cohorts
2. Results relating to the hospitalisation-based comorbidity indices
  - a. Results of the (earlier) validation exercise.
  - b. Prevalence and impact of comorbid conditions identified in hospitalisation data.
  - c. Development and validation of the site-specific hospitalisation-based comorbidity indices.
3. Results relating to the pharmaceutical-based comorbidity indices
  - a. Results of the validation exercise
  - b. Prevalence and impact of comorbid conditions identified in the community pharmaceutical data.
  - c. Development and validation of the pharmaceutical-based comorbidity indices.
4. Results relating to the development and validation of the simplified index.

# Section 1: Description of (main) study cohorts

## Development cohort

There were 14,096 patients included in the development cohort. Of those, 3999 (28%) had been diagnosed with colon, 1377 (10%) with rectal, 5076 (36%) with breast, 481 (3%) with ovarian, 742 (5%) with uterine, 256 (2%) with liver, 705 (5%) with stomach, 813 (6%) with renal and 647 (4.5%) with bladder cancers (Table 13).

Table 13 shows the crude and age/sex standardised proportions of patients in the development cohort by sex, age, ethnicity, stage and Charlson scores. Table 14 shows a comparison of crude proportions of patients by sex, age, ethnicity, and Charlson scores as well as the number and crude proportions of all-cause and non-cancer deaths by cancer site category (colorectal, breast, gynaecological, upper gastrointestinal and urological) for the development compared with the validation cohorts.

The sex and age distributions were largely as expected. In the development cohort, just over half the patients with colorectal cancer, and about two-thirds of those with upper gastrointestinal or urological cancers were male. Women with breast and gynaecological cancers tended to be younger than patients diagnosed with other cancers, with two-thirds of breast cancer patients and 55% of gynaecological patients aged under 65 years, compared with 29%, 40% and 36% for colorectal, upper gastrointestinal and urological cancers respectively (Table 14).

Maori made up 9.1% of the entire development cohort included in this study, but were clearly over-represented compared with other sites among those with cancers of the liver and stomach (age and sex adjusted prevalence estimates 28.5% and 23.3% respectively), and underrepresented among those with colon cancers (age and sex adjusted prevalence estimate 5.4%) (Table 13).

Extent of disease at diagnosis varied across cancer sites as expected. Over half of all uterine and breast cancer patients were diagnosed with localised disease compared with around a quarter for colorectal cancer patients, 13-17% for ovarian and liver cancer, 9% for stomach cancer and 6% for bladder cancer. Nearly two-thirds of ovarian cancer patients were diagnosed with advanced disease. A high proportion of liver and bladder cancers (both crude estimates of 73%) were missing staging data, as well as over a third of stomach and rectal cancers. Less than 5% of ovarian cancers, and 8-14% of colon, breast, uterine and renal cancers were missing stage data.

Overall 75.7% of all the cancer patients combined had a Charlson score of 0, and 7.2% had a score of 3 or more. There were relatively low levels of comorbidity as measured by the Charlson score for patients with breast cancer (age adjusted prevalence estimates of 87.3% with score of 0). In contrast, those with upper gastrointestinal cancers were less likely to have scores of 0 (age and sex adjusted 28.5% for liver and 59.2% for stomach), and more likely to have scores of 3 or more (age and sex adjusted 34.4% and 13.7% respectively) than patients with other cancers (Table 13).

The proportion of patients dying from any cause over the entire follow-up period was highest for those with liver or stomach cancers (66-72%) and lowest for breast cancer (7.8-10.4%); these differences were largely driven by cancer-specific deaths. The proportion of patients dying from non-cancer causes was low for all groups (1.3-6.1%), particularly among women with breast or gynaecological cancers (Table 14).

**Table 13: Crude and age/sex standardised proportions of patients by specific cancer site, and sex, age, ethnicity, stage and Charlson scores**

	All Sites n=14096		Colon n= 3999		Rectal n = 1377		Breast n =5076		Ovarian n = 481		Uterine n = 742		Liver n = 256		Stomach n = 705		Renal n = 813		Bladder n = 647		
	n	%	Crude	Std*	Crude	Std*	Crude	Std**	Crude	Std**	Crude	Std**	Crude	Std*	Crude	Std*	Crude	Std*	Crude	Std*	
<b>Sex</b>																					
Male	4454	31.6	49	-	61.7	-	-	-	-	-	-	-	79.3	-	63.7	-	65.7	-	70.5	-	
Female	9642	68.4	50.9	-	38.3	-	100	-	100	-	100	-	20.7	-	36.3	-	34.3	-	29.5	-	
<b>Age</b>																					
25-49 yr	2220	15.8	5.6	-	9.2	-	28	-	16.8	-	13.5	-	17.2	-	11.8	-	14	-	3.7	-	
50-64 yr	4202	29.8	20.6	-	26.9	-	36.5	-	35.8	-	43.5	-	33.6	-	25.3	-	33.7	-	18.4	-	
65-74 yr	3501	24.8	30.9	-	31.7	-	17.8	-	21.4	-	23.9	-	27.3	-	27.4	-	26.6	-	26.1	-	
75+ yr	4173	29.6	42.9	-	32.2	-	17.7	-	26	-	19.1	-	21.9	-	35.6	-	25.7	-	51.8	-	
<b>Ethnicity</b>																					
Maori	1287	9.1	4	5.4	6.5	7	11.5	10.1	8.5	8.2	12	11.3	28.5	28.1	19.4	23.3	10	10.1	5	8.1	
Non-Maori	12809	90.9	96	94.6	93.5	93	88.5	89.9	91.5	91.8	88	88.7	71.5	71.9	80.6	76.7	90	89.9	95.1	91.9	
<b>Stage</b>																					
Localised	5034	35.7	26.4	25.6	25	25.1	51.4	50.2	13.5	13.6	61.7	60.4	14.1	17.2	9.4	9	44.9	46.7	5.3	5.5	
Regional	4579	32.5	45.5	46.4	29.5	28.3	34.4	33.4	18.3	18.2	21.3	21.1	0.4	0.8	20	20.7	17.2	15.4	12.2	14.3	
Advanced	1944	13.8	18.8	20.2	11	11.2	3.6	3.8	63.6	63.4	5.9	6.5	12.1	12.5	31.5	34	24.2	24.1	9.4	13.8	
Unstaged	2539	18	9.4	7.8	34.5	35.4	10.6	12.6	4.6	4.8	11.1	12	73.4	69.5	39.2	36.3	13.7	13.8	73.1	66.3	
<b>Charlson Score<sup>†</sup></b>																					
0	10664	75.7	69.1	74.5	76.8	80.3	87.3	83.8	79.6	78.7	77.8	75.8	25.4	28.5	55.6	59.2	69.5	69.9	66.5	76.9	
1	1819	12.9	16.6	14.1	12.4	10.6	7.5	9.1	13.3	13.9	14.8	16.0	29.7	29.0	21.0	20.0	13.0	13.1	15.6	10.7	
2	602	4.3	5.7	4.7	4.3	3.7	2.1	2.7	2.9	3.2	2.6	2.8	9.4	8.2	7.7	7.1	5.4	5.4	8.3	6.3	
3+	1011	7.2	8.6	6.7	6.5	5.5	3.1	4.3	4.2	4.3	4.9	5.4	35.5	34.4	15.7	13.7	12.1	11.6	9.6	6.2	

\*age and sex standardised; \*\*age standardised, † Comorbidity score (with 0 being lowest value)

**Table 14: Crude sex, age, ethnicity and Charlson scores of patients included in the development and validation cohorts by cancer site**

	Colorectal		Breast		Gynaecological		Liver/Stomach		Urological											
	Development*	Validation**	Development	Validation	Development	Validation	Development	Validation	Development	Validation										
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>														
<b>Sex</b>																				
Male	2812	49%	2113	49%	0	0%	0	0%	0	0%	0	0%	652	-60%	508	62%	990	-62%	752	60%
Female	2564	62%	1934	62%	5076	61%	4059	60%	1223	64%	1041	64%	309	-44%	225	43%	470	-47%	382	47%
<b>Age</b>																				
25-49 yrs	351	7%	267	7%	1423	28%	1120	28%	181	15%	176	17%	127	-13%	85	12%	138	-9%	122	11%
50-64yrs	1196	22%	939	23%	1854	37%	1555	38%	495	40%	418	40%	264	-27%	218	30%	393	-27%	301	27%
65-74 yrs	1672	31%	1222	30%	901	18%	713	18%	280	23%	243	23%	263	-27%	185	25%	385	-26%	307	27%
75+ yrs	2157	40%	1619	40%	898	18%	671	17%	267	22%	204	20%	307	-32%	245	33%	544	-37%	404	36%
<b>Ethnicity</b>																				
Maori	248	5%	217	5%	586	12%	484	12%	130	11%	129	12%	210	-22%	152	21%	113	-8%	80	7%
Non-Maori	5128	95%	3830	95%	4490	88%	3575	88%	1093	89%	912	88%	751	-78%	581	79%	1347	-92%	1054	93%
<b>Charlson Score</b>																				
0	3821	71%	3039	75%	4431	87%	3590	88%	960	78%	836	80%	547	-57%	456	62%	1030	-71%	813	72%
1	834	16%	520	13%	380	7%	252	6%	174	14%	103	10%	206	-21%	156	21%	226	-15%	177	16%
2	287	5%	219	5%	106	2%	115	3%	33	3%	49	5%	63	-7%	55	8%	89	-6%	64	6%
3+	434	8%	269	7%	159	3%	102	3%	56	5%	53	5%	145	-15%	66	9%	115	-8%	80	7%
<b>Deaths<sup>†</sup></b>																				
All-cause	1957	36%	1199	30%	527	10%	317	8%	397	32%	274	26%	696	-72%	485	66%	618	-42%	365	32%
Non-cancer	255	5%	152	4%	130	3%	80	2%	30	2%	14	1%	36	-4%	36	5%	77	-5%	69	6%

\* diagnosed between 1 July 2006 and 30 June 2008; \*\* diagnosed between 1 July 2008 and 31 December 2009; † during entire follow up period

## Validation cohort

There were 11,014 patients included in the validation cohort; of whom 4047 (37%) had colorectal cancer, 4059 (37%) had breast, 1041 (9%) had gynaecological, 733 (7%) had upper gastrointestinal and 1134 (10%) had urological cancers (Table 14)

The sex, age, ethnicity and Charlson scores of the validation cohort were very similar in all respects to those of the development cohort (Table 14).

## **Section 2: Use of hospitalisation data to measure comorbidity**

### **Results of the validation exercise for hospitalisation data**

As discussed in the previous chapter, this validation exercise was carried out prior to beginning the other work described in this thesis. The cohorts described in this section are therefore not the same as the primary study cohorts used in the remainder of this thesis. As a reminder, patients involved in this data validation exercise were participants in an earlier study on colon cancer survival for which hospital notes data on comorbidity were collected and compared with routinely collected administrative data (see Methods/Section 1/Data sources/Hospital notes review). Comorbid conditions were coded using ICD-9 codes, and the validation exercise focused on conditions included in the Charlson index (see Methods/Section 2/Validation of NMDS data).

#### **Cohorts used in the hospitalisation validation exercise**

A total of 685 patients with colon cancer diagnosed between 1996 and 2003 met the eligibility criteria for the validation exercise, and full data were obtained for 92% of these to give an initial study sample of 642 (308 Māori and 334 non-Māori). When these cases were matched to the routine hospitalisation data, 73 were excluded because they did not have an admission that met the criteria for the index admission giving a final cohort for this validation exercise of 569 patients, 515 having an admission for surgical resection of colon cancer.

Table 15 and 16 show the comparison of medical notes data with administrative data with 1 and 8 year lookback respectively. They show that there were differences in the comorbidity data obtained from these two data sources. For most conditions, higher numbers of patients were identified with notes review data than administrative data, and this effect was more marked with 1 year than 8 year lookback. This pattern was

reversed for diabetes and renal disease for both lookback periods, as well as non-colorectal malignancy, cardiac valve disease and hemiplegia with the longer lookback period.

There was very good agreement ( $\kappa = 0.77$  and  $0.75$  for 1 and 8-year lookback respectively) between the sources of data for only one condition (mild to moderate diabetes). For the 1 year lookback, 11 conditions showed moderate agreement ( $\kappa$  0.40 to 0.74), and the remaining five showed poor agreement ( $\kappa < 0.40$ ). Agreement between the two data sources improved with the longer lookback period with 14 conditions showing moderate and two showing poor agreement.

As expected, both Charlson scores and comorbidity counts tended to be higher when calculated from data extracted from medical notes than from administrative data with 1 or 8 year lookback, and the highest scores were obtained by combining both data sources (Figure 6). For the Charlson index, agreement between the medical notes data and the administrative data was somewhat better for the longer lookback period ( $\kappa = 0.66$ ; 95% CI: 0.57-0.75) than the shorter one ( $\kappa = 0.61$ ; 95% CI: 0.51-0.70).

**Table 15: Comparison of ascertainment of comorbidity using data from medical notes or administrative data from index admission and one year prior**

Condition	Total number (%) with condition recorded in notes or admin data		Total no (%*) in notes		Total no (%*) in admin data		Total no (%*) in both		p-value**	Kappa coefficient	95% confidence Intervals for kappa
Myocardial infarction	53	(9.3)	49	(92.5)	21	(39.6)	17	(32.1)	<0.001	0.46	0.31-0.60
Congestive heart failure	74	(13.0)	64	(86.5)	30	(40.5)	20	(27.0)	<0.001	0.38	0.25-0.51
Peripheral vascular disease	27	(4.7)	24	(88.9)	13	(48.1)	10	(37.0)	0.013	0.53	0.33-0.72
Cerebrovascular disease	46	(8.1)	39	(84.8)	15	(32.6)	8	(17.4)	0.001	0.27	0.11-0.43
Dementia	14	(2.5)	13	(92.9)	5	(35.7)	4	(28.6)	0.021	0.44	0.15-0.72
Chronic pulmonary disease	141	(24.8)	128	(90.8)	74	(52.5)	61	(43.3)	<0.001	0.53	0.44-0.61
GI ulcer disease	26	(4.6)	22	(84.6)	9	(34.6)	5	(19.2)	0.007	0.31	0.09-0.52
Diabetes (mild to moderate)	94	(16.5)	73	(77.7)	84	(89.4)	63	(67.0)	<0.001	0.77	0.69-0.85
Diabetes with end organ damage	28	(4.9)	21	(75.0)	18	(64.3)	11	(39.3)	0.630	0.55	0.36-0.74
Hemiplegia or paraplegia	15	(2.6)	9	(60.0)	12	(80.0)	6	(40.0)	0.511	0.56	0.31-0.82
Moderate or severe renal disease	24	(4.2)	7	(29.2)	22	(91.7)	5	(20.8)	<0.001	0.33	0.11-0.55
Any malignancy (except colon or rectal) including lymphoma or leukaemia	39	(6.9)	25	(64.1)	27	(69.2)	13	(33.3)	0.857	0.48	0.30-0.65
Angina <sup>‡</sup>	74	(13.0)	69	(93.2)	22	(29.7)	17	(23.0)	<0.001	0.33	0.21-0.46
Essential hypertension <sup>‡</sup>	239	(42.0)	216	(90.4)	152	(63.6)	129	(54.0)	<0.001	0.56	0.49-0.63
Cardiac arrhythmias <sup>‡</sup>	82	(14.4)	78	(95.1)	30	(36.6)	26	(31.7)	<0.001	0.44	0.32-0.56
CV valve disease <sup>‡</sup>	22	(3.9)	13	(59.1)	15	(68.2)	6	(27.3)	0.801	0.41	0.18-0.65
Other neurological condition <sup>‡ a</sup>	17	(3.0)	13	(76.5)	9	(52.9)	5	(29.4)	0.391	0.44	0.18-0.71

\*as a percentage of Column 1 (Total number with condition recorded in notes or admin data)

\*\*Testing whether the proportion of patients with condition is significantly different between the medical notes and administrative data

<sup>‡</sup>Condition not included in Charlson Comorbidity Index

**Table 16: Comparison of ascertainment of comorbidity using data from medical notes or administrative data from index admission and eight years prior**

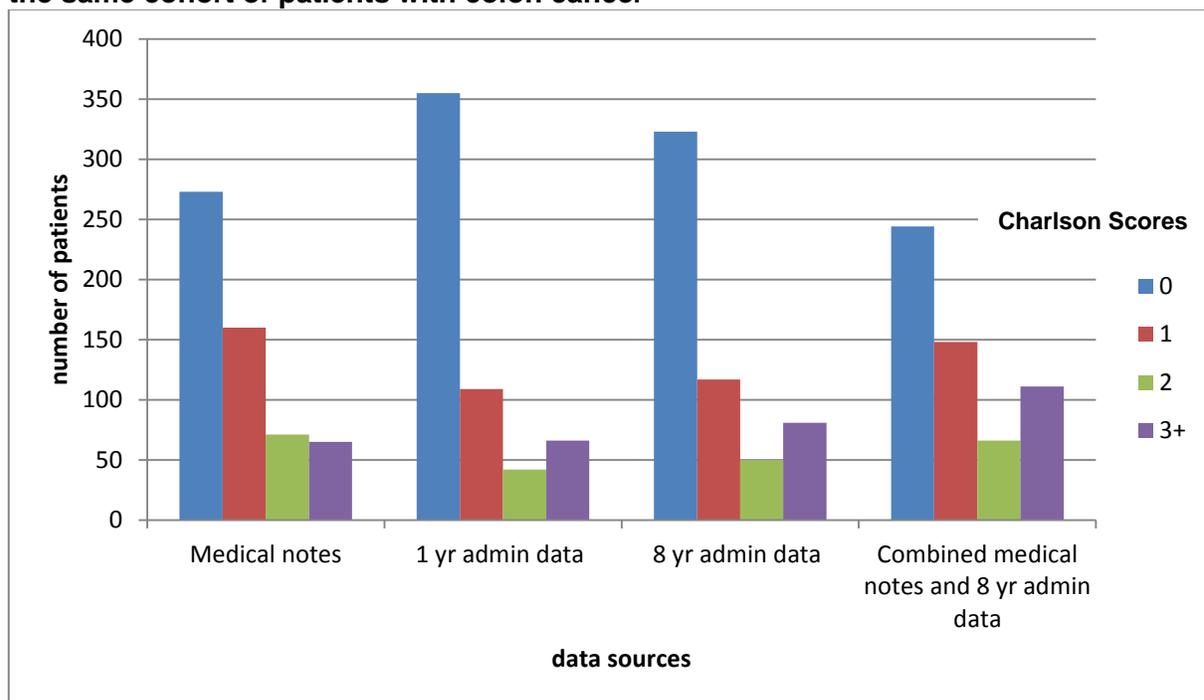
Condition	Total number (%) with condition recorded in notes or admin data	Total no (%*) in notes	Total no (%*) in admin data	Total no (%*) in both	p-value**	Kappa coefficient	95% confidence Intervals for kappa
Myocardial infarction	55 (9.7)	49 (89.1)	35 (63.6)	29 (52.7)	0.009	0.67	0.55-0.79
Congestive heart failure	80 (14.1)	64 (80.0)	49 (61.3)	33 (41.3)	0.040	0.54	0.42-0.66
Peripheral vascular disease	29 (5.1)	24 (82.8)	19 (65.5)	14 (48.3)	0.302	0.64	0.47-0.81
Cerebrovascular disease	49 (8.6)	39 (79.6)	27 (55.1)	17 (34.7)	0.050	0.49	0.33-0.64
Dementia	14 (2.5)	13 (92.9)	6 (42.9)	5 (35.7)	0.039	0.52	0.25-0.79
Chronic pulmonary disease	147 (25.8)	128 (87.1)	91 (61.9)	72 (49.0)	<0.001	0.58	0.49-0.66
GI ulcer disease	28 (4.9)	22 (78.6)	13 (46.4)	7 (25.0)	0.078	0.38	0.17-0.59
Diabetes (mild to moderate)	99 (17.4)	73 (73.7)	90 (90.9)	64 (64.6)	0.006	0.75	0.67-0.83
Diabetes with end organ damage	29 (5.1)	9 (72.4)	8 (69.0)	12 (41.4)	1.00	0.57	0.39-0.75
Hemiplegia or paraplegia	18 (3.2)	9 (50.0)	16 (88.9)	7 (38.9)	0.065	0.55	0.31-0.79
Moderate or severe renal disease	25 (4.4)	7 (28.0)	23 (92.0)	5 (20.0)	<0.001	0.32	0.10-0.54
Any malignancy (except colon or rectal) including lymphoma or leukaemia	42 (7.4)	25 (59.5)	33 (78.6)	16 (38.1)	0.170	0.53	0.37-0.69
Angina <sup>‡</sup>	76 (13.4)	69 (90.8)	39 (51.3)	32 (42.1)	<0.001	0.55	0.44-0.67
Essential hypertension <sup>‡</sup>	247 (43.4)	216 (87.4)	175 (70.9)	144 (58.3)	<0.001	0.60	0.53-0.67
Cardiac arrhythmias <sup>‡</sup>	92 (16.2)	78 (84.8)	54 (58.7)	40 (43.5)	0.001	0.56	0.45-0.66
CV valve disease <sup>‡</sup>	26 (4.6)	13 (50.0)	21 (80.8)	8 (30.8)	0.096	0.46	0.24-0.67
Other neurological condition <sup>‡ a</sup>	18 (3.2)	13 (72.2)	12 (66.7)	7 (38.9)	1.00	0.55	0.31-0.79

\*as a percentage of Column 1 (Total number with condition recorded in notes or admin data)

\*\*Testing whether the proportion of patients with condition is significantly different between the medical notes and administrative data

<sup>‡</sup>Condition not included in Charlson Comorbidity Index

**Figure 6: Comparison of number of patients with Charlson index scores of 0, 1, 2 or 3+ calculated using medical notes and administrative data (1 or 8 year lookback) for the same cohort of patients with colon cancer**



Comorbidity measures added significantly to the ability of the base model (which included sex, age, year of registration, stage, grade and subsite) to explain all-cause survival regardless of whether comorbidity was measured using the Charlson score or individual conditions, or whether data was collected from medical notes, administrative data or both (in all cases likelihood ratio test  $p < 0.0001$  for model including comorbidity measured compared with base model).

In this cohort, the baseline hazard ratio of all-cause mortality for Māori compared with non-Māori was 1.34 (95% CI 1.03-1.74). When this was adjusted for comorbidity using data from both sources combined, the excess hazard ratio decreased to 1.17 (0.89-1.53). Adjusting for comorbidity using either notes or administrative-based data alone resulted in

somewhat less reduction in the hazard ratio to 1.23 (95% CI 0.94-1.60), and 1.26 (95% CI 0.96-1.64) respectively (Table 17).

**Table 17: Table showing hazard ratio of all-cause mortality for Māori compared with non- Māori**

Model	Hazard ratio	95% CI
Baseline model*	1.34	1.03-1.74
Baseline model* + comorbidity** (data from notes review)	1.23	0.94-1.60
Baseline model* + comorbidity** (data from NMDS)	1.26	0.96-1.64
Baseline model* + comorbidity** (data from both sources)	1.17	0.89-1.53

\*Includes sex, age (25-54, 55-64, 65-74, 75+), year of registration (single year), stage (1-4), grade (poor, moderately, well differentiated) and site (right, left, rectosigmoid)

\*\*Individual conditions were added to the model (previous MI, CHF, cerebrovascular disease, diabetes, respiratory disease, cardiac arrhythmias, peripheral vascular disease, renal disease)

## Comment on findings from NMDS validation exercise

There were differences in the comorbidity data held in the routine administrative hospitalisation database in New Zealand compared with those collected by a physician from medical records. In general, more comorbidity was identified from medical records, however some conditions were more frequently identified from administrative data, notably diabetes and renal failure. Agreement between the two data sources improved with a longer lookback period for the administrative data. Despite these differences, any of the measures of comorbidity that were used, regardless of the source of the data, improved the ability of the multivariable model to predict all-cause survival in this cohort of colon cancer patients.

Both the kappa coefficients for the individual conditions and those for the Charlson and comorbidity count (0.66 and 0.77 respectively) compare favourably with similar comparisons carried out elsewhere (Kieszak, Flanders et al. 1999; van Doorn, Bogardus et al. 2001). Overall, the validation exercise provides evidence that it is not unreasonable to use New Zealand routine hospitalisation data to measure comorbidity in the context of

cancer at least for the purposes of risk adjustment, and a longer lookback period is likely to be better for this purpose than a short one.

## Prevalence of comorbid conditions using hospitalisation data

Having established that the routine hospitalisation data were adequate for measuring comorbidity among cancer patients in New Zealand for the purposes of this thesis, the next task was to optimise the measurement of comorbidity using these data. After the extensive process described in the previous chapter (under Methods/Section 2: Use of hospitalisation data to measure comorbidity/Optimising the identification of comorbid conditions using hospitalisation data), 50 conditions were identified which were further evaluated. Table 18 shows the number and prevalence of each of the 50 individual comorbid conditions, within each of the individual cancer sites. By far the most common condition identified was hypertension with prevalence ranging from 8.0 to 20.9% across cancer sites, and 13% overall. Cardiac conditions were also prevalent (cardiac arrhythmias 3.5-13.5%; congestive heart failure 2.3-8.2%; angina 2.1-6.4%; and other cardiac conditions 2.1-9.9%); as was diabetes both with (2.3-13.3%) and without (2.9-12.9%) complications. Other relatively common conditions were metabolic disorders (including hyperlipidaemias and hypercholesterolemia) (3.8-13.3%); coagulopathies and other blood disorders (2.5-12.4%); chronic pulmonary disease (2.5-11.1%); other malignancies (1.5-8.7%); inflammatory bowel disease (2.2-6.6%); and chronic renal disease (1.4-7.5%).

In general, the prevalence of conditions was higher in cancers with older age structures (bladder, colorectal, and stomach cancers) as expected. In addition, comorbid conditions that can be caused by smoking such as ischaemic heart disease, peripheral vascular disease and chronic respiratory conditions tended, not surprisingly, to be higher in patients with cancers that are also associated with smoking, particularly liver, stomach, renal and bladder cancers (Table 18). There was also notably higher prevalence of obesity among those with uterine cancer (8.6%) compared with other cancers, and a higher prevalence of diabetes among those with upper gastrointestinal and uterine cancers. Nearly half (44.1%) of all those with liver cancer were identified as having chronic viral hepatitis compared with 1% or less of those with other cancers.

**Table 18: Prevalence n (%) of conditions identified in administrative hospitalisation data in 9 (development) cancer Cohorts**

	<b>Colon n = 3999</b>	<b>Rectal n = 1377</b>	<b>Breast n = 5076</b>	<b>Ovarian n = 481</b>	<b>Uterine n = 742</b>	<b>Liver n = 256</b>	<b>Stomach n = 705</b>	<b>Renal n = 813</b>	<b>Bladder n = 647</b>
<b>AIDS</b>	0	0	0	0	1 (0.1)	2 (0.8)	0	0	0
<b>Alcohol abuse</b>	36 (0.9)	13 (0.9)	21(0.4)	3 (0.6)	3 (0.4)	34 (13.3)	4 (0.57)	3 (0.4)	7 (1.1)
<b>Anaemia deficiency</b>	<b>NI**</b>	<b>NI**</b>	68 (1.3)	11 (2.3)	22 (3.0)	11 (4.3)	<b>NI**</b>	29 (3.6)	19 (2.9)
<b>Angina</b>	232 (5.8)	37 (2.7)	106 (2.1)	10 (2.1)	22 (3.0)	7 (2.7)	45 (6.4)	35 (4.3)	33 (5.1)
<b>Anxiety/Behavioural disorders</b>	38 (1.0)	8 (0.6)	48 (1.0)	3 (0.6)	7 (0.9)	3 (1.2)	10 (1.4)	9 (1.1)	6 (0.9)
<b>Bowel disease: Inflammatory</b>	242 (6.1)	65 (4.7)	114 (2.2)	20 (4.2)	20 (2.7)	17 (6.6)	29 (4.1)	28 (3.4)	25 (3.9)
<b>Cardiac arrhythmias</b>	380 (9.5)	101 (7.3)	195 (3.8)	17 (3.5)	30 (4.0)	27 (10.6)	95 (13.5)	67 (8.2)	67 (10.4)
<b>Cardiac diseases: other</b>	319 (8.0)	85 (6.2)	134 (2.6)	10 (2.1)	23 (3.1)	12 (4.7)	70 (9.9)	58 (7.1)	51 (7.9)
<b>Cardiac valve disease</b>	134 (3.4)	25 (1.8)	56 (1.1)	6 (1.3)	15 (2.0)	4 (1.6)	26 (3.7)	17 (2.1)	20 (3.1)
<b>Cerebrovascular diseases</b>	203 (5.1)	52 (3.8)	103 (2.0)	17 (3.5)	17 (2.3)	15 (5.9)	44 (6.2)	40 (4.9)	30 (4.6)
<b>Chronic pulmonary disease</b>	252 (6.3)	78 (5.7)	147 (2.9)	12 (2.5)	21 (2.8)	16 (6.3)	78 (11.1)	44 (5.4)	53 (8.2)
<b>Coagulopathy/blood disorders</b>	497 (12.4)	82 (6.0)	126 (2.5)	28 (5.8)	34 (4.6)	<b>NI**</b>	82 (11.6)	68 (8.4)	51 (7.9)
<b>Congestive heart failure</b>	232 (5.8)	45 (3.3)	115 (2.3)	12 (2.5)	20 (2.7)	15 (5.9)	58 (8.2)	38 (4.7)	46 (7.1)
<b>Connective tissue disease</b>	40 (1.0)	8 (0.6)	26 (0.5)	3 (0.6)	6 (0.8)	4 (1.6)	7 (1.0)	12 (1.5)	9 (1.4)
<b>Dementia</b>	72 (1.8)	19 (1.4)	37 (0.7)	5 (1.0)	1 (0.1)	6 (2.3)	8 (1.1)	12 (1.5)	22 (3.4)
<b>Diabetes: uncomplicated</b>	237 (5.9)	65 (4.7)	145 (2.9)	25 (5.2)	62 (8.4)	33 (12.9)	41 (5.8)	45 (5.5)	33 (5.1)
<b>Diabetes: with complications</b>	199 (5.0)	53 (3.9)	116 (2.3)	18 (3.7)	57 (7.7)	34 (13.3)	71 (10.1)	63 (7.8)	33 (5.1)
<b>Drug abuse</b>	6 (0.2)	6 (0.4)	7 (0.1)	2 (0.4)	1 (0.1)	5 (2.0)	6 (0.9)	0	0
<b>Endocrine disorders</b>	65 (1.6)	12 (0.9)	46 (0.9)	9 (1.9)	13 (1.8)	3 (1.2)	16 (2.3)	22 (2.7)	3 (0.5)
<b>Epilepsy</b>	19 (0.5)	5 (0.4)	14 (0.3)	3 (0.6)	1 (0.13)	4 (1.6)	1 (0.1)	6 (0.74)	0
<b>Eye problems</b>	133 (3.3)	36 (2.6)	75 (1.5)	8 (1.7)	13 (1.8)	9 (3.5)	32 (4.5)	21 (2.6)	14 (2.2)
<b>GI ulcer/Upper GI disease</b>	111 (2.8)	17 (1.2)	37 (0.7)	7 (1.5)	6 (0.8)	<b>NI**</b>	<b>NI**</b>	24 (3.0)	9 (1.4)
<b>Hepatitis; chronic viral</b>	9 (0.2)	4 (0.3)	16 (0.3)	3 (0.6)	3 (0.4)	113 (44.1)	7 (1.0)	9 (1.1)	3 (0.5)
<b>Hypertension: primary</b>	662 (16.6)	177 (12.9)	405 (8.0)	55 (11.4)	104 (14.0)	45 (17.6)	147 (20.9)	131 (16.1)	101 (15.6)
<b>Immune system disorders</b>	3 (0.1)	0	6 (0.1)	1 (0.2)	0	1 (0.39)	5 (0.7)	1 (0.1)	0
<b>Infection: chronic NOS</b>	5 (0.1)	0	3 (0.1)	1 (0.2)	1 (0.1)	0	1 (0.14)	0	0

	Colon n = 3999	Rectal n = 1377	Breast n = 5076	Ovarian n = 481	Uterine n = 742	Liver n = 256	Stomach n = 705	Renal n = 813	Bladder n = 647
Inner ear disorder	85 (2.1)	16 (1.2)	44 (0.9)	7 (1.5)	7 (0.9)	3 (1.2)	22 (3.1)	16 (2.0)	12 (1.9)
Intestinal disorders	NI**	NI**	90 (1.8)	14 (2.9)	10 (1.4)	11 (4.3)	27 (3.8)	38 (4.7)	15 (2.3)
Joint/spinal disorders	76 (1.9)	20 (1.5)	46 (0.9)	10 (2.1)	9 (1.2)	2 (0.78)	17 (2.4)	13 (1.6)	12 (1.9)
Liver disease: moderate/severe	66 (1.7)	10 (0.7)	18 (0.4)	6 (1.3)	6 (0.8)	NI**	18 (2.6)	17 (2.1)	7 (1.1)
Major psychiatric disorders	59 (1.5)	19 (1.4)	50 (1.0)	4 (0.8)	7 (0.9)	5 (2.0)	12 (1.7)	12 (1.5)	6 (0.93)
Malignancy (not primary)	191 (4.8)	120 (8.7)	76 (1.5)	23 (4.8)	28 (3.8)	10 (3.9)	35 (5.0)	39 (4.8)	28 (4.3)
Malnutrition & nutritional disorders	43 (1.1)	9 (0.7)	19 (0.4)	6 (1.3)	1 (0.1)	0	11 (1.6)	4 (0.5)	9 (1.4)
Mental disorders & brain damage	4 (0.1)	4 (0.3)	2 (0.04)	2 (0.4)	0	2 (0.8)	1 (0.1)	0	3 (0.5)
Mental retardation	7 (0.2)	3 (0.2)	4 (0.1)	1 (0.2)	3 (0.4)	2 (0.8)	5 (0.7)	2 (0.3)	0
Metabolic disorders	351 (8.8)	91 (6.6)	195 (3.8)	31 (6.4)	51 (6.9)	34 (13.3)	89 (12.6)	91 (11.2)	52 (8.0)
Muscular & peripheral nerve disorders	32 (0.8)	8 (0.6)	18 (0.4)	1 (0.2)	4 (0.5)	3 (1.2)	14 (2.0)	10 (1.2)	1 (0.15)
Myocardial infarction	233 (5.8)	65 (4.7)	100 (2.0)	13 (2.7)	17 (2.3)	5 (2.0)	61 (8.7)	37 (4.6)	61 (9.4)
Obesity	77 (1.9)	25 (1.8)	92 (1.8)	12 (2.5)	64 (8.6)	15 (5.9)	27 (3.8)	28 (3.4)	15 (2.3)
Osteoporosis & bone disorders	53 (1.3)	12 (0.9)	33 (0.7)	10 (2.1)	4 (0.5)	1 (0.4)	6 (0.9)	5 (0.6)	12 (1.9)
Other neurological disorders	81 (2.0)	21 (1.5)	44 (0.9)	10 (2.1)	5 (0.7)	8 (3.1)	11 (1.6)	14 (1.7)	10 (1.6)
Pancreatitis	3 (0.1)	1 (0.1)	1 (0.02)	0	0	0	2 (0.3)	0	2 (0.3)
Paralysis	92 (2.3)	21 (1.5)	58 (1.1)	9 (1.9)	6 (0.8)	6 (2.3)	27 (3.8)	24 (3.0)	14 (2.2)
Peripheral vascular disease	140 (3.5)	31 (2.3)	50 (1)	5 (1.0)	7 (0.9)	6 (2.3)	29 (4.1)	27 (3.3)	22 (3.4)
Pulmonary circulation disorders	44 (1.1)	5 (0.4)	19 (0.4)	5 (1.0)	3 (0.4)	1 (0.4)	10 (1.4)	8 (1.0)	3 (0.5)
Renal disease: moderate/severe	185 (4.6)	48 (3.5)	73 (1.4)	13 (2.7)	15 (2.0)	14 (5.5)	53 (7.5)	NI*	42 (6.5)
Sleep disorders	24 (0.6)	4 (0.3)	9 (0.2)	3 (0.6)	4 (0.5)	1 (0.4)	6 (0.9)	16 (2.0)	1 (0.2)
Tuberculosis	0	2 (0.2)	2 (0.04)	0	0	1 (0.4)	0	0	1 (0.2)
Urinary tract problem: chronic	66 (1.7)	23 (1.7)	14 (0.3)	1 (0.2)	5 (0.7)	4 (1.6)	9 (1.3)	NI**	NI**
Venous insufficiency	14 (0.4)	2 (0.2)	11 (0.2)	1 (0.2)	1 (0.1)	1 (0.4)	6 (0.9)	1 (0.1)	1 (0.2)

**Note.** \*Only included if identified before index date to ensure complications of disease or treatment not included **NI\*\***:Not included as comorbid condition for this site because closely related to the primary cancer of interest, or its treatment. **NOS**: Not otherwise specified

## Impact of comorbid conditions on mortality among cancer cohorts

Tables 19 and 20 show the crude and age/stage adjusted HRs for these conditions on all-cause and non-cancer mortality respectively within each site category, and Table 21 shows the crude, and age, sex, site and stage adjusted HR for each condition on all patients combined across sites.

### All-cause mortality

The general pattern was for those with comorbid conditions to have higher all-cause mortality than those without the condition (Table 19). Age and stage adjusted hazard ratios were almost always greater than one but rarely greater than 2.5. The impact of dementia, neurological conditions and renal disease were the most consistently marked across sites with HRs ranging from 1.5-4.4; 1.5-3.0 and 1.4-2.5 respectively. Other conditions with a strong impact on all-cause mortality in at least some sites included congestive heart failure, chronic respiratory disease, epilepsy, nutritional disorders and venous insufficiency. However, the strongest association overall was between alcohol abuse and mortality among those with gynaecological (HR=31.9; 13.7-74.0) and breast (HR=4.7; 2.5-9.3) cancers. The impact of alcohol abuse on mortality was considerably less for the other cancer sites. Of note, these associations were based on small numbers, and the estimates are thus imprecise. Diabetes without complications had the lowest adverse effect on mortality with adjusted HRs ranging between 0.7 (0.4-1.2) among those with breast cancer to 1.3 (0.9-1.8) amongst those with gynaecological cancers.

The impact of comorbidity varied somewhat across sites, but not in a consistent manner. In general, the relative impact was somewhat more marked for many conditions among those with gynaecological cancers, and less so for those with upper gastrointestinal cancers. For example, the age and stage adjusted HRs for dementia were 4.4 (1.9-10.1) for gynaecological, 1.5 (0.8-2.6) for upper GI, 2.7 (2.1-3.4) for colorectal, 1.8 (1.2-2.9) for breast, and 2.3 (1.6-3.3) for urological cancers.

For all sites combined (Table 21), the pattern was similar with all HRs adjusted for age, sex, site and stage being greater than one except for diabetes without complications (HR=0.9; 0.8-1.0). The condition with the strongest overall association with all-cause mortality was, somewhat surprisingly, epilepsy (HR=2.6; 1.9-3.7), followed by dementia (HR=2.4; 2.0-2.8), sleep disorders (HR=2.1; 1.5-3.0), renal disease (HR=1.9; 1.7-2.1), congestive heart failure (HR=1.8; 1.6-2.0), and neurological conditions (HR=1.8; 1.5-2.2).

## **Non-cancer mortality**

Table 20 shows the crude and age/stage adjusted HRs for non-cancer mortality by cancer site. Where there were fewer than five deaths from a specified condition within a cancer cohort, estimates were withheld because of unstable estimates. Despite this, some estimates are still based on small numbers, and thus confidence intervals for individual conditions within site are often wide.

The adjusted HRs for individual conditions tended to be larger than the equivalent HRs for all-cause mortality. In other words, comorbid conditions had a greater impact on a relative scale on non-cancer mortality than on all-cause mortality. This is not surprising given that all-cause mortality is likely to be largely driven by cancer-related death. For example, those with reported hypertension had around twice the risk of non-cancer death, but only a maximum of 40% increased risk of all-cause death. Similarly, while renal disease was associated with an approximate doubling of all-cause death, it was associated with a 3-6 fold increase in risk of non-cancer death. A number of other conditions had consistently high associations with non-cancer death, including cardiac valve disorders (HRs 2.4-3.7), cerebrovascular disease (HRs 2.4-3.5), congestive heart failure (HRs 2.5-6.2), chronic respiratory disease (HRs 2.4-4.1), dementia (HRs 2.6-9.1), diabetes with complications (HRs 1.9-3.4), and previous myocardial infarction (HRs 2.3-3.9). Peripheral vascular disease was also associated with a high risk of non-cancer death, among those with breast, upper GI and urological cancers (HRs 3.6, 2.0-6.7; 5.1, 2.0-13.0 and 4.6, 2.4-8.9 respectively).

Table 21 shows the crude and age, sex, site and stage adjusted HRs for non-cancer death among all patients combined. After adjustment, four conditions resulted in an approximate four-fold increase in risk of non-cancer death compared with those without the condition: sleep disorders (HR=4.1; 1.7-9.9), renal diseases (HR=4.0; 3.1-5.0), dementia (HR=3.8; 2.8-5.3) and congestive heart failure (HR=3.5; 2.8-4.4). A further 13 conditions resulted in approximately a three-fold increase in risk (alcohol abuse (HR=2.9; 1.7-5.2), cardiac valve disorders (HR=3.0, 2.3-4.0) cerebrovascular disease (HR=3.0; 2.3-3.8), chronic respiratory disease (HR=3.0; 2.4-3.7), epilepsy (HR=2.8; 1.2-6.8), liver disease (HR=2.5; 1.5-4.2), nutritional disorders (HR=3.2; 2.0-5.0), previous myocardial infarction (HR=2.5; 2.0-3.2), neurological conditions (HR=2.9; 2.0-4.1), hemi/para/quadriplegia (HR=2.8; 2.0-3.9), peripheral nerve and muscular disorders (HR=3.3; 1.9-5.7), pulmonary circulation disorders (HR=2.6; 1.5-4.4) and peripheral vascular disease (HR=2.7; 2.0-3.6)).

In contrast, there was little or no association between non-cancer mortality and diabetes without complications (HR=1.0; 0.7-1.4), upper gastrointestinal conditions (HR=1.1; 0.7-1.8) or urinary tract disorders (HR=1.1; 0.7-1.9).

**Table 19: Crude and age/stage standardised hazard ratios (HR) of all-cause mortality by C3 condition and cancer site**

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Alcohol abuse	<i>crude</i>	2.3	(1.6-3.2)	4.7	(2.4-9.1)	19.4	(8.5-44.2)	1.4	(0.9-1.9)	1.4	(0.6-3.3)
	<i>Adjusted*</i>	2.0	(1.4-2.9)	4.7	(2.5-9.3)	31.9	(13.7-74)	1.3	(0.9-1.8)	1.6	(0.7-3.9)
Anaemia	<i>crude</i>	-	-	3.1	(1.9-4.9)	1.2	(0.7-2.1)	-	-	1.7	(1.2-2.5)
	<i>Adjusted*</i>	-	-	1.4	(0.9-2.2)	1.7	(1.0-3.1)	-	-	1.2	(0.8-1.7)
Angina	<i>crude</i>	1.4	(1.2-1.7)	2.1	(1.4-3.3)	1.2	(0.7-2.1)	1.2	(0.9-1.6)	1.3	(1.0-1.9)
	<i>Adjusted*</i>	1.3	(1.0-1.5)	1.1	(0.7-1.7)	1.7	(1.0-3.1)	1.1	(0.8-1.6)	1.0	(0.7-1.4)
Anxiety disorders	<i>crude</i>	2.1	(1.4-3.0)	2.8	(1.6-4.8)	-	-	2.5	(1.4-4.4)	0.9	(0.4-2.0)
	<i>Adjusted*</i>	2.2	(1.5-3.2)	1.1	(0.6-1.9)	-	-	1.9	(1.1-3.4)	0.9	(0.4-2.0)
Cardiac Arrhythmias	<i>crude</i>	1.7	(1.5-1.9)	3.4	(2.6-4.6)	2.2	(1.5-3.3)	1.2	(1.0-1.5)	2.0	(1.6-2.5)
	<i>Adjusted*</i>	1.4	(1.2-1.6)	1.5	(1.1-2.0)	1.2	(0.8-1.9)	1.1	(0.8-1.3)	1.3	(1.1-1.7)
Cardiac valve disorders	<i>crude</i>	1.8	(1.4-2.2)	6.0	(4.0-8.9)	2.1	(1.1-3.8)	1.2	(0.8-1.7)	1.7	(1.1-2.6)
	<i>Adjusted*</i>	1.5	(1.2-1.9)	1.8	(1.2-2.8)	1.9	(1.0-3.7)	1.1	(0.7-1.7)	1.5	(1.0-2.4)
Cerebrovascular disease	<i>crude</i>	2.1	(1.8-2.5)	5.5	(4.1-7.6)	3.4	(2.2-5.1)	1.3	(1.0-1.8)	1.9	(1.4-2.5)
	<i>Adjusted*</i>	1.6	(1.3-1.9)	2.0	(1.4-2.7)	1.6	(1.1-2.5)	1.0	(0.8-1.4)	1.4	(1.0-1.9)
Congestive heart failure	<i>crude</i>	2.2	(1.9-2.6)	5.3	(3.9-7.2)	3.8	(2.5-5.7)	1.5	(1.2-2.0)	2.9	(2.3-3.8)
	<i>Adjusted*</i>	1.8	(1.5-2.1)	1.4	(1.0-1.9)	2.3	(1.5-3.5)	1.3	(1.0-1.8)	2.5	(1.9-3.2)
Coagulopathies/ blood disorders	<i>crude</i>	1.6	(1.4-1.9)	4.0	(2.9-5.5)	3.1	(2.2-4.3)	-	-	2.3	(1.8-2.9)
	<i>Adjusted*</i>	1.4	(1.2-1.6)	1.9	(1.4-2.7)	2.2	(1.6-3.1)	-	-	2.1	(1.6-2.7)
Connective tissue disorders	<i>crude</i>	2.4	(1.7-3.4)	3.0	(1.4-6.2)	-	-	1.1	(0.6-2.1)	1.8	(1.0-3.1)
	<i>Adjusted*</i>	2.1	(1.5-3.0)	1.6	(0.8-3.4)	-	-	1.1	(0.6-2.1)	1.3	(0.7-2.3)
Chronic respiratory disease	<i>crude</i>	2.3	(2.0-2.6)	3.8	(2.8-5.1)	1.6	(0.9-2.7)	1.4	(1.1-1.7)	2.2	(1.7-2.9)
	<i>Adjusted*</i>	1.7	(1.5-2.0)	1.5	(1.1-2.0)	1.5	(0.9-2.6)	1.2	(0.9-1.5)	2.4	(1.9-3.2)
Dementia	<i>crude</i>	4.3	(3.4-5.5)	9.8	(6.4-15)	13.2	(5.8-29.8)	2.1	(1.2-3.6)	5.2	(3.6-7.5)
	<i>Adjusted*</i>	2.7	(2.1-3.4)	1.8	(1.2-2.9)	4.4	(1.9-10.1)	1.5	(0.8-2.6)	2.3	(1.6-3.3)

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Diabetes no complications	<i>crude</i>	0.9	(0.8-1.1)	1.1	(0.6-1.7)	1.3	(0.9-1.8)	0.8	(0.6-1.0)	1.1	(0.8-1.5)
	<i>Adjusted*</i>	0.8	(0.7-1.0)	0.7	(0.4-1.2)	1.3	(0.9-1.8)	0.8	(0.6-1.1)	0.8	(0.6-1.2)
Diabetes with complications	<i>crude</i>	1.5	(1.3-1.8)	2.6	(1.8-3.8)	1.9	(1.4-2.7)	1.2	(1.0-1.6)	1.5	(1.2-2.0)
	<i>Adjusted*</i>	1.4	(1.1-1.6)	1.6	(1.1-2.3)	1.6	(1.2-2.3)	1.1	(0.9-1.4)	1.2	(0.9-1.6)
Endocrine disorders	<i>crude</i>	2.1	(1.6-2.8)	3.2	(1.8-5.5)	1.6	(0.8-3.0)	1.0	(0.6-1.7)	1.9	(1.1-3.2)
	<i>Adjusted*</i>	1.6	(1.2-2.1)	1.7	(1.0-2.9)	1.2	(0.7-2.3)	1.3	(0.8-2.3)	1.3	(0.8-2.2)
Epilepsy	<i>crude</i>	2.4	(1.5-4.0)	4.6	(2.1-9.3)	-	-	2.3	(0.9-5.5)	-	-
	<i>Adjusted*</i>	1.9	(1.2-3.1)	4.0	(1.8-9.0)	-	-	4.5	(1.8-10.9)	-	-
Eye conditions	<i>crude</i>	1.7	(1.4-2.2)	3.1	(2.0-4.9)	3.0	(1.8-5.1)	1.2	(0.9-1.8)	1.2	(0.8-2.0)
	<i>Adjusted*</i>	1.6	(1.3-2.0)	1.7	(1.1-2.7)	1.9	(1.1-3.2)	1.0	(0.7-1.5)	1.1	(0.7-1.8)
Hepatitis (chronic)	<i>crude</i>	1.5	(0.7-3.2)	-	-	-	-	0.7	(0.6-0.9)	-	-
	<i>Adjusted*</i>	1.3	(0.6-3.0)	-	-	-	-	1.0	(0.8-1.3)	-	-
Upper gastrointestinal conditions	<i>crude</i>	2.3	(1.8-2.8)	2.0	(0.9-4.2)	2.9	(1.4-5.9)	-	-	1.6	(1.0-2.6)
	<i>Adjusted*</i>	1.7	(1.4-2.2)	1.1	(0.5-2.3)	1.2	(0.6-2.3)	-	-	1.1	(0.7-1.7)
Hypertension	<i>crude</i>	1.7	(1.5-1.9)	2.6	(2.1-3.2)	1.9	(1.4-2.4)	1.2	(1.0-1.5)	1.4	(1.1-1.7)
	<i>Adjusted*</i>	1.3	(1.2-1.5)	1.1	(0.9-1.4)	1.4	(1.1-1.8)	1.0	(0.9-1.2)	1.2	(1.0-1.5)
Inflammatory bowel conditions	<i>crude</i>	1.6	(1.3-1.9)	2.7	(1.9-4.0)	2.3	(1.5-3.5)	1.2	(0.9-1.7)	1.8	(1.2-2.6)
	<i>Adjusted*</i>	1.5	(1.2-1.7)	1.6	(1.1-2.4)	1.4	(0.9-2.1)	1.1	(0.8-1.6)	1.7	(1.2-2.4)
Inner ear conditions	<i>crude</i>	1.7	(1.3-2.2)	2.7	(1.5-4.9)	2.1	(1.0-4.5)	1.5	(1.0-2.3)	2.1	(1.3-3.3)
	<i>Adjusted*</i>	1.4	(1.0-1.8)	1.3	(0.7-2.3)	1.5	(0.7-3.2)	1.3	(0.9-2.1)	1.8	(1.1-2.9)
Intestinal conditions	<i>crude</i>	-	-	2.0	(1.2-3.2)	1.6	(0.9-2.8)	1.1	(0.8-1.6)	0.9	(0.6-1.4)
	<i>Adjusted*</i>	-	-	1.2	(0.8-2.0)	0.8	(0.4-1.4)	1.3	(0.9-1.9)	1.1	(0.7-1.7)
Joint and spinal conditions	<i>crude</i>	1.9	(1.5-2.5)	4.1	(2.5-6.8)	1.7	(0.9-3.3)	2.1	(1.3-3.3)	2.3	(1.5-3.7)
	<i>Adjusted*</i>	1.4	(1.0-1.8)	2.1	(1.3-3.5)	1.4	(0.7-2.7)	1.3	(0.8-2.0)	1.5	(0.9-2.4)

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Liver disease: moderate/severe	<i>crude</i>	2.5	(1.9-3.4)	2.1	(0.8-5.6)	2.9	(1.4-6.1)	-	-	1.5	(0.9-2.7)
	<i>Adjusted*</i>	1.9	(1.4-2.5)	3.1	(1.2-8.4)	1.7	(0.8-3.5)	-	-	1.2	(0.7-2.1)
Major psychiatric disorders	<i>crude</i>	2.0	(1.5-2.7)	3.1	(1.8-5.2)	-	-	1.9	(1.2-3.2)	0.9	(0.4-2.0)
	<i>Adjusted*</i>	2.1	(1.5-2.8)	1.9	(1.1-3.3)	-	-	1.7	(1.0-2.9)	0.7	(0.3-1.4)
Nutritional disorders	<i>crude</i>	1.6	(1.1-2.3)	7.9	(4.4-14)	14.3	(6.7-30.6)	1.7	(0.9-3.2)	2.5	(1.3-4.9)
	<i>Adjusted*</i>	1.2	(0.8-1.7)	3.6	(2.0-6.6)	3.8	(1.8-8.3)	1.7	(0.9-3.2)	2.2	(1.1-4.2)
Metabolic conditions	<i>crude</i>	1.3	(1.2-1.6)	2.1	(1.5-2.9)	2.1	(1.5-2.8)	1.0	(0.8-1.3)	1.3	(1.0-1.6)
	<i>Adjusted*</i>	1.3	(1.1-1.5)	1.2	(0.9-1.7)	1.4	(1.0-2.0)	1.0	(0.8-1.2)	1.3	(1.0-1.7)
Previous myocardial infarctions	<i>crude</i>	1.8	(1.5-2.1)	3.3	(2.3-4.8)	3.2	(2.0-5.0)	1.4	(1.1-1.9)	2.0	(1.5-2.6)
	<i>Adjusted*</i>	1.4	(1.2-1.7)	1.5	(1.0-2.2)	1.9	(1.2-2.9)	1.2	(0.9-1.6)	1.5	(1.1-1.9)
Neurological conditions	<i>crude</i>	2.3	(1.8-3.0)	4.0	(2.4-6.7)	4.6	(2.6-8.2)	2.6	(1.6-4.1)	3.4	(2.1-5.5)
	<i>Adjusted*</i>	1.5	(1.2-2.0)	1.6	(1.0-2.7)	2.6	(1.4-4.6)	2.1	(1.3-3.4)	3.0	(1.9-4.8)
Obesity	<i>crude</i>	1.4	(1.0-1.8)	1.9	(1.2-3.1)	0.9	(0.6-1.4)	1.0	(0.7-1.4)	1.0	(0.7-1.7)
	<i>Adjusted*</i>	1.5	(1.2-2.1)	1.8	(1.1-2.9)	1.3	(0.8-2.0)	1.1	(0.7-1.5)	1.4	(0.9-2.3)
osteoporosis and bone conditions	<i>crude</i>	2.2	(1.6-3.0)	4.5	(2.5-8.0)	4.3	(2.3-8.1)	0.9	(0.4-2.1)	2.5	(1.4-4.4)
	<i>Adjusted*</i>	1.8	(1.3-2.4)	1.3	(0.7-2.3)	2.2	(1.2-4.3)	0.5	(0.2-1.1)	1.0	(0.6-1.8)
Other cardiac conditions	<i>crude</i>	1.3	(1.1-1.5)	2.8	(2.0-3.9)	1.6	(0.9-2.6)	1.4	(1.1-1.8)	1.4	(1.1-1.9)
	<i>Adjusted*</i>	1.2	(1.0-1.4)	1.1	(0.8-1.6)	1.4	(0.8-2.3)	1.2	(0.9-1.5)	1.3	(1.0-1.7)
Hemi/para/ quadraplegia	<i>crude</i>	2.6	(2.1-3.3)	4.1	(2.6-6.3)	3.4	(1.9-6.2)	1.4	(1.0-2.0)	1.5	(1.0-2.4)
	<i>Adjusted*</i>	1.8	(1.4-2.2)	1.6	(1.0-2.5)	2.4	(1.3-4.3)	1.3	(0.9-1.9)	1.3	(0.8-2.0)
Muscular/ peripheral nerve	<i>crude</i>	1.5	(1.0-2.4)	4.2	(1.9-9.4)	-	-	1.1	(0.6-1.9)	1.4	(0.6-3.3)
	<i>Adjusted*</i>	1.6	(1.1-2.5)	2.6	(1.1-5.7)	-	-	1.0	(0.5-1.7)	0.9	(0.4-2.2)
Pulmonary circulation disorders	<i>crude</i>	2.0	(1.4-3.0)	-	-	-	-	1.0	(0.5-2.0)	1.6	(0.8-3.5)
	<i>Adjusted*</i>	1.6	(1.1-2.3)	-	-	-	-	1.1	(0.6-2.2)	2.0	(1.4-3.0)

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Peripheral vascular disease	<i>crude</i>	1.6	(1.3-2.0)	4.3	(2.6-6.9)	4.1	(2.1-8.0)	1.9	(1.3-2.7)	2.0	(1.4-2.8)
	<i>Adjusted*</i>	1.2	(1.0-1.5)	1.8	(1.1-2.9)	3.1	(1.6-6.1)	1.4	(0.9-2.0)	1.9	(1.3-2.8)
Renal disease	<i>crude</i>	2.6	(2.2-3.0)	7.0	(5.0-9.8)	4.7	(3.0-7.2)	1.4	(1.1-1.9)	-	-
	<i>Adjusted*</i>	2.0	(1.7-2.4)	2.5	(1.8-3.6)	2.3	(1.5-3.5)	1.4	(1.0-1.8)	-	-
Sleep disorders	<i>crude</i>	1.4	(0.8-2.4)	-	-	-	-	1.6	(0.7-3.5)	0.9	(0.4-2.0)
	<i>Adjusted*</i>	2.0	(1.1-3.4)	-	-	-	-	1.5	(0.7-3.3)	2.2	(1.0-5.0)
Urinary tract disorders	<i>crude</i>	1.5	(1.1-2.0)	-	-	-	-	1.3	(0.7-2.4)	-	-
	<i>Adjusted*</i>	0.9	(0.7-1.2)	-	-	-	-	1.3	(0.7-2.4)	-	-
Venous insufficiency	<i>crude</i>	3.5	(1.9-6.3)	-	-	-	-	1.6	(0.7-3.5)	-	-
	<i>Adjusted*</i>	2.2	(1.2-4.1)	-	-	-	-	1.9	(0.8-4.2)	-	-
Other malignancies	<i>crude</i>	1.7	(1.4-2.0)	2.1	(1.3-3.5)	1.2	(0.8-1.9)	1.2	(0.9-1.7)	1.4	(1.0-1.9)
	<i>Adjusted*</i>	1.3	(1.1-1.6)	1.6	(1.0-2.7)	1.2	(0.8-1.9)	1.1	(0.8-1.6)	1.2	(0.9-1.7)

\*adjusted for age and stage

- data withheld because of small numbers and unstable estimates

**Table 20 : Crude and age/stage standardised hazard ratios (HR) of non-cancer mortality by C3 condition and cancer site**

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Alcohol abuse	<i>crude</i>	-	-	10.7	(4.4-26.2)	-	-	-	-	-	-
	<i>Adjusted*</i>	-	-	9.8	(4.0-24.1)	-	-	-	-	-	-
Anaemia	<i>crude</i>	-	-	6.1	(3.1-11.9)	-	-	-	-	-	-
	<i>Adjusted*</i>	-	-	1.9	(1.0-3.8)	-	-	-	-	-	-
Angina	<i>crude</i>	2.3	(1.5-3.5)	5.7	(3.2-10.1)	-	-	3.0	(1.2-7.8)	2.4	(1.1-5.2)
	<i>Adjusted*</i>	1.8	(1.2-2.7)	1.5	(0.8-2.7)	-	-	2.4	(0.9-6.2)	1.7	(0.8-3.6)
Anxiety disorders	<i>crude</i>	3.6	(1.6-8.2)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	2.7	(1.2-6.1)	-	-	-	-	-	-	-	-
Cardiac Arrhythmias	<i>crude</i>	3.7	(2.7-4.9)	10.9	(7.4-16.1)	6.6	(2.5-17.2)	2.2	(1.0-4.8)	2.6	(1.4-4.7)
	<i>Adjusted*</i>	2.3	(1.7-3.1)	2.6	(1.7-3.8)	1.8	(0.7-4.8)	1.4	(0.6-3.2)	1.7	(0.9-3.1)
Cardiac valve disorders	<i>crude</i>	4.1	(2.7-6.3)	20.8	(12.9-33.5)	-	-	-	-	3.7	(1.6-8.6)
	<i>Adjusted*</i>	2.7	(1.7-4.1)	3.7	(2.3-6.1)	-	-	-	-	2.4	(1.1-5.7)
Cerebrovascular disease	<i>crude</i>	5.5	(4.0-7.6)	12.0	(7.5-19.2)	10.5	(4.0-27.5)	-	-	4.3	(2.3-8.2)
	<i>Adjusted*</i>	3.3	(2.4-4.6)	2.7	(1.7-4.3)	2.4	(0.9-6.7)	-	-	3.5	(1.8-6.7)
Congestive heart failure	<i>crude</i>	5.5	(4.0-7.5)	17.3	(11.6-26.0)	14.9	(6.0-36.7)	6.2	(3.0-12.9)	8.8	(5.3-14.7)
	<i>Adjusted*</i>	3.2	(2.3-4.4)	2.5	(1.6-3.8)	3.4	(1.3-8.8)	4.2	(1.9-9.2)	6.2	(3.6-10.5)
Coagulopathies/ blood disorders	<i>crude</i>	2.5	(1.9-3.4)	8.6	(5.3-13.8)	6.8	(2.8-16.7)	-	-	4.1	(2.3-7.1)
	<i>Adjusted*</i>	1.7	(1.3-2.4)	3.1	(1.9-5.1)	3.3	(1.3-8.5)	-	-	3.5	(2.0-6.1)
Connective tissue disorders	<i>crude</i>	2.8	(1.2-6.9)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	1.8	(0.7-4.4)	-	-	-	-	-	-	-	-
Chronic respiratory disease	<i>crude</i>	4.1	(3.0-5.7)	9.1	(5.9-14.1)	-	-	3.1	(1.4-6.8)	5.7	(3.4-9.7)

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
	<i>Adjusted*</i>	2.7	(2.0-3.8)	2.6	(1.7-4.1)	-	-	2.4	(1.1-5.3)	4.1	(2.4-7.0)
Dementia	<i>crude</i>	7.0	(4.2-11.9)	22.7	(12.5-41.4)	-	-	-	-	15.7	(7.9-31.1)
	<i>Adjusted*</i>	3.1	(1.8-5.3)	2.6	(1.4-4.7)	-	-	-	-	9.4	(4.7-19.1)
Diabetes no complications	<i>crude</i>	1.0	(0.6-1.7)	1.4	(0.6-3.3)	4.2	(1.8-9.8)	-	-	-	-
	<i>Adjusted*</i>	0.9	(0.5-1.5)	0.8	(0.3-2.0)	2.8	(1.2-6.7)	-	-	-	-
Diabetes with complications	<i>crude</i>	2.5	(1.6-3.7)	6.4	(3.8-10.9)	6.6	(3.0-14.9)	3.6	(1.7-7.4)	3.9	(2.2-6.8)
	<i>Adjusted*</i>	1.9	(1.3-2.9)	2.8	(1.6-4.7)	3.2	(1.4-7.4)	2.8	(1.3-5.9)	3.4	(1.9-6)
Endocrine disorders	<i>crude</i>	3.5	(1.8-6.6)	5.1	(2.1-12.4)	-	-	-	-	-	-
	<i>Adjusted*</i>	2.0	(1.0-3.7)	1.8	(0.7-4.5)	-	-	-	-	-	-
Epilepsy	<i>crude</i>	-	-	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	-	-	-	-	-	-	-	-	-	-
Eye conditions	<i>crude</i>	2.2	(1.3-3.8)	6.3	(3.3-12.1)	-	-	-	-	-	-
	<i>Adjusted*</i>	1.5	(0.9-2.6)	2.4	(1.2-4.5)	-	-	-	-	-	-
Hepatitis (chronic)	<i>crude</i>	-	-	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	-	-	-	-	-	-	-	-	-	-
Upper gastrointestinal conditions	<i>crude</i>	2.2	(1.2-4.2)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	1.6	(0.8-3.0)	-	-	-	-	-	-	-	-
Hypertension	<i>crude</i>	3.3	(2.6-4.3)	6.2	(4.3-8.9)	5.2	(2.5-10.8)	2.7	(1.3-5.2)	2.8	(1.7-4.5)
	<i>Adjusted*</i>	2.2	(1.7-2.9)	1.7	(1.2-2.5)	1.9	(0.9-4.0)	2.0	(1.0-4.1)	2.1	(1.3-3.5)
Inflammatory bowel conditions	<i>crude</i>	1.9	(1.2-2.9)	4.1	(2.1-7.8)	-	-	-	-	2.8	(1.2-6.5)
	<i>Adjusted*</i>	1.7	(1.1-2.7)	2.0	(1.1-3.9)	-	-	-	-	2.8	(1.2-6.5)
Inner ear conditions	<i>crude</i>	2.6	(1.4-4.9)	9.4	(4.8-18.4)	-	-	-	-	-	-
	<i>Adjusted*</i>	1.5	(0.8-2.9)	2.2	(1.1-4.5)	-	-	-	-	-	-
Intestinal conditions	<i>crude</i>	-	-	-	-	-	-	-	-	-	-

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
	<i>Adjusted*</i>	-	-	-	-	-	-	-	-	-	-
Joint and spinal conditions	<i>crude</i>	3.3	(1.9-5.9)	7.5	(3.5-16)	-	-	-	-	-	-
	<i>Adjusted*</i>	1.9	(1.0-3.4)	2.3	(1.0-4.9)	-	-	-	-	-	-
Liver disease: moderate/severe	<i>crude</i>	3.1	(1.6-6.4)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	3.3	(1.7-6.8)	-	-	-	-	-	-	-	-
Major psychiatric disorders	<i>crude</i>	2.5	(1.2-5.3)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	2.1	(1.0-4.5)	-	-	-	-	-	-	-	-
Nutritional disorders	<i>crude</i>	1.9	(0.7-5.0)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	1.5	(1.9-5.0)	-	-	-	-	-	-	-	-
Metabolic conditions	<i>crude</i>	1.9	(1.4-2.8)	3.8	(2.3-6.5)	4.2	(1.7-10.2)	2.1	(0.9-4.5)	2.2	(1.2-3.9)
	<i>Adjusted*</i>	1.7	(1.2-2.4)	1.7	(1.0-2.9)	2.2	(0.9-5.4)	2.1	(0.9-4.6)	2.2	(1.2-4.0)
Previous myocardial infarctions	<i>crude</i>	3.9	(2.8-5.5)	10.4	(6.4-16.7)	11.9	(4.5-31.2)	3.4	(1.4-8.1)	3.3	(1.8-6.1)
	<i>Adjusted*</i>	2.6	(1.8-3.6)	2.5	(1.5-4.1)	3.9	(1.5-10.6)	2.3	(0.9-5.7)	2.3	(1.2-4.3)
Neurological conditions	<i>crude</i>	5.4	(3.4-8.6)	12.7	(6.8-23.6)	-	-	-	-	-	-
	<i>Adjusted*</i>	3.1	(1.9-5.0)	3.1	(1.6-5.7)	-	-	-	-	-	-
Obesity	<i>crude</i>	1.3	(0.6-3.0)	2.8	(1.2-6.3)	-	-	-	-	2.4	(1.0-5.9)
	<i>Adjusted*</i>	1.5	(0.7-3.5)	2.8	(1.2-6.4)	-	-	-	-	3.7	(1.5-9.2)
osteoporosis and bone conditions	<i>crude</i>	3.0	(1.4-6.4)	12.6	(6.2-25.8)	-	-	-	-	-	-
	<i>Adjusted*</i>	1.5	(0.7-3.2)	1.7	(0.8-3.6)	-	-	-	-	-	-
Other cardiac conditions	<i>crude</i>	2.2	(1.6-3.1)	8.0	(5.0-12.8)	-	-	2.1	(0.8-5.5)	2.9	(1.6-5.2)
	<i>Adjusted*</i>	1.7	(1.2-2.4)	1.9	(1.1-3.0)	-	-	1.6	(0.6-4.2)	2.1	(1.2-3.9)
Hemi/para/ quadraplegia	<i>crude</i>	6.2	(4.0-9.6)	10.1	(5.6-18.3)	-	-	-	-	3.0	(1.2-7.4)
	<i>Adjusted*</i>	3.6	(2.3-5.6)	2.2	(1.2-4.1)	-	-	-	-	2.7	(1.1-6.7)
Muscular/ peripheral nerve	<i>crude</i>	3.6	(1.6-8.1)	-	-	-	-	-	-	-	-

		Colorectal		Breast		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
	<i>Adjusted*</i>	2.9	(1.3-6.4)	-	-	-	-	-	-	-	-
Pulmonary circulation disorders	<i>crude</i>	4.5	(2.2-9.1)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	3.1	(1.5-6.3)	-	-	-	-	-	-	-	-
Peripheral vascular disease	<i>crude</i>	2.7	(1.7-4.4)	13.0	(7.2-23.5)	-	-	8.5	(3.5-20.4)	6.3	(3.3-11.9)
	<i>Adjusted*</i>	1.6	(1.0-2.6)	3.6	(2.0-6.7)	-	-	5.1	(2.0-13.0)	4.6	(2.4-8.9)
Renal disease	<i>crude</i>	5.1	(3.6-7.3)	22.0	(14.2-34.1)	20.7	(8.3-51.6)	4.7	(2.2-10.4)	-	-
	<i>Adjusted*</i>	3.3	(2.3-4.7)	5.7	(3.6-9.0)	4.6	(1.7-12.5)	3.8	(1.7-8.6)	-	-
Sleep disorders	<i>crude</i>	-	-	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	-	-	-	-	-	-	-	-	-	-
Urinary tract disorders	<i>crude</i>	1.9	(0.9-4.0)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	1.1	(0.5-2.4)	-	-	-	-	-	-	-	-
Venous insufficiency	<i>crude</i>	-	-	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	-	-	-	-	-	-	-	-	-	-
Other malignancies	<i>crude</i>	1.6	(1.0-2.5)	-	-	-	-	-	-	-	-
	<i>Adjusted*</i>	1.2	(0.8-1.9)	-	-	-	-	-	-	-	-

\*adjusted for age and stage

-- data withheld because of small numbers and unstable estimates

**Table 21: Crude and adjusted hazard ratios (HR) of all-cause and non-cancer mortality by C3 condition for all sites combined**

	All-cause mortality				Non-cancer mortality			
	Crude		Adjusted*		Crude		Adjusted*	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Alcohol abuse	3.2	(2.6-4.0)	1.7	(1.3-2.1)	4.5	(2.6-7.6)	2.9	(1.7-5.2)
Anaemia	2.1	(1.9-2.3)	1.3	(1.2-1.5)	3.3	(2.6-4.4)	1.8	(1.4-2.4)
Angina	1.8	(1.5-2.0)	1.2	(1.0-1.3)	3.3	(2.5-4.4)	1.7	(1.3-2.2)
Anxiety disorders	1.7	(1.3-2.2)	1.6	(1.2-2.1)	2.8	(1.6-5.0)	1.8	(1.0-3.1)
Cardiac Arrhythmias	2.3	(2.1-2.5)	1.3	(1.2-1.4)	5.0	(4.1-6.1)	2.2	(1.7-2.7)
Cardiac valve disorders	2.4	(2.0-2.8)	1.6	(1.3-1.8)	7.0	(5.3-9.2)	3.0	(2.3-4.0)
Cerebrovascular disease	2.7	(2.4-3.0)	1.5	(1.3-1.7)	6.7	(5.3-8.5)	3.0	(2.3-3.8)
Congestive heart failure	3.1	(2.7-3.4)	1.8	(1.6-2.0)	9.1	(7.4-11.2)	3.5	(2.8-4.4)
Coagulopathies and other blood disorders	2.4	(2.2-2.6)	1.4	(1.3-1.6)	4.1	(3.3-5.1)	2.1	(1.7-2.6)
Connective tissue disorders	2.2	(1.7-2.9)	1.5	(1.2-2.0)	3.5	(2-6.2.0)	1.7	(0.9-3.0)
Chronic respiratory disease	2.6	(2.4-2.9)	1.6	(1.5-1.8)	5.7	(4.6-7.1)	3.0	(2.4-3.7)
Dementia	5.2	(4.4-6.1)	2.4	(2.0-2.8)	13.3	(9.6-18.2)	3.8	(2.8-5.3)
Diabetes without complications	1.2	(1.1-1.4)	0.9	(0.8-1.0)	1.3	(0.9-1.8)	1.0	(0.7-1.4)
Diabetes with complications	2.1	(1.9-2.3)	1.3	(1.1-1.4)	4.1	(3.2-5.2)	2.4	(1.9-3.1)
Endocrine disorders	2.1	(1.8-2.6)	1.5	(1.3-1.9)	3.9	(2.6-6.0)	2.2	(1.4-3.3)
Epilepsy	2.8	(2.0-3.9)	2.6	(1.9-3.7)	3.3	(1.4-8.0)	2.8	(1.2-6.8)
Eye conditions	2.1	(1.8-2.4)	1.4	(1.2-1.6)	3.5	(2.4-4.9)	1.9	(1.3-2.7)
Hepatitis	2.3	(1.8-2.8)	1.1	(0.8-1.4)	1.2	(0.6-2.8)	1.5	(0.6-3.9)
Upper gastrointestinal	2.8	(2.4-3.2)	1.2	(1.1-1.4)	2.2	(1.4-3.4)	1.1	(0.7-1.8)
Hypertension	2.0	(1.8-2.1)	1.3	(1.2-1.4)	4.2	(3.5-5.0)	2.1	(1.7-2.5)
Inflammatory bowel	2.0	(1.7-2.2)	1.4	(1.3-1.6)	2.4	(1.8-3.3)	1.7	(1.2-2.3)
Inner ear conditions	2.2	(1.8-2.6)	1.4	(1.2-1.7)	4.0	(2.6-6.0)	1.7	(1.1-2.6)
Intestinal conditions	1.3	(1.2-1.5)	1.0	(0.9-1.2)	1.9	(1.4-2.6)	1.1	(0.8-1.5)
Joint and spinal conditions	2.4	(2.0-2.9)	1.5	(1.2-1.8)	4.2	(2.8-6.3)	2.0	(1.3-3.0)
Liver disease: mod/severe	3.0	(2.6-3.5)	1.2	(1.0-1.4)	3.0	(2-4.7.0)	2.5	(1.5-4.2)
Major psychiatric disorders	1.9	(1.5-2.4)	1.7	(1.4-2.1)	3.1	(1.9-5.0)	2.2	(1.3-3.6)
Nutritional disorders	2.8	(2.2-3.6)	1.8	(1.4-2.3)	7.1	(4.5-11.2)	3.2	(2.0-5.0)
Metabolic conditions	1.8	(1.6-1.9)	1.2	(1.1-1.3)	2.7	(2.1-3.4)	1.8	(1.4-2.3)
Previous myocardial infarctions	2.5	(2.2-2.7)	1.5	(1.3-1.6)	5.6	(4.4-7.1)	2.5	(2.0-3.2)
Neurological conditions	3.0	(2.5-3.6)	1.8	(1.5-2.2)	6.6	(4.7-9.4)	2.9	(2.0-4.1)

	All-cause mortality				Non-cancer mortality			
	Crude		Adjusted*		Crude		Adjusted*	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Obesity	1.4	(1.2-1.7)	1.4	(1.2-1.6)	2.0	(1.3-3.0)	2.3	(1.5-3.5)
Osteoporosis/ bone conditions	2.5	(2.0-3.2)	1.3	(1.1-1.7)	4.8	(3-7.7.0)	1.6	(1.0-2.6)
Other cardiac conditions	1.8	(1.6-2.1)	1.2	(1.1-1.3)	3.6	(2.8-4.6)	1.9	(1.5-2.4)
Hemi/para/ quadraplegia	2.7	(2.3-3.2)	1.6	(1.4-1.9)	6.1	(4.4-8.4)	2.8	(2.0-3.9)
Muscle/ Peripheral nerve	2.2	(1.7-2.9)	1.3	(1.0-1.8)	5.4	(3.2-9.2)	3.3	(1.9-5.7)
Pulmonary circulation	2.1	(1.6-2.8)	1.3	(1.0-1.7)	4.8	(2.8-8.1)	2.6	(1.5-4.4)
Peripheral vascular disease	2.4	(2.1-2.8)	1.4	(1.2-1.7)	6.0	(4.5-8.0)	2.7	(2.0-3.6)
Renal disease	3.2	(2.8-3.6)	1.9	(1.7-2.1)	8.3	(6.6-10.3)	4.0	(3.1-5.0)
Sleep disorders	1.8	(1.2-2.6)	2.1	(1.5-3.0)	2.4	(1-5.7.0)	4.1	(1.7-9.9)
Urinary tract disorders	2.4	(2.0-2.9)	1.2	(1.0-1.5)	2.5	(1.5-4.2)	1.1	(0.7-1.9)
Venous insufficiency	2.5	(1.7-3.9)	1.7	(1.1-2.6)	4.8	(2.0-11.6)	2.0	(0.8-4.9)
Other malignancies	1.9	(1.7-2.2)	1.3	(1.2-1.5)	1.9	(1.3-2.7)	1.2	(0.8-1.7)

\*adjusted for age, sex, site and stage

## **Development of the site-specific hospitalisation-based comorbidity indices**

The next step in the process was to develop site-specific comorbidity indices for the five sites. To remind the reader, conditions were included in a particular site index if they had a minimum prevalence of 0.05% among patients within that cancer site cohort. Conditions were excluded if they were likely to be related to the primary cancer (e.g. liver and renal conditions were excluded for patients with upper GI and urological cancers respectively). Each condition was weighted according to its impact on non-cancer death using either the log (HR) estimates from the site-specific age/stage adjusted models, or, where there were less than 5 non-cancer deaths, substituted weights based on the log (HR) from the age, sex, site and stage adjusted models of non-cancer deaths with all sites combined. Indices were then calculated for each patient by summing log (HRs) for each of the conditions recorded for that patient.

Table 22 shows the list of conditions included in each of the cancer site specific indices, along with the parameter estimates (log HR), and related HRs for each condition. The number of conditions included at each site varied according to their prevalence in each cohort, and the number of conditions excluded because of association with the primary condition. Thirty-eight conditions were included for upper GI and urological cancers, 37 for colorectal, 34 for gynaecological and 33 for breast. Twenty-six conditions were included in all five site-specific indices.

**Table 22: List of conditions in the site-specific C3 indices, coefficient estimates and HRs from site specific age/ stage-adjusted models or age/sex/site/stage adjusted all-site models with non-cancer death as outcome in development cohorts**

	Colorectal		Breast		Gynaecological		Liver/Stomach		Urological	
	Coeff	HR	Coeff	HR	Coeff	HR	Coeff	HR	Coeff	HR
Alcohol abuse	1.03*	2.8	NI	NI	NI	NI	1.17*	3.2	1.32*	3.8
Anaemia	NI	NI	0.64	1.9	0.73*	2.1	NI	NI	0.72*	2.1
Angina	0.58	1.8	0.40	1.5	0.64*	1.9	0.87	2.4	0.50	1.7
Anxiety/Behavioural Disorders	0.99	2.7	0.59*	1.8	0.70*	2.0	0.61*	1.9	0.69*	2.0
Cardiac Arrhythmia	0.84	2.3	0.94	2.6	0.58	1.8	0.33	1.4	0.51	1.7
Cardiac Valve Disorder	0.98	2.7	1.32	3.7	1.36*	3.9	1.19*	3.3	0.89	2.4
Cerebrovascular Disease	1.21	3.4	0.99	3.1	0.87	2.4	1.18*	3.3	1.25	3.5
Coronary Heart Failure	1.16	3.2	0.90	2.5	1.22	3.4	1.44	4.2	1.82	6.2
Coagulopathy / Blood Disorders	0.56	1.8	1.14	3.1	1.19	3.3	NI	NI	1.25	3.5
Connective Tissue Disease	0.59	1.8	0.53*	1.7	0.63*	1.9	0.55*	1.7	0.62*	1.9
CPD and Asthma	1.00	2.7	0.96	2.6	1.36*	3.9	0.86	2.4	1.41	4.1
Dementia	1.14	3.1	0.94	2.6	NI	NI	1.46*	4.3	2.24	9.4
Diabetes no complications	-0.13	0.9	-0.18	0.8	1.05	2.9	0.33	1.4	-0.03*	1.0
Diabetes with Complications	0.64	1.9	1.01	2.8	1.18	3.2	1.02	2.8	1.22	3.4
Endocrine Disorders	0.68	2.0	0.61	1.8	0.95*	2.6	0.83*	2.3	0.94*	2.6
Epilepsy	NI	NI	NI	NI	NI	NI	1.13*	3.1	NI	NI
Eye Problems	0.43	1.5	0.86	2.4	0.78*	2.2	0.68*	2.0	0.77*	2.2
GI Disease	0.46	1.6	0.11*	1.1	0.14*	1.2	NI	NI	0.13*	1.1
Hepatitis: chronic viral	NI	NI	NI	NI	NI	NI	0.42*	1.5	0.47*	1.6
Hypertension	0.78	2.2	0.53	1.7	0.63	1.9	0.70	2.0	0.76	2.2
Inflammatory Bowel Disorder	0.55	1.7	0.70	2.0	0.65*	1.9	0.57*	1.8	0.64*	1.9
Inner Ear Disorder	0.43	1.5	0.80	2.2	0.67*	2.0	0.59*	1.8	0.66*	1.9
Intestinal Disorders	NI	NI	0.11*	1.1	0.13*	1.1	0.12*	1.1	0.13*	1.1
Joint or Spinal Disorders	0.63	1.9	0.82	2.3	0.86*	2.4	0.75*	2.1	0.84*	2.3

	Colorectal		Breast		Gynaecological		Liver/Stomach		Urological	
	Coeff	HR	Coeff	HR	Coeff	HR	Coeff	HR	Coeff	HR
Liver disease - Mod/Severe	1.21	3.4	NI	NI	1.15*	3.2	NI	NI	1.13*	3.1
Major Psychiatric Condition	0.75	2.1	0.82*	2.3	0.98*	2.7	0.85*	2.4	0.96*	2.6
Malnutrition	1.11*	3.0	NI	NI	1.44*	4.2	1.26*	3.5	1.42*	4.1
Metabolic Disorder	0.51	1.7	0.53	1.7	0.77*	2.2	0.72	2.1	0.80	2.2
Myocardial Infarction	0.94	2.6	0.91	2.5	1.37	3.9	0.84	2.3	0.83	2.3
Neurological Conditions	1.14	3.1	1.12	3.1	1.32*	3.8	1.15*	3.2	1.30*	3.7
Obesity	0.43	1.5	1.03	2.8	1.03*	2.8	0.90*	2.5	1.02*	2.8
Osteoporosis/Bone Disorders	0.40	1.5	0.55	1.7	0.61*	1.9	0.54*	1.7	0.61*	1.8
Other Cardiac Conditions	0.53	1.7	0.62	1.9	0.77*	2.2	0.48	1.6	0.76	2.1
Other Malignancy	0.20	1.2	0.18*	1.2	0.21*	1.2	0.18*	1.2	0.21*	1.2
Paralysis	1.28	3.6	0.80	2.2	1.28*	3.6	1.12*	3.1	0.99	2.7
Muscle/peripheral nerve Dis	1.05	2.9	NI	NI	NI	NI	1.30*	3.7	1.47*	4.3
Pulmonary Circulation Dis	1.14	3.1	NI	NI	NI	NI	1.03*	2.8	1.16*	3.2
Peripheral Vascular Disease	0.47	1.6	1.29	3.7	1.22*	3.4	1.63	5.1	1.54	4.7
Renal Disease	1.18	3.3	1.74	5.7	1.53	4.6	1.34	3.8	NI	NI
Sleep Disorder	1.35*	3.9	NI	NI	1.75*	5.7	1.53*	4.6	1.72*	5.6
Urinary Tract Disorder	0.12	1.1	NI	NI	NI	NI	0.13*	1.1	NI	NI
Venous Insufficiency	NI	NI	NI	NI	NI	NI	0.76*	2.2	NI	NI

NI: Not included because prevalence less than 0.5%, or condition closely related to primary disease.

\* Weight substituted based on parameter estimates from age/sex/stage/site/ adjusted models from all sites combined.

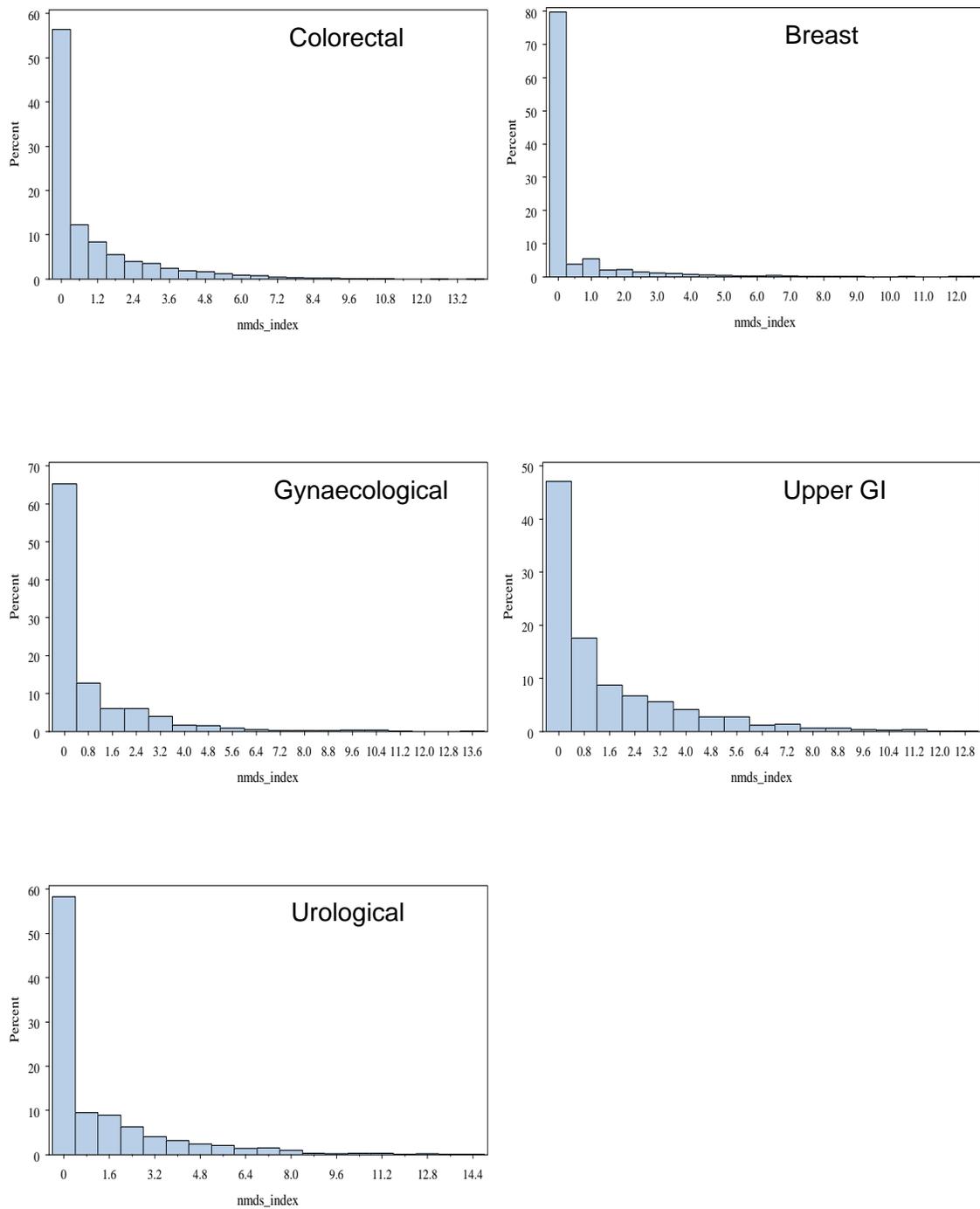
## **Performance and validation of the site-specific hospitalisation-based comorbidity indices**

Figure 7 and Table 23 show the descriptive statistics for the resultant comorbidity indices in the development cohorts. The ranges of C3 scores across individuals are similar by site, with the lowest scores at or just below zero and the highest scores around 13-14. The C3 scores tended to be lower among patients with breast cancer (78% with a score of zero or below, and 5% with a score of 4 or more), and highest among those with upper gastrointestinal cancers (41% with score zero or below and 19% with a score of 4 or more), a pattern that is entirely consistent with the age and likely comorbidity profiles of those cohorts. The other three cancer sites were intermediate between these two with just over a half of all patients with colorectal or urological patients scoring 0 or below, and 62% of gynaecological patients.

Similar patterns across cancer sites are seen with the Charlson comorbidity scores, but considerably higher proportions of patients scored 0 (87% of breast, 79% of gynaecological, 71% for each of urological and colorectal, and 57% of urological cancer patients).

The Spearman's rank correlation coefficients which measured the correlation between ranked Charlson scores and C3 index scores ranged from 0.61 for colorectal cancer to 0.78 for upper gastrointestinal cancers in the development cohorts (Table 23) supporting concurrent validity of the C3 indices. The range of correlation coefficients between Charlson and the C3 indices were very similar in the validation cohorts (data not shown).

**Figure 7: Distribution of site-specific C3 index scores**



**Table 23: Score distributions of C3 indices and comparison with Charlson index scores from development cohorts**

	Colorectal (n=5376)	Breast (n=5076)	Gynaecol (n=1223)	Upper GI (n=961)	Urological (n=1460)
<b>Distributions of C3 index scores</b>					
Range	-0.13 - 14.01	-0.18 - 12.58	0 - 13.99	0 - 12.83	-0.03 - 14.17
Mean (SD)	0.98 (1.68)	0.43 (1.22)	0.85 (1.68)	1.45 (2.14)	1.27 (2.17)
Median (IQR)	0.00 (1.24)	0.00 (0.00)	0.00 (1.05)	0.41 (2.19)	0.00 (1.69)
<b>Correlation with Charlson index*</b>					
	0.61	0.71	0.76	0.78	0.71
<b>Charlson score categories</b>					
0 (%)	71.1	87.3	78.5	56.9	70.5
1 (%)	15.5	7.5	14.2	21.4	15.5
2 (%)	5.3	2.1	2.7	6.6	6.1
3+ (%)	8.1	3.1	4.6	15.1	7.9
<b>Total</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>
<b>C3 index score categories</b>					
≤0 (%)	53.9	78.4	61.7	40.9	54.8
>0 and ≤1 (%)	15.7	8.7	10.1	19.6	12.3
>1 and ≤2 (%)	12.3	5.5	12.3	12.9	9.7
>2 and ≤3 (%)	6.4	2.7	6.8	7.9	7.9
>4 (%)	11.7	4.7	9.2	18.7	15.4
<b>Total</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>

SD, Standard deviation; IQR, Interquartile range ; \*Spearman's rank coefficient.

Table 24 shows the results of analyses using the validation cohorts. These analyses compared the ability of C3 indices to discriminate between those who died (from any cause, or from a non-cancer cause) within a year of diagnosis compared with the NCI and the Charlson indices. We used bootstrapping to calculate 95% confidence intervals around the c-statistics and the difference between the c-statistics. For the all deaths outcome, non-convergence (due to quasi-complete separation) of the logistic regression models was rare (>98% of bootstrap samples converged across all cancer sites), with a similarly high convergence rate for non-cancer deaths for colorectal cancer and urological cancer. However, for non-cancer deaths, model convergence was only 90.9% for breast cancer patients; 62.3% for the upper gastrointestinal cancer group; and for the gynaecological cancers, no bootstrapped model converged for non-cancer deaths because of relatively small numbers of deaths in these categories.

For colorectal, and upper GI cancers, particularly for non-cancer death, the C3 indices performed better than the other indices, with confidence intervals around the difference in c-statistics excluding the null. However, for upper GI cancers for all-cause mortality, urological, gynaecological and breast cancers, there was no difference in c-statistics between models that included Charlson compared with those that included C3 indices.

The AICs shown in Table 25 suggest that models that included C3 indices performed better than either Charlson or NCI indices for colorectal cancer, and marginally better than Charlson for upper gastrointestinal or urological cancers. However, according to this criterion the C3 indices performed slightly less well than Charlson and NCI indices for breast, and the Charlson index for gynaecological cancers.

These results demonstrated the validity of site-specific comorbidity indices for a range of cancer sites. The indices incorporated all conditions included in other commonly used comorbidity indices, as well as those identified as important in terms of impact on quality and length of life by cancer clinicians. Although these indices performed generally as well or better than either the Charlson or NCI comorbidity indices, any improvement was modest.

**Table 24: Concordance statistics from logistic regression models predicting death from all-causes or non-cancer causes, within one year of diagnosis using the validation cohorts: median (2.5th percentile from bootstrapped c-indices, 97.5th percentile)**

Cancer site	Deaths	Baseline model*	Baseline* + C3 index	Baseline* + Charlson	Baseline* + NCI index	Difference: C3 index vs. Charlson	Difference: C3 index vs. NCI index	% bootstraps converged
<b>Colorectal</b>	All-cause	0.82 (0.81, 0.84)	0.84 (0.82, 0.85)	0.83 (0.82, 0.85)	0.83 (0.82, 0.85)	0.003 (0, 0.007)	0.003 (0, 0.007)	100
	Non-cancer	0.75 (0.70, 0.79)	0.80 (0.76, 0.84)	0.79 (0.74, 0.83)	0.79 (0.75, 0.83)	0.016 (0.001, 0.036)	0.012 (-0.005, 0.032)	99.96
<b>Breast</b>	All-cause	0.90 (0.88, 0.93)	0.92 (0.89, 0.94)	0.91 (0.89, 0.93)	0.91 (0.89, 0.93)	0.003 (-0.001, 0.009)	0.002 (-0.002, 0.008)	100
	Non-cancer	0.91 (0.87, 0.94)	0.94 (0.91, 0.96)	0.93 (0.90, 0.96)	0.94 (0.90, 0.96)	0.006 (-0.006, 0.027)	0.003 (-0.011, 0.022)	90.88
<b>Gynaecol</b>	All-cause	0.90 (0.88, 0.92)	0.91 (0.89, 0.93)	0.91 (0.89, 0.93)	n/a	0 (-0.004, 0.004)		98.16
	Non-cancer	**	**	**				0
<b>Upper GI</b>	All-cause	0.78 (0.74, 0.81)	0.78 (0.75, 0.81)	0.78 (0.75, 0.81)	n/a	0 (-0.006, 0.006)		99.85
	Non-cancer	0.67 (0.59, 0.75)	0.76 (0.67, 0.83)	0.71 (0.62, 0.79)		0.050 (0.007, 0.109)		62.32
<b>Urological</b>	All-cause	0.85 (0.83, 0.88)	0.86 (0.84, 0.88)	0.86 (0.83, 0.88)	n/a	0.003 (0, 0.008)		99.97
	Non-cancer	0.79 (0.73, 0.85)	0.82 (0.76, 0.87)	0.82 (0.76, 0.87)		0.003 (-0.010, 0.020)		100

\* Including age, sex (where relevant) and stage; \*\* no bootstrap model converged.

**Table 25: Akaike Information Criteria (AICs) from logistic regression models predicting death from all-causes or non-cancer causes, within one year of diagnosis using the validation cohorts**

Cancer site	Deaths	Baseline model*	Baseline* + C3 index	Baseline* + Charlson	Baseline* + NCI index
<b>Colorectal</b>	All-cause	3296.5	<b>3216.9</b>	3242.6	3244.3
	Non-cancer	911.6	<b>869.8</b>	884.9	884.6
<b>Breast</b>	All-cause	1011.5	984.3	981.2	978.1
	Non-cancer	363.1	337.4	335.9	332
<b>Gynaecological</b>	All-cause	644.2	626.2	619.1	NA
	Non-cancer	86.8	88	86.3	
<b>Upper GI</b>	All-cause	824.3	824.1	824.3	NA
	Non-cancer	244.3	233.4	242.2	
<b>Urological</b>	All-cause	939.8	928.9	937.7	NA
	Non-cancer	371.1	359.7	363.1	

\*including age, sex (where relevant) and stage; AICs are from the "canonical" application of the model (i.e. the model run on the original cohort for each cancer); bolded numbers indicate a greater than 10 point difference between models including C3 compared with those including Charlson and/or NCI indices; NA = not applicable;.

## **Section 3: Use of pharmaceutical data to measure comorbidity**

This section describes the validation of data on comorbidity obtained from a routine pharmaceutical database, the prevalence and impact of conditions identified through this mechanism, and the development and validation of pharmaceutical data-based comorbidity indices.

### **Results of the comparison exercise of pharmaceutical data with hospital notes review data**

Table 26 shows a comparison of conditions using each of the hospital notes review data and the community pharmaceutical data. Patients included in the manual review were a subset of those included in the *development* cohort and were diagnosed with liver, rectal or stomach cancers (n=189, 194 and 336 respectively). Prevalence estimates varied between the two data sources as expected. For example, angina was almost twice as likely to be identified in the hospital notes review than the pharmaceutical data, whilst hypertension was more commonly identified in the latter. Because some medications can be used for either (or both) of angina and hypertension, these categories were combined, and the resulting overall prevalence estimates were similar (44% from notes review data compared with 49% from pharmaceutical data;  $p=0.002$ ). The prevalence of chronic respiratory disease and diabetes were high in this cohort, but reasonably similar across the two data sources (for respiratory disease; 14% for notes review and 17% for pharmaceutical data for respiratory disease;  $p=0.04$ , and for diabetes 25% and 21% respectively;  $p<0.001$ ). In contrast, anxiety and depression were nearly three times more frequently identified in the pharmaceutical data (16.0%) than hospital notes review data (5.6%), although the prevalence estimates of other major psychiatric disorders were not significantly different (1.8% and 1.1% respectively).

The kappa coefficients suggest there is very good agreement between the two sources of data for diabetes ( $\kappa=0.83$ ); and moderate agreement for hypertension (alone;  $\kappa=0.58$ ); ischaemic heart disease combined with hypertension ( $\kappa=0.62$ ); cardiac arrhythmias ( $\kappa=0.42$ ); and congestive heart failure ( $\kappa=0.55$ ). For the remaining conditions (angina, chronic respiratory disease, peptic ulcer disease, anxiety or depression and major psychiatric conditions), agreement was poor ( $\kappa<0.4$ ). It is interesting to note that two of the conditions for which prevalence estimates were similar, had low kappa coefficients (chronic respiratory disease and major psychiatric conditions). The low agreement is not particularly surprising for respiratory disease categories which are not exact matches for each other. The pharmaceutical data included (only) medications for reactive airways disease, whereas the notes review data include non-reactive chronic lung conditions.

**Table 26: Comparison of comorbid conditions identified in hospital notes review and community pharmaceutical data**

<b>Condition</b>	<b>Prevalence: Notes review</b>	<b>Prevalence: Pharms data</b>	<b>p-value*</b>	<b>Kappa coefficient</b>	<b>95% CI for kappa</b>
Angina	14.1%	7.7%	<0.001	0.37	0.27-0.48
Hypertension	38.7%	48.5%	<0.001	0.58	0.52-0.64
Ischaemic heart disease/ hypertension	44.1%	49.1%	0.002	0.62	0.56-0.68
Cardiac arrhythmias	15.0%	5.2%	<0.001	0.42	0.32-0.53
Congestive heart failure	9.9%	15.0%	<0.001	0.55	0.46-0.64
Chronic respiratory disease	13.8%	17.0%	0.04	0.33	0.24-0.42
Peptic ulcer disease	24.0%	42.0%	<0.001	0.3	0.23-0.37
Diabetes mellitus	25.3%	20.6%	<0.001	0.83	0.78-0.88
Anxiety or depression	5.6%	16.0%	<0.001	0.26	0.17-0.36
Other major psychiatric disorder (with psychosis)	1.1%	1.8%	0.17	0.37	0.11-0.64

\*Testing whether the proportion of patients with condition is significantly different between the medical notes and administrative data

## Prevalence of comorbid conditions using pharmaceutical data

Table 27 shows the number and prevalence of each of the 19 individual comorbid conditions included in the PBCI by cancer site in the development cohort. As for conditions identified using hospitalisation data, the most commonly identified condition was hypertension (34.0-52.4% across cancer sites). Other common conditions for which medications were prescribed were gastric acid disorder (20.5-51.5%), hyperlipidaemia (16.9-30.8%), conditions requiring antiplatelet medication (13.6-26.0%) and reactive airway disease (13.2-17.5%). Cardiac conditions (e.g., cardiac arrhythmias: 2.3-5.9%, congestive heart failure: 6.5-16.6%, and angina: 4.0-9.5%) and diabetes (6.1-18.8%) were also common.

The prevalence of conditions varied somewhat across sites, with lower prevalence among patients with breast and gynaecological cancers consistent with their younger age, and gender.

## **Impact of comorbid conditions on mortality among cancer cohorts**

Table 28 and 29 show the crude and age/stage adjusted HRs for the conditions identified in the pharmaceutical data on all-cause and non-cancer mortality respectively within each site category. Table 27 also shows the coefficient estimates and hazard ratios from age, site and stage adjusted Cox regression models from all sites combined giving the association of each condition with non-cancer mortality in the full combined development cohort.

### **All-cause mortality**

There were no conditions that were strongly associated with all-cause mortality with very few adjusted HRs greater than 2 (Table 28). The associations between individual conditions and all-cause mortality were similar across sites for most conditions, and statistical imprecision is a possible explanation for the few where there was more marked variation. Medications that were primarily aimed at protecting from future poor health (specifically antiplatelet, lipid lowering and antihypertensive medications) tended to have no adverse effect on mortality, with adjusted HRs ranging between 0.9 and 1.1 for all three of these medication categories, in all cancer sites.

### **Non-cancer mortality**

As for the hospitalisation-based indices, the association of comorbidity with non-cancer death was generally stronger than those with all-cause death (Table 29). Again, the associations were reasonably consistent across sites, although the relative impact varied across different comorbid conditions. The highest relative impacts were for congestive heart failure (adjusted HRs ranged across sites between 2.1 (1.0-4.7) for gynaecological cancers to 5.5 (2.6-11.5) for upper GI cancers), psychotic illness (HR=2.8; 1.6-6.9 for

breast cancers to HR=2.9; 1.5-5.6 for colorectal cancers), and cardiac arrhythmias (HR=2.1; 0.8-5.4 for gynaecological cancers to HR=3.5; 1.5-8.2 for upper GI cancers).

**Table 27: Prevalence n (%) of conditions included in the PBCI index by site, and coefficient estimates and hazard ratios from age/site and stage-adjusted Cox regression models with non-cancer mortality as outcomes in the full (combined) development cohort**

<b>PBCI Conditions</b>	<b>Colorectal (n=5376)</b>	<b>Breast (n=5076)</b>	<b>Gynaecological (n=1223)</b>	<b>Upper GI (n=961)</b>	<b>Urological (n=1460)</b>	<b>Coeff</b>	<b>HR (all sites)</b>
<b>Anaemia</b>	957 (17.8)*	238 (4.7)	111 (9.1)	152 (15.8)*	135 (9.2)	0.93	2.5
<b>Anticoagulation</b>	355 (6.6)	123 (2.4)	33 (2.7)	75 (7.8)	100 (6.8)	0.79	2.2
<b>Antiplatelet</b>	1346 (25.0)	690 (13.6)	231 (18.9)	223 (23.2)	380 (26.0)	0.46	1.6
<b>Anxiety and tension</b>	689 (12.8)	628 (12.4)	134 (11.0)	109 (11.3)	187 (12.8)	0.32	1.4
<b>Cardiac arrhythmias</b>	283 (5.3)	115 (2.3)	43 (3.5)	57 (5.9)	76 (5.2)	1.04	2.8
<b>Congestive heart failure</b>	638 (11.9)	330 (6.5)	114 (9.3)	160 (16.6)	198 (13.6)	1.16	3.2
<b>Depression</b>	673 (12.5)	759 (15.0)	155 (12.7)	106 (11.0)	214 (14.7)	0.35	1.4
<b>Diabetes</b>	524 (9.8)	310 (6.1)	170 (13.9)	181 (18.8)	163 (11.2)	0.41	1.5
<b>Epilepsy</b>	195 (3.6)	120 (2.4)	31 (2.5)	29 (3.0)	43 (2.9)	0.6	1.8
<b>Gastric acid disorder</b>	1824 (33.9)	1040 (20.5)	288 (23.5)	495 (51.5)*	458 (31.4)	0.34	1.4
<b>Hyperlipidaemia</b>	1516 (28.2)	859 (16.9)	293 (24.0)	256 (26.6)	449 (30.8)	0.15	1.2
<b>Hypothyroidism</b>	334 (6.2)	321 (6.3)	101 (8.3)	46 (4.8)	89 (6.1)	0.09	1.1
<b>Ischemic heart disease/Angina</b>	473 (8.8)	204 (4.0)	57 (4.7)	89 (9.3)	139 (9.5)	0.74	2.1
<b>Ischemic heart disease/Hypertension</b>	2685 (49.9)	1728 (34.0)	561 (45.9)	473 (49.2)	765 (52.4)	0.51	1.7
<b>Osteoporosis/Paget's</b>	570 (10.6)	455 (9.0)	107 (8.7)	75 (7.8)	141 (9.7)	0.53	1.7
<b>Parkinson's disease</b>	51 (1.0)	40 (0.8)	11 (0.9)	5 (0.5)	15 (1.0)	0.97	2.6
<b>Psychotic illness</b>	108 (2.0)	94 (1.9)	21 (1.7)	19 (2.0)	25 (1.7)	1.06	2.9
<b>Reactive airway disease</b>	810 (15.0)	672 (13.2)	166 (13.6)	168 (17.5)	226 (15.5)	0.62	1.9
<b>Steroids-responsive conditions</b>	596 (11.1)	404 (8.0)	109 (8.9)	116 (12.1)	180 (12.3)	0.54	1.7

\*excluded from calculation of PBCI

**Table 28: Crude and age/stage standardised hazard ratios (HR) of all-cause mortality by PBCI condition and cancer site**

		Breast		Colorectal		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
<b>Anaemia</b>	<i>crude</i>	2.4	(1.8-3.2)	-	-	1.0	(0.7-1.5)	-	-	2.0	(1.6-2.5)
	<i>Adjusted*</i>	1.4	(1.1-1.9)	-	-	1.4	(1.0-2.0)	-	-	1.4	(1.1-1.8)
<b>Anticoagulation</b>	<i>crude</i>	2.2	(1.5-3.3)	1.4	(1.2-1.7)	1.8	(1.1-2.9)	1.3	(1.0-1.7)	1.4	(1.0-1.8)
	<i>Adjusted*</i>	1.2	(0.8-1.8)	1.3	(1.1-1.6)	1.3	(0.8-2.2)	1.2	(0.9-1.5)	1.2	(0.9-1.6)
<b>Antiplatelet</b>	<i>crude</i>	2.1	(1.7-2.5)	1.3	(1.2-1.4)	1.3	(1.0-1.7)	1.2	(1.0-1.4)	1.2	(1.0-1.4)
	<i>Adjusted*</i>	1.1	(0.9-1.4)	1.1	(1.0-1.2)	1.0	(0.8-1.3)	1.1	(0.9-1.3)	1.1	(0.9-1.3)
<b>Anxiety</b>	<i>crude</i>	1.7	(1.3-2.1)	1.3	(1.1-1.4)	1.3	(0.9-1.7)	1.5	(1.2-1.8)	1.3	(1.1-1.7)
	<i>Adjusted*</i>	1.1	(0.9-1.4)	1.1	(1.0-1.3)	1.0	(0.7-1.3)	1.3	(1.1-1.7)	1.2	(1.0-1.5)
<b>Cardiac arrhythmias</b>	<i>crude</i>	3.7	(2.6-5.2)	1.7	(1.5-2.1)	2.3	(1.5-3.5)	1.5	(1.1-2)	2.1	(1.6-2.8)
	<i>Adjusted*</i>	1.3	(0.9-1.8)	1.5	(1.3-1.8)	1.5	(1.0-2.3)	1.3	(0.9-1.7)	1.6	(1.2-2.1)
<b>Congestive heart failure</b>	<i>crude</i>	3.7	(3.0-4.7)	2.2	(2.0-2.5)	2.2	(1.7-2.9)	1.6	(1.4-2.0)	1.8	(1.5-2.2)
	<i>Adjusted*</i>	1.5	(1.2-1.9)	1.7	(1.5-2.0)	1.7	(1.3-2.3)	1.4	(1.1-1.7)	1.5	(1.2-1.8)
<b>Depression</b>	<i>crude</i>	1.5	(1.2-1.8)	1.3	(1.1-1.5)	1.0	(0.8-1.4)	1.3	(1.1-1.7)	1.1	(0.9-1.4)
	<i>Adjusted*</i>	1.4	(1.2-1.8)	1.2	(1.1-1.4)	1.0	(0.8-1.4)	1.2	(0.9-1.5)	1.1	(0.9-1.3)
<b>Diabetes</b>	<i>crude</i>	1.6	(1.2-2.1)	1.0	(0.9-1.2)	1.2	(0.9-1.6)	1.0	(0.8-1.2)	1.3	(1.0-1.6)
	<i>Adjusted*</i>	1.2	(0.9-1.7)	0.9	(0.8-1.1)	1.4	(1.0-1.8)	1.0	(0.8-1.2)	1.0	(0.8-1.3)
<b>Epilepsy</b>	<i>crude</i>	2.5	(1.7-3.6)	1.4	(1.1-1.7)	2.1	(1.3-3.3)	1.1	(0.7-1.6)	1.6	(1.1-2.4)
	<i>Adjusted*</i>	2.6	(1.7-3.8)	1.2	(0.9-1.5)	1.7	(1.1-2.8)	0.8	(0.5-1.2)	1.5	(1.0-2.2)
<b>Gastric acid disorders</b>	<i>crude</i>	1.8	(1.5-2.2)	1.2	(1.1-1.3)	1.4	(1.2-1.8)	-	-	1.0	(0.9-1.2)
	<i>Adjusted*</i>	1.3	(1.1-1.6)	1.1	(1.0-1.2)	1.1	(0.9-1.4)	-	-	1.0	(0.8-1.2)
<b>Hyperlipidaemia</b>	<i>crude</i>	1.2	(0.9-1.5)	1.0	(0.9-1.1)	1.0	(0.8-1.3)	1.0	(0.9-1.2)	0.9	(0.8-1.1)
	<i>Adjusted*</i>	0.9	(0.8-1.2)	0.9	(0.8-1.0)	1.1	(0.8-1.3)	0.9	(0.8-1.1)	0.9	(0.7-1.1)
<b>Hypothyroidism</b>	<i>crude</i>	1.2	(0.8-1.6)	1.2	(1.0-1.5)	1.0	(0.7-1.4)	1.6	(1.2-2.2)	1.2	(0.9-1.6)
	<i>Adjusted*</i>	0.9	(0.7-1.3)	1.2	(1.0-1.4)	0.9	(0.6-1.3)	1.5	(1.0-1-2)	1.3	(0.9-1.7)

		Breast		Colorectal		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
<b>IHD/ Angina</b>	<i>crude</i>	2.4	(1.8-3.3)	1.4	(1.2-1.7)	1.9	(1.3-2.8)	1.4	(1.1-1.8)	1.5	(1.2-1.9)
	<i>Adjusted*</i>	1.2	(0.9-1.6)	1.3	(1.1-1.5)	1.1	(0.7-1.6)	1.3	(1.0-1.7)	1.1	(0.8-1.4)
<b>IHD/ Hypertension</b>	<i>crude</i>	1.7	(1.4-2.0)	1.2	(1.1-1.3)	1.2	(1.0-1.4)	1.2	(1.0-1.4)	1.3	(1.1-1.6)
	<i>Adjusted*</i>	0.9	(0.8-1.1)	1.0	(1.0-1.2)	1.0	(0.8-1.2)	1.0	(0.9-1.2)	1.1	(0.9-1.3)
<b>Osteoporosis/ Pagets</b>	<i>crude</i>	2.4	(1.9-3.0)	1.5	(1.3-1.7)	2.0	(1.5-2.6)	1.6	(1.2-2.1)	1.6	(1.3-2.1)
	<i>Adjusted*</i>	1.4	(1.1-1.7)	1.2	(1.0-1.4)	1.1	(0.8-1.5)	1.6	(1.2-2.1)	1.3	(1.0-1.6)
<b>Parkinson's disease</b>	<i>crude</i>	2.4	(1.3-4.7)	2.1	(1.4-3.0)	2.8	(1.3-5.9)	-	-	3.0	(1.6-5.4)
	<i>Adjusted*</i>	1.3	(0.6-2.4)	1.5	(1.1-2.2)	1.2	(0.6-2.6)	-	-	2.5	(1.4-4.6)
<b>Psychotic illness</b>	<i>crude</i>	2.3	(1.4-3.6)	2.2	(1.7-2.8)	1.4	(0.7-2.8)	1.4	(0.9-2.4)	1.8	(1.1-3.1)
	<i>Adjusted*</i>	1.8	(1.1-2.8)	1.8	(1.4-2.3)	1.4	(0.7-2.9)	1.4	(0.8-2.3)	1.3	(0.8-2.2)
<b>Reactive airway disease</b>	<i>crude</i>	1.5	(1.2-1.9)	1.4	(1.2-1.6)	1.2	(0.9-1.6)	1.2	(1.0-1.5)	1.6	(1.3-1.9)
	<i>Adjusted*</i>	1.2	(1.0-1.5)	1.3	(1.2-1.5)	1.5	(1.2-2.0)	1.2	(1.0-1.5)	1.3	(1.0-1.5)
<b>Steroid-responsive conditions</b>	<i>crude</i>	1.7	(1.3-2.2)	1.5	(1.3-1.7)	1.4	(1.0-1.9)	1.1	(0.9-1.4)	1.2	(1.0-1.6)
	<i>Adjusted*</i>	2.4	(1.8-3.2)	1.3	(1.1-1.4)	1.0	(0.7-1.5)	1.2	(0.9-1.4)	2.0	(1.6-2.5)

\*adjusted for age and stage.

- data withheld because of small numbers and unstable estimates

**Table 29: Crude and age/stage standardised hazard ratios (HR) of non-cancer mortality by PBCI condition and cancer site**

		Breast		Colorectal		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
<b>Anaemia</b>	<i>crude</i>	4.9	(3.1-7.7)	-	-	3.9	(1.7-8.7)	-	-	2.8	(1.6-5.1)
	<i>Adjusted*</i>	2.4	(1.5-3.8)	-	-	2.9	(1.2-6.8)	-	-	2.4	(1.3-4.3)
<b>Anticoagulation</b>	<i>crude</i>	5.6	(3.2-9.8)	3.6	(2.6-4.9)	-	-	3.2	(1.4-7.2)	3.0	(1.6-5.4)
	<i>Adjusted*</i>	1.8	(1.1-3.2)	2.5	(1.8-3.4)	-	-	2.2	(1.0-5.2)	2.1	(1.2-3.9)
<b>Antiplatelet</b>	<i>crude</i>	4.2	(2.9-6.0)	2.8	(2.2-3.6)	2.7	(1.3-5.7)	1.4	(0.7-3.0)	1.6	(1.0-2.6)
	<i>Adjusted*</i>	1.4	(1.0-2.0)	1.9	(1.5-2.5)	1.1	(0.5-2.4)	1.0	(0.5-2.1)	1.2	(0.7-1.9)
<b>Anxiety</b>	<i>crude</i>	3.0	(2.1-4.5)	1.8	(1.3-2.5)	-	-	1.7	(0.6-4.3)	1.8	(1.0-3.1)
	<i>Adjusted*</i>	1.3	(0.9-1.9)	1.4	(1.0-1.9)	-	-	1.2	(0.5-3.1)	1.5	(0.9-2.7)
<b>Cardiac arrhythmias</b>	<i>crude</i>	10.5	(6.6-16.6)	5.1	(3.7-6.9)	8.8	(3.6-21.7)	5.1	(2.2-11.6)	3.9	(2.1-7.4)
	<i>Adjusted*</i>	2.2	(1.4-3.5)	3.3	(2.4-4.5)	2.1	(0.8-5.4)	3.5	(1.5-8.2)	2.4	(1.2-4.5)
<b>Congestive heart failure</b>	<i>crude</i>	9.6	(6.7-13.7)	6.6	(5.1-8.4)	6.3	(2.9-13.5)	7.1	(3.7-13.8)	3.8	(2.3-6.1)
	<i>Adjusted*</i>	2.1	(1.4-3.1)	3.9	(3.0-5.1)	2.1	(1.0-4.7)	5.5	(2.6-11.5)	2.5	(1.6-4.2)
<b>Depression</b>	<i>crude</i>	2.1	(1.4-3.1)	1.7	(1.3-2.4)	-	-	-	-	1.0	(0.5-1.9)
	<i>Adjusted*</i>	1.7	(1.2-2.6)	1.5	(1.1-2.0)	-	-	-	-	0.9	(0.5-1.8)
<b>Diabetes</b>	<i>crude</i>	2.4	(1.4-4.0)	1.4	(1.0-2.0)	5.0	(2.4-10.3)	2.1	(1.0-4.1)	1.5	(0.8-2.8)
	<i>Adjusted*</i>	1.5	(0.9-2.6)	1.3	(0.9-1.8)	3.9	(1.9-8.0)	1.9	(0.9-3.8)	1.4	(0.8-2.6)
<b>Epilepsy</b>	<i>crude</i>	2.6	(1.2-5.6)	2.0	(1.2-3.3)	-	-	-	-	-	-
	<i>Adjusted*</i>	2.2	(1.0-4.8)	1.8	(1.1-3.0)	-	-	-	-	-	-
<b>Gastric acid disorders</b>	<i>crude</i>	3.7	(2.6-5.2)	1.7	(1.3-2.2)	2.3	(1.1-4.8)	-	-	1.3	(0.8-2.1)
	<i>Adjusted*</i>	1.8	(1.2-2.5)	1.3	(1.0-1.7)	1.7	(0.8-3.6)	-	-	1.1	(0.7-1.7)
<b>Hyperlipidaemia</b>	<i>crude</i>	1.5	(1.0-2.3)	1.7	(1.3-2.2)	1.4	(0.6-3.0)	2.0	(1.0-3.9)	0.8	(0.5-1.4)
	<i>Adjusted*</i>	0.9	(0.6-1.3)	1.4	(1.1-1.8)	1.0	(0.4-2.1)	1.8	(0.9-3.5)	0.7	(0.4-1.2)
<b>Hypothyroidism</b>	<i>crude</i>	1.4	(0.8-2.6)	1.3	(0.8-2.1)	2.3	(0.9-5.9)	4.4	(1.7-11.5)	1.6	(0.7-3.4)
	<i>Adjusted*</i>	0.7	(0.4-1.3)	1.0	(0.6-1.5)	1.2	(0.5-3.2)	3.4	(1.3-8.9)	1.3	(0.6-2.7)

		Breast		Colorectal		Gynaecological		Upper GI		Urological	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
<b>IHD/ Angina</b>	<i>crude</i>	5.9	(3.8-9.2)	3.8	(2.8-5.0)	7.1	(3.0-16.6)	3.6	(1.6-7.9)	2.0	(1.1-3.7)
	<i>Adjusted*</i>	1.5	(1.0-2.4)	2.6	(1.9-3.5)	2.1	(0.9-4.9)	2.3	(1.0-5.3)	1.3	(0.7-2.5)
<b>IHD/ Hypertension</b>	<i>crude</i>	3.7	(2.6-5.3)	3.4	(2.6-4.5)	4.0	(1.7-9.4)	2.9	(1.4-6.1)	1.5	(1.0-2.4)
	<i>Adjusted*</i>	1.1	(0.8-1.7)	2.2	(1.6-3.0)	1.4	(0.6-3.5)	2.3	(1.0-4.9)	1.1	(0.7-1.7)
<b>Osteoporosis/ Pagets</b>	<i>crude</i>	5.8	(4.0-8.3)	2.1	(1.5-2.9)	4.6	(2.1-10.4)	-	-	1.7	(0.9-3.2)
	<i>Adjusted*</i>	1.9	(1.3-2.8)	1.4	(1.0-1.9)	1.7	(0.8-4.0)	-	-	1.2	(0.6-2.3)
<b>Parkinson's disease</b>	<i>crude</i>	-	-	5.6	(3.0-10.5)	-	-	-	-	-	-
	<i>Adjusted*</i>	-	-	3.6	(1.9-6.9)	-	-	-	-	-	-
<b>Psychotic illness</b>	<i>crude</i>	5.0	(2.6-9.6)	3.7	(2.2-6.4)	7.6	-	-	-	-	-
	<i>Adjusted*</i>	2.9	(1.5-5.6)	2.8	(1.6-4.8)	2.4	-	-	-	-	-
<b>Reactive airway disease</b>	<i>crude</i>	2.0	(1.4-3.1)	2.3	(1.7-3.0)	4.5	(2.1-9.2)	1.9	(0.9-4.0)	2.1	(1.2-3.5)
	<i>Adjusted*</i>	1.4	(0.9-2.1)	1.9	(1.4-2.5)	4.5	(2.1-9.4)	1.5	(0.7-3.4)	1.9	(1.2-3.3)
<b>Steroid-responsive conditions</b>	<i>crude</i>	2.4	(1.5-3.8)	2.3	(1.7-3.1)	2.3	(0.9-6.1)	1.9	(0.8-4.4)	2.2	(1.3-3.8)
	<i>Adjusted*</i>	1.5	(0.9-2.3)	1.8	(1.3-2.4)	1.5	(0.6-4.1)	1.6	(0.7-3.6)	1.9	(1.1-3.3)

\*adjusted for age and stage

- data withheld because of small numbers and unstable estimates

## Development of the pharmaceutical-based comorbidity index

As described in the Methods chapter, the pharmaceutical-based comorbidity index (PBCI) was based on the 19 conditions that could be identified using pharmaceutical data, for which the prevalence was greater than 0.5%, and there were at least 5 non-cancer deaths in the entire combined development cohort. Because there was reasonable consistency in the association of each condition with non-cancer mortality across sites, weights from the entire development cohort (all cancers combined) were used, rather than site-specific weights, as were used in the C3 indices. The weights were the parameter estimates (log(HRs)) from Cox regression models of non-cancer mortality for each condition, adjusted for age, site and stage for all sites combined. Indices that were based on site-specific weights were also developed, but resulted in almost identical results (not presented here), so results relating to the 'all-sites' weights are used throughout. These HRs and their logs are presented in Table 27.

## Performance and validation pharmaceutical-based comorbidity index

Figure 8 and **Table 30** show the descriptive statistics for the PBCI index in the development cohorts. The ranges of PBCI scores were similar across cancer sites with scores ranging from 0 to 7-8. Women with breast cancer had notably lower PBCI scores than any other site; the median score for women with breast cancer was 0.51 compared with 0.84-1.00 for the other sites. Thirty-nine percent of women with breast cancer had a score of 0 compared with 23%, 25%, 29% and 32% of patients with urological, colorectal, gynaecological and upper GI cancers respectively. Around a quarter of patients had a PBCI score of 2 or more among those with urological (26%), upper GI (24%) and colorectal (23%) cancers; while only 13% of women with breast cancer scored this highly.

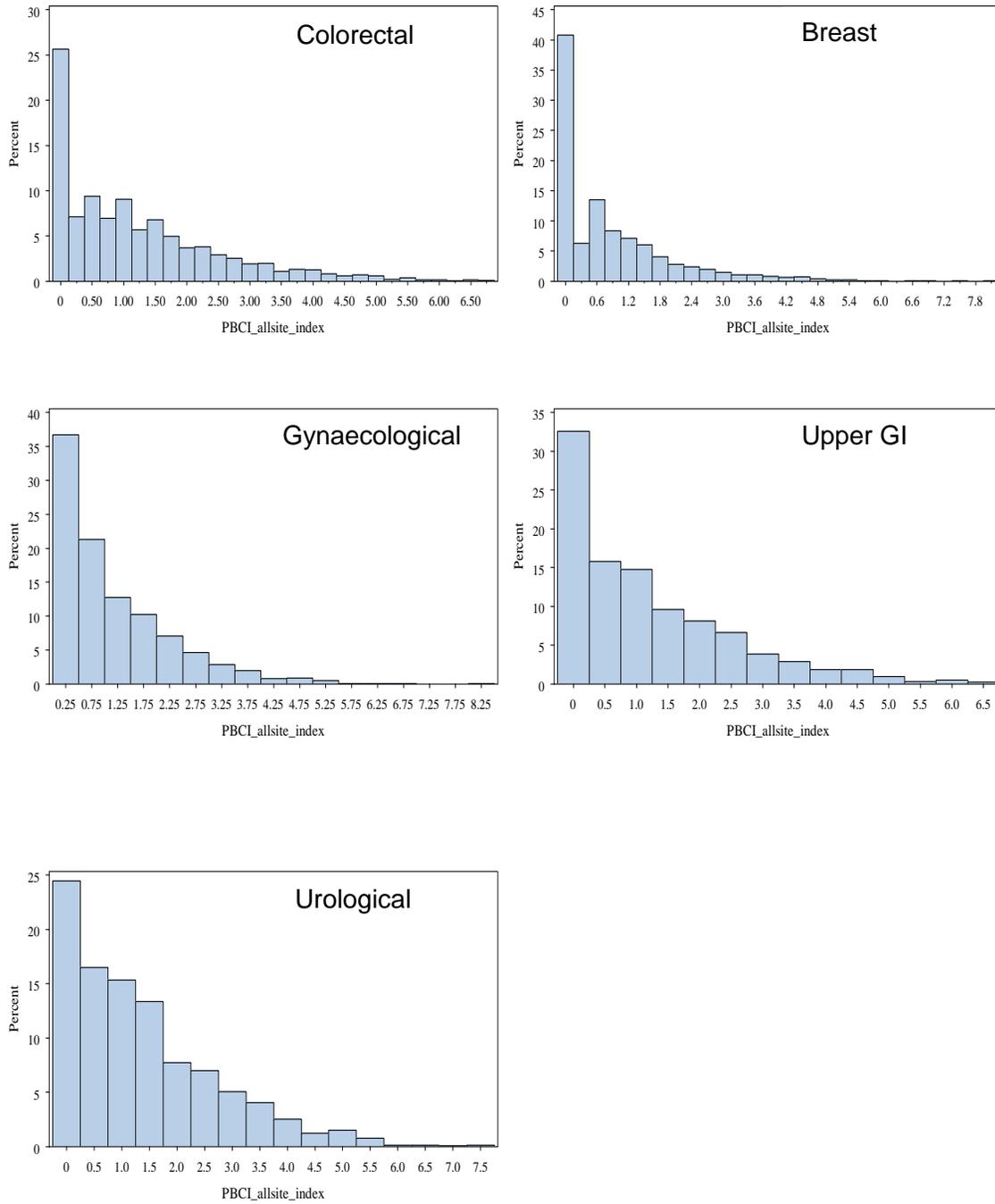
The Spearman's rank correlation coefficients that measure the correlations between ranked Charlson scores and PBCI scores for the development cohort ranged from 0.37 to

0.45, suggesting only moderate correlations but still supporting concurrent validity of the PBCI index (Table 30). The ranges of correlation scores were similar in the validation cohort (data not shown).

Table 31 and Table 32 show the results of analyses using the *validation* cohort. The baseline models, which included age, sex (where relevant) and stage were good at discriminating between those who died and those who did not for both all cause and non-cancer deaths, with most c-statistics around 0.80 or greater (Table 31). All three comorbidity indices tended to improve the baseline models' predictive abilities. For all sites, for all-cause mortality, the differences in the c-statistics among models with comorbidity measures added were negligible regardless of which measure of comorbidity was used. For non-cancer mortality, which is more closely associated with comorbidity, for cancers associated with higher comorbidity (colorectal cancer, upper gastrointestinal and urological cancers), the hospitalisation-based indices (either C3 or Charlson) outperformed PBCI. In contrast, for the cancers of younger women with less comorbidity (breast and gynaecological cancers), PBCI appeared to perform as well or better than the hospitalisation indices. In the case of breast cancer, adding PBCI to the baseline model resulted in the highest c-statistic of any single index, and similar or greater reduction in the AIC. For gynaecological cancers there was failure to converge in the bootstrapped models for non-cancer deaths because of relatively small numbers of deaths in these categories, so it was not possible to confidently provide c-statistics or their 95% confidence intervals. However, adding PBCI to the baseline model resulted in the greatest reduction of AIC compared with any other single index, suggesting a pattern similar to breast cancer (although given the small numbers of deaths involved, these too should be treated with caution).

Adding both sources of data resulted little or no change in the c-statistic compared to the 'best' index for each site, albeit that in all cases, both for all-cause and non-cancer deaths the two combined almost always resulted in the highest c-statistic.

**Figure 8: Distribution of PBCI by site**



**Table 30: Score distributions of PBCI Index, and correlation with Charlson index scores in development cohort**

	Colorectal	Breast	Gynaecological	Upper GI	Urological
<b>Distribution of PBCI scores</b>					
<b>Range</b>	0 to 6.83	0 to 8.13	0 to 8.35	0 to 6.71	0 to 7.65
<b>Mean (SD)</b>	1.23 (1.27)	0.86 (1.11)	1.08 (1.17)	1.19 (1.32)	1.36 (1.35)
<b>Median (IQR)</b>	0.92 (1.85)	0.51 (1.29)	0.84 (1.36)	0.86 (1.32)	1.00 (1.73)
<b>Correlation with Charlson Index*</b>					
	0.42	0.40	0.37	0.42	0.45
<b>PBCI Index Score</b>					
0 (%)	25.2	38.7	29.2	31.6	23.2
>0, <=1 (%)	28.9	29.1	28.8	23.2	27.0
>1, <=2 (%)	23.2	18.9	23.0	21.4	24.3
>2, <=3 (%)	12.4	7.2	11.7	12.9	12.5
>3 (%)	10.3	6.2	7.4	10.8	13.0
<b>Total</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>

\*Spearman's rank coefficient; SD: Standard deviation; IQR: Interquartile range

**Table 31: Bootstrapped c-indices (median, 95% CI) for comorbidity-adjusted models by site (10,000 bootstrap estimates) predicting deaths from all and non-cancer causes within one year of diagnosis using the validation cohort**

Cancer site	Deaths	Baseline model*	Baseline* + PBC index	Baseline* + C3 index	Baseline* + Charlson	Baseline* + PBC & C3 index	% bs converged	n deaths
<b>Colorectal</b>	All-cause	0.822 (0.806, 0.837)	0.830 (0.814, 0.845)	0.835 (0.820, 0.850)	0.832 (0.817, 0.847)	0.835 (0.821, 0.850)	100	923
	Non-cancer	0.746 (0.700, 0.791)	0.793 (0.751, 0.832)	0.802 (0.762, 0.841)	0.785 (0.743, 0.826)	0.809 (0.769, 0.847)	99.96	105
<b>Breast</b>	All-cause	0.903 (0.878, 0.925)	0.913 (0.89, 0.934)	0.915 (0.892, 0.936)	0.912 (0.887, 0.933)	0.917 (0.894, 0.937)	100	194
	Non-cancer	0.908 (0.871, 0.938)	0.948 (0.922, 0.969)	0.939 (0.908, 0.962)	0.932 (0.894, 0.960)	0.953 (0.926, 0.972)	91.39	44
<b>Gynaecological</b>	All-cause	0.897 (0.875, 0.917)	0.901 (0.879, 0.921)	0.908 (0.886, 0.927)	0.908 (0.887, 0.927)	0.908 (0.887, 0.928)	98.07	203
	Non-cancer	n/a	n/a	n/a	n/a	n/a	0	9
<b>Upper GI</b>	All-cause	0.775 (0.741, 0.808)	0.780 (0.746, 0.813)	0.780 (0.746, 0.813)	0.780 (0.746, 0.813)	0.782 (0.748, 0.815)	99.91	421
	Non-cancer	0.665 (0.586, 0.747)	0.722 (0.632, 0.806)	0.758 (0.669, 0.832)	0.705 (0.616, 0.786)	0.762 (0.677, 0.837)	61.81	28
<b>Urological</b>	All-cause	0.853 (0.829, 0.876)	0.855 (0.831, 0.878)	0.861 (0.838, 0.884)	0.858 (0.834, 0.880)	0.862 (0.838, 0.884)	99.98	300
	Non-cancer	0.795 (0.732, 0.847)	0.812 (0.752, 0.863)	0.820 (0.762, 0.871)	0.817 (0.759, 0.868)	0.822 (0.764, 0.871)	94.75	50
<b>All sites</b>	All-cause	0.894 (0.887, 0.901)	0.897 (0.89, 0.903)	0.899 (0.892, 0.906)	0.898 (0.891, 0.905)	0.900 (0.893, 0.906)	100	2041
	Non-cancer	0.821 (0.797, 0.843)	0.857 (0.837, 0.875)	0.856 (0.836, 0.875)	0.845 (0.824, 0.866)	0.865 (0.846, 0.883)	99.91	236

\*Baseline model includes age, sex (where relevant) and stage of cancer.

**Table 32. Reduction in AIC from Cox proportional hazard models predicting deaths from all- cause and non-cancer causes within one year of diagnosis using the validation cohort.**

CoD	Model	Colorectal	Breast	Gynaecological	Liver / Stomach	Urological
<b>All-cause</b>	<b><i>Baseline*</i></b>	<b>17998.1</b>	<b>4492.6</b>	<b>3220.0</b>	<b>5712.3</b>	<b>4511.3</b>
	<i>PBCI Index</i>	61.4	24.1	6.7	2.9	0.5
	<i>NMDS Index</i>	78.7	31.1	29.5	3.6	13.2
	<i>Charlson</i>	60.7	44.7	34.8	3.7	3.0
	<i>PBCI + C3 Index</i>	89.9	34.9	27.6	2.7	11.8
	<i>PBCI + Charlson</i>	82.1	50.1	33.8	3.2	1.3
<b>Non-cancer</b>	<b><i>Baseline*</i></b>	<b>2297.0</b>	<b>1064.4</b>	<b>157.7</b>	<b>439.7</b>	<b>867.7</b>
	<i>PBCI Index</i>	56.6	48.2	16.2	15.4	13.2
	<i>C3 Index</i>	62.9	34.8	6.4	9.2	19.2
	<i>Charlson</i>	49.3	48.5	6.2	2.3	10.7
	<i>PBCI + C3 Index</i>	75.1	52.3	14.4	14.6	19.3
	<i>PBCI + Charlson</i>	70.7	65.9	15.1	13.4	15.1

\*Includes age, sex (where relevant) and stage. Greater reduction in AIC from baseline indicates better performance

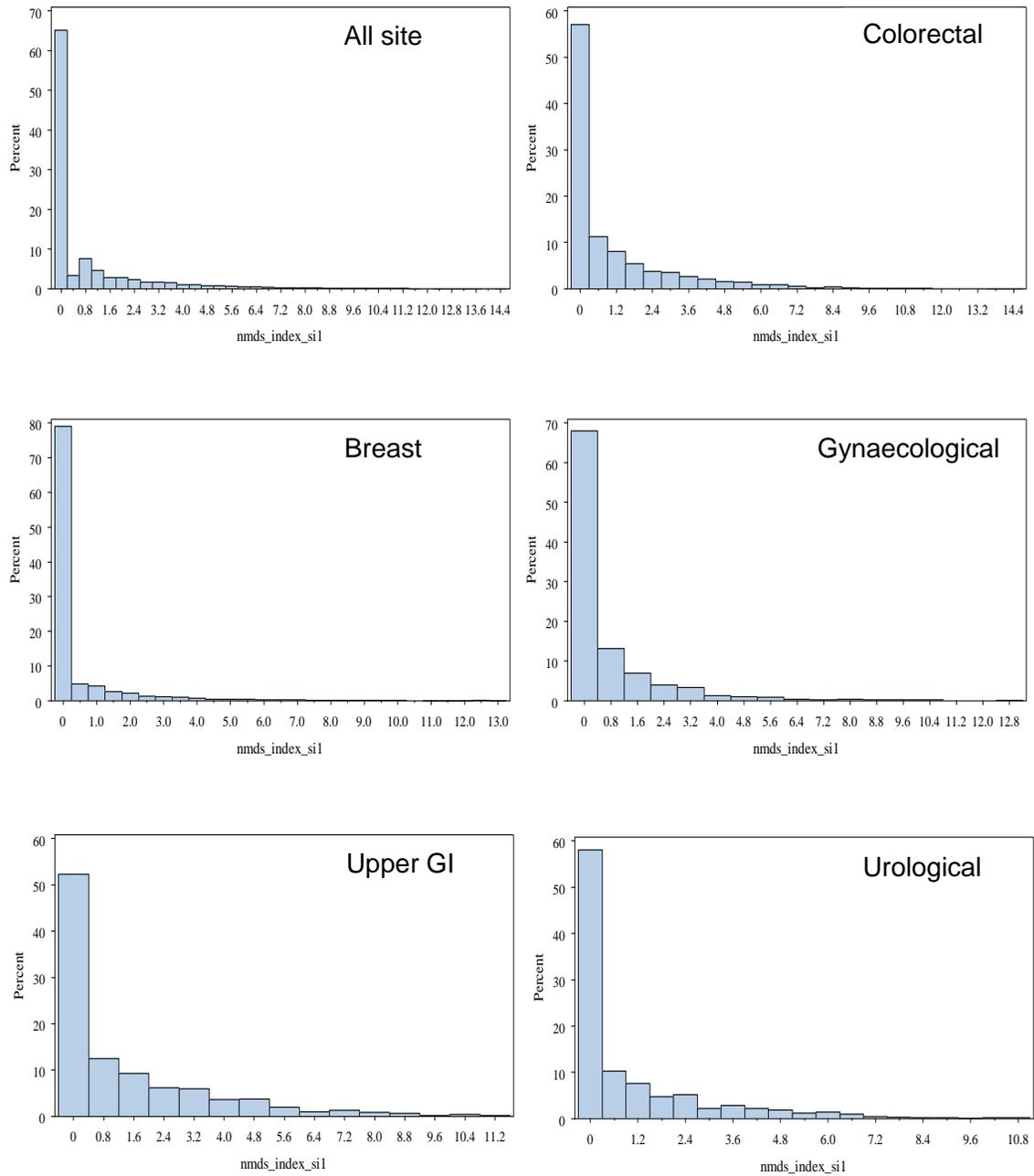
## Section 4: Development and validation of simplified comorbidity index

The final part of the analysis related to the development and validation of simplified comorbidity indices that could be used in the context of cancer. The three simplified indices were 1) a single hospitalisation index which included all conditions in the C3 indices, but applied all-site weights rather than site-specific weights; 2) as for the first simplified index, but only the nineteen conditions with prevalence greater than 2% and hazard ratio for non-cancer death (adjusted for age and stage) of at least 1.2 were included; 3) as for second simplified index, but weights were further simplified by dividing by the smallest parameter estimate and rounding to the nearest integer.

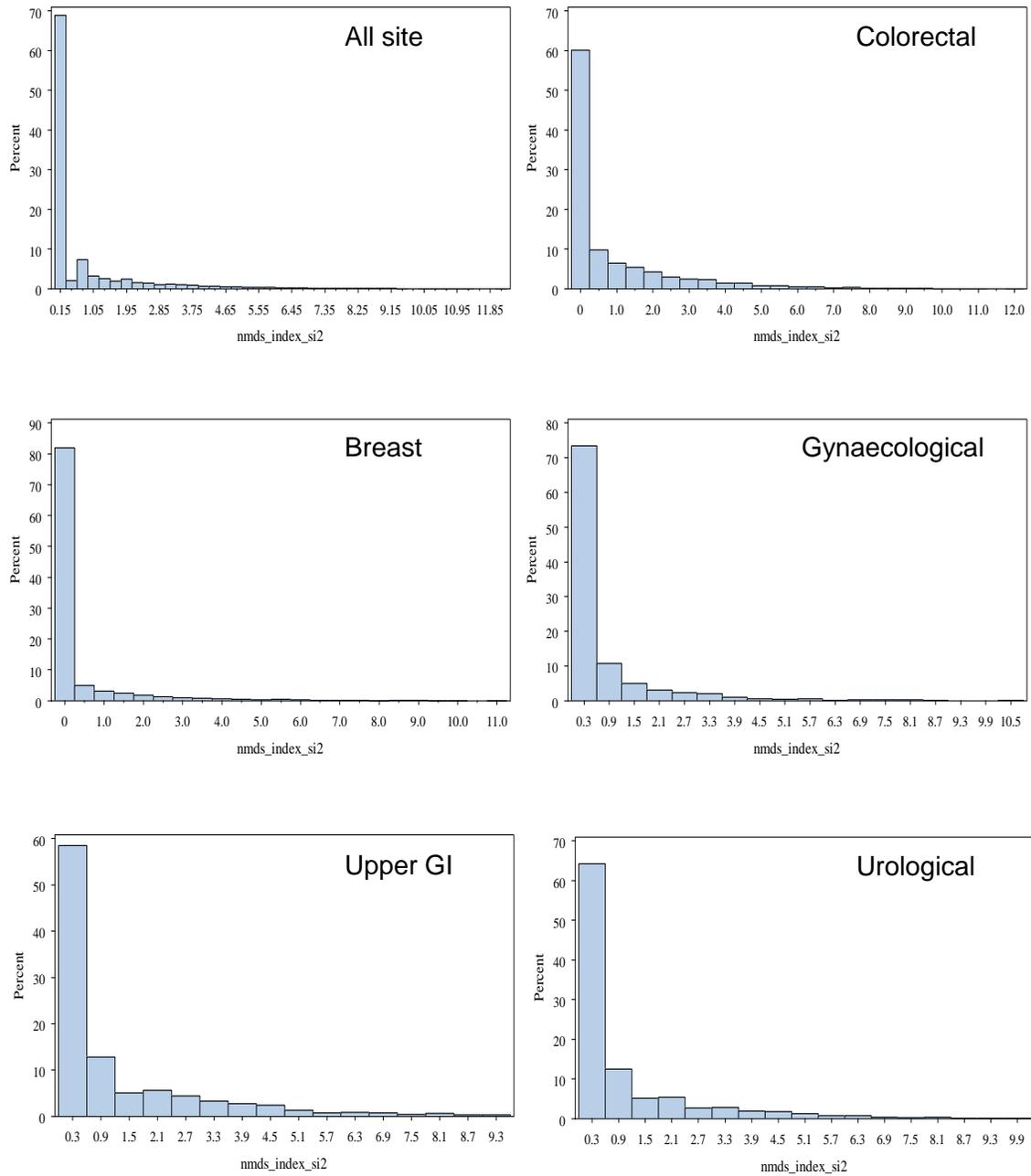
Figures 9-11 and Table 33 show the score distribution of the three simplified indices by site, and for all-sites combined in the development cohorts. In general, and as for the other comorbidity measures, the highest mean scores were for patients with upper gastrointestinal cancers, followed by colorectal and urological cancers. The lowest mean scores were among those with breast cancer. For all the simplified indices, the lowest scores were 0 (for simplified indices 2 and 3) or just below (for simplified index 1) across all sites. The highest scores varied by index with the highest score in the colorectal cancer cohort (14.6 for simplified index 1, 12.2 for simplified index 2 and 22 for simplified index 3).

When compared with the Charlson index scores, the Spearman's rank correlation coefficients were similar across indices within particular cancer sites, but varied across sites with the highest correlations for urological cancers (correlation coefficients = 0.70-0.71) and the lowest for gynaecological cancers (0.57-0.59). The correlation coefficients tended to be slightly higher in the validation dataset, and in all cases were in the range of 0.70 to 0.80.

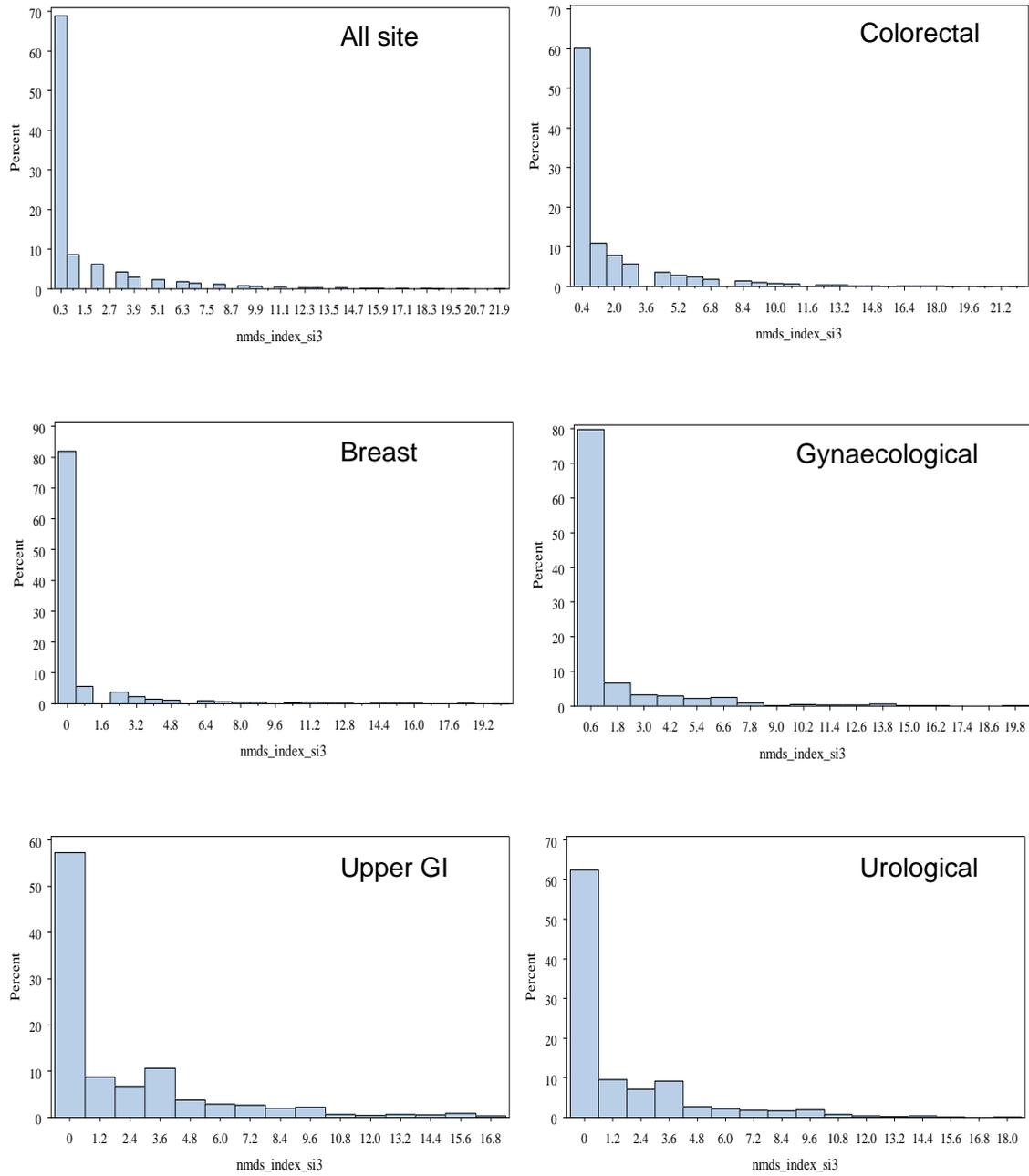
**Figure 9: Score distribution of simplified index 1 by site**



**Figure 10: Score distribution of simplified index 2 by site**



**Figure 11: Score distribution of simplified index 3 by site**



**Table 33: Score distributions of simplified indices and correlation with Charlson index scores in development cohort by site**

	<b>Low value</b>	<b>High value</b>	<b>Median</b>	<b>IQR</b>	<b>Mean</b>	<b>SD</b>	<b>Spearman's correlation* (Charlson)</b>
<b>All sites combined (n=14096)</b>							
Simplified index 1	-0.03	14.58	0.00	0.92	0.83	1.65	0.69
Simplified index 2	0.00	12.18	0.00	0.75	0.67	1.40	0.69
Simplified index 3	0.00	22.00	0.00	1.00	1.17	2.49	0.69
<b>CRC (n=5376)</b>							
Simplified index 1	-0.03	14.58	0.00	1.38	1.05	1.79	0.69
Simplified index 2	0.00	12.18	0.00	1.09	0.86	1.52	0.68
Simplified index 3	0.00	22.00	0.00	2.00	1.49	2.69	0.69
<b>Breast (n=5076)</b>							
Simplified index 1	-0.03	13.06	0.00	0.00	0.46	1.28	0.64
Simplified index 2	0.00	11.21	0.00	0.00	0.37	1.07	0.69
Simplified index 3	0.00	20.00	0.00	0.00	0.64	1.90	0.70
<b>Gynaecological (n=1223)</b>							
Simplified index 1	-0.03	12.79	0.00	0.76	0.70	1.50	0.57
Simplified index 2	0.00	10.56	0.00	0.72	0.57	1.26	0.59
Simplified index 3	0.00	20.00	0.00	1.00	1.02	2.31	0.59
<b>Upper GI</b>							
Simplified index 1	-0.03	11.12	0.39	2.15	1.40	2.08	0.72
Simplified index 2	0.00	9.38	0.00	1.60	1.08	1.79	0.67
Simplified index 3	0.00	17.00	0.00	3.00	1.94	3.26	0.68
<b>Urological</b>							
Simplified index 1	-0.03	10.86	0.00	1.44	1.06	1.80	0.70
Simplified index 2	0.00	9.98	0.00	1.09	0.85	1.54	0.71
Simplified index 3	0.00	18.00	0.00	2.00	1.46	2.68	0.71

\*Spearman's rank coefficient compared with Charlson score

Table 34 and Table 35 show the results of the validation of the simplified indices and summarise the comparisons between the Charlson, C3, PBCI, 'gold standard (C3 + PBCI combined) and the three summary indices. Some of these results have been shown previously in the validation of the C3 and PBCI indices but are repeated here to facilitate comparisons. Table 34 provides a summary of concordance statistics with 95% confidence intervals calculated using bootstrapping, and AICs for logistic regression models of one-year all-cause or non-cancer death with baseline models including age, stage and sex where relevant (and site for all sites combined). Table 35 shows the difference between the c-statistics generated from baseline logistic regression models that include each of the simplified indices compared with the same baseline models that include either Charlson or the 'gold standard' measure of comorbidity.

## All-cause death

For all-cause death, adding any measure of comorbidity tended to result in an increase in the c-statistic, and reduction in the AIC compared with baseline, but that the improvement for **gynaecological**, **upper GI** and **urological** cancers was very minimal (Table 34). There was little difference in the improvement regardless of which index was used, particularly for these latter three sites with no statistically significant difference in the c-statistics from models that included either the Charlson index or the gold standard, and any of the simplified indices for gynaecological, upper GI or urological cancers (Table 35). For **all-sites combined**, and for **colorectal** cancer specifically, the gold standard approach performed similarly to the C3 and SI1 indices suggesting that the main driver of this performance was the full hospitalisation-based indices regardless of whether weights were site-specific (C3) or from all-sites (SI1) models. The c-statistics were higher and the AICs 10 units or more lower for these indices compared with the others (Charlson, SI2, SI3 and PBCI). The other two simplified indices (SI2 and 3) tended to perform similarly to the Charlson index for all-cause mortality. For **breast** cancer, the patterns were similar, but the Charlson index performed as well as any other index.

## Non-cancer death

For non-cancer death, the inclusion of any measure of comorbidity in the logistic regression models tended to have a greater impact on both c-statistics and AICs, and consequently the differences between the indices were more distinguishable (Table 34 and Table 35). For **all-sites combined**, the gold standard approach outperformed all others and resulted in a clearly higher c-statistics, statistically significant differences between c-statistics for it compared with SI1, 2 or 3, and AIC at least 19 units lower than any other index. The C3, C3-based simplified indices and PBCI all performed similarly to each other, and clearly outperformed the Charlson index, with statistically significant difference between each of the S1-3 indices and the Charlson index and AICs at least 25 units lower in all cases.

For **colorectal cancer**, the gold standard approach was only marginally better than the C3 and SI1-3 indices all of which performed very similarly to each other. The PBCI performed somewhat less well than the C3-based indices, but all out-performed the Charlson index with higher c-statistics and AICs from models including each of the C3-based indices being at least 15 points lower than those including the Charlson index. However, the difference between the c-statistics was only statistically significant for SI1 compared with the Charlson index.

For **upper GI cancers**, the gold standard, C3 and simplified indices performed similarly to each other and outperformed the Charlson index. There were statistically significant difference in c-statistics from models including the simplified models compared with the Charlson index in all cases, and no such differences between the simplified indices and the gold standard approach. The PBCI also seemed to slightly outperform the Charlson index, but did not perform as well as the C3-based indices.

For **urological cancers**, the difference in performance between the indices was minimal. The simplified indices performed very similarly to both Charlson and the gold standard approach.

For **breast cancer**, the pharmaceutical-based measures (PBCI) resulted in higher c-statistics and lower AIC (by at least 20 units) than any of the hospitalisation measures. The

hospitalisation-based indices (C3, SI1-3 and Charlson) all performed reasonably similarly to each other. The differences in c-statistics between the gold standard and SI2 and 3 were statistically significant, but there was no significant differences between in c-statistics from models including the simplified indices compared with those including the Charlson index.

For **gynaecological** cancer, it was not possible to estimate c-statistics and bootstrapped confidence intervals because of lack of convergence of the models, so these are not presented here. However, the patterns from the simple modelling approach suggest a similar pattern as for breast cancer with higher c-statistics for models that include pharmaceutical-based indices (PBCI and gold standard c-statistics both 0.939; compared with the hospitalisation-based indices; 0.909-0.915). These results should be interpreted with caution, however, given the small number of non-cancer deaths in this cohort.

**Table 34 Comparison of concordance statistics and AICs from logistic regression models predicting deaths from all- and non-cancer causes within one year of diagnosis using the validation cohorts by cancer site and for all sites combined**

Model	All-cause mortality		Non-cancer mortality	
	C-statistic (95% CI)	AIC	C-statistic (95% CI)	AIC
<b>All sites (n=11014)</b>				
Baseline*	0.894 (0.887, 0.901)	6699.5	0.821 (0.797, 0.843)	1990.3
Charlson	0.898 (0.891, 0.905)	6598.6	0.845 (0.824, 0.866)	1920.8
C3/NMDS	0.899 (0.892, 0.906)	6572.3	0.856 (0.836, 0.875)	1894.8
PBCI	0.897 (0.89, 0.903)	6632.9	0.857 (0.837, 0.875)	1893.4
C3+PBCI	0.9 (0.893, 0.906)	6567.3	0.865 (0.846, 0.883)	1867.5
Simplified index 1	0.899 (0.893, 0.906)	6564.7	0.859 (0.838, 0.878)	1886.5
Simplified index 2	0.898 (0.891, 0.905)	6597.9	0.855 (0.834, 0.875)	1892.4
Simplified index 3	0.898 (0.891, 0.905)	6599.1	0.855 (0.833, 0.874)	1891.2
<b>CRC (n=4047)</b>				
Baseline*	0.822 (0.806, 0.837)	3296.5	0.746 (0.7, 0.791)	911.6
Charlson	0.832 (0.817, 0.847)	3242.6	0.785 (0.743, 0.826)	884.9
C3/NMDS	0.835 (0.82, 0.85)	3216.9	0.802 (0.762, 0.841)	869.8
PBCI	0.83 (0.814, 0.845)	3251.1	0.793 (0.751, 0.832)	877.3
C3+PBCI	0.835 (0.821, 0.85)	3213.2	0.809 (0.769, 0.847)	864.1
Simplified index 1	0.835 (0.82, 0.85)	3214.9	0.804 (0.762, 0.842)	868
Simplified index 2	0.832 (0.818, 0.847)	3237.9	0.8 (0.759, 0.84)	866.6
Simplified index 3	0.833 (0.818, 0.847)	3238.5	0.8 (0.759, 0.84)	866.2
<b>Breast (n=4059)</b>				
Baseline*	0.903 (0.878, 0.925)	1011.5	0.908 (0.871, 0.938)	363.1
Charlson	0.912 (0.887, 0.933)	981.2	0.932 (0.894, 0.96)	335.9
C3/NMDS	0.915 (0.892, 0.936)	984.3	0.939 (0.908, 0.962)	337.4
PBCI	0.913 (0.89, 0.934)	991.8	0.948 (0.922, 0.969)	322.6

C3+PBCI	0.917 (0.894, 0.937)	981.8	0.953 (0.926, 0.972)	319.5
Simplified index 1	0.916 (0.892, 0.936)	982.7	0.942 (0.912, 0.964)	334.7
Simplified index 2	0.913 (0.889, 0.933)	990.8	0.935 (0.902, 0.96)	341.7
Simplified index 3	0.913 (0.889, 0.933)	990.4	0.936 (0.902, 0.96)	339.6

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**Gynaecological (n=1041)**

Baseline*	0.897 (0.875, 0.917)	644.2	--	--
Charlson	0.908 (0.887, 0.927)	619.1	--	--
C3/NMDS	0.908 (0.886, 0.927)	626.2	--	--
PBCI	0.901 (0.879, 0.921)	641.6	--	--
C3+PBCI	0.908 (0.887, 0.928)	628.2	--	--
Simplified index 1	0.909 (0.887, 0.928)	623.1	--	--
Simplified index 2	0.907 (0.885, 0.927)	626.1	--	--
Simplified index 3	0.908 (0.886, 0.927)	624.5	--	--

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**Upper GI (n=733)**

Baseline*	0.775 (0.741, 0.808)	824.3	0.665 (0.586, 0.747)	244.3
Charlson	0.78 (0.746, 0.813)	824.3	0.705 (0.616, 0.786)	242.2
C3/NMDS	0.78 (0.746, 0.813)	824.1	0.758 (0.669, 0.832)	233.4
PBCI	0.78 (0.746, 0.813)	822.6	0.722 (0.632, 0.806)	238.5
C3+PBCI	0.782 (0.748, 0.815)	824.3	0.762 (0.677, 0.837)	234.6
Simplified index 1	0.78 (0.746, 0.813)	823.9	0.762 (0.675, 0.835)	232.9
Simplified index 2	0.78 (0.746, 0.812)	823.5	0.779 (0.693, 0.848)	230.1
Simplified index 3	0.78 (0.745, 0.812)	823.8	0.774 (0.688, 0.844)	231.6

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**Urological (n=1134)**

Baseline*	0.853 (0.829, 0.876)	939.8	0.795 (0.732, 0.847)	371.1
Charlson	0.858 (0.834, 0.88)	937.7	0.817 (0.759, 0.868)	363.1
C3/NMDS	0.861 (0.838, 0.884)	928.9	0.82 (0.762, 0.871)	359.7
PBCI	0.855 (0.831, 0.878)	940.5	0.812 (0.752, 0.863)	364.8

C3+PBCI	0.862 (0.838, 0.884)	929.7	0.822 (0.764, 0.871)	360.8
Simplified index 1	0.861 (0.837, 0.883)	931.3	0.818 (0.759, 0.869)	360.7
Simplified index 2	0.859 (0.835, 0.881)	935.5	0.818 (0.757, 0.871)	361.6
Simplified index 3	0.858 (0.834, 0.881)	936.3	0.818 (0.756, 0.871)	361.6

\* includes age, stage and sex (where relevant). – Indicates not estimable because of lack of convergence in bootstrapping.

Note: greater than 10 point difference in AIC suggests a meaningful difference between models including different measures of comorbidity (for a given site and outcome).

**Table 35: Differences in concordance statistics (95% confidence intervals) from baseline logistic regression models including each simplified index compared with Charlson or with 'gold standard' approach for 1-year all and non-cancer mortality**

	All-cause mortality				Non-cancer mortality			
	Charlson		'Gold standard'		Charlson		'Gold standard'	
	Difference in c-stats	95% CI	Difference in c-stats	95% CI	Difference in c-stats	95% CI	Difference in c-stats	95% CI
<b>All sites*</b>								
Simplified index 1	0.0012	(0.0002, 0.0023)	0	(-0.0007, 0.0004)	0.0048	(0.0009, 0.0086)	-0.0146	(-0.0147, -0.0145)
Simplified index 2	0	(-0.0011, 0.001)	-0.0013	(-0.0022, -0.0006)	0.0093	(0.0014, 0.0184)	-0.0103	(-0.0196, -0.003)
Simplified index 3	0	(-0.001, 0.0009)	-0.0013	(-0.0022, -0.0006)	0.0089	(0.0014, 0.0177)	-0.0106	(-0.0202, -0.0032)
<b>CRC*</b>								
Simplified index 1	0.0034	(0.0005, 0.0066)	-0.0003	(-0.0024, 0.001)	0.0174	(0.0019, 0.0381)	-0.0044	(-0.0191, 0.0038)
Simplified index 2	0.0008	(-0.0021, 0.0036)	-0.003	(-0.0056, -0.0009)	0.0145	(-0.0026, 0.036)	-0.008	(-0.0224, 0.0026)
Simplified index 3	0.0008	(-0.0019, 0.0036)	-0.0029	(-0.0056, -0.0007)	0.0145	(-0.0017, 0.0346)	-0.0079	(-0.0231, 0.0032)
<b>Breast*</b>								
Simplified index 1	0.0036	(-0.0009, 0.0092)	-0.0012	(-0.007, 0.0022)	0.0096	(-0.0028, 0.0309)	-0.0099	(-0.0291, 0.0038)
Simplified index 2	0.0008	(-0.0031, 0.0052)	-0.0041	(-0.0102, -0.0002)	0.0021	(-0.0086, 0.0226)	-0.0171	(-0.0371, -0.0036)
Simplified index 3	0.0006	(-0.0032, 0.0053)	-0.0042	(-0.0105, -0.0003)	0.0024	(-0.0084, 0.0233)	-0.0167	(-0.0369, -0.0031)
<b>Gynaecological**</b>								
Simplified index 1	0.0006	(-0.0037, 0.0052)	0.0002	(-0.003, 0.0033)	--		--	
Simplified index 2	-0.0007	(-0.0048, 0.0034)	-0.0011	(-0.0043, 0.0017)	--		--	
Simplified index 3	-0.0003	(-0.0042, 0.0038)	-0.0007	(-0.0039, 0.0024)	--		--	
<b>Upper GI *</b>								
Simplified index 1	0.0003	(-0.0061, 0.0063)	-0.0013	(-0.0115, 0.0032)	0.0536	(0.0065, 0.1133)	0.0012	(-0.032, 0.0202)
Simplified index 2	-0.0002	(-0.0059, 0.0058)	-0.002	(-0.012, 0.0037)	0.0709	(0.0195, 0.1366)	0.0168	(-0.0205, 0.0503)
Simplified index 3	-0.0003	(-0.0058, 0.0053)	-0.0021	(-0.0121, 0.0035)	0.0656	(0.0176, 0.128)	0.012	(-0.0254, 0.0425)
<b>Urological *</b>								
Simplified index 1	0.0026	(-0.0005, 0.0072)	-0.0008	(-0.0036, 0.0014)	0.0005	(-0.0131, 0.0168)	-0.003	(-0.0162, 0.0037)
Simplified index 2	0.0006	(-0.0027, 0.0045)	-0.0028	(-0.0071, 0.0002)	0.0008	(-0.0166, 0.0177)	-0.0029	(-0.0206, 0.0072)
Simplified index 3	0.0005	(-0.0029, 0.0042)	-0.003	(-0.0074, 0.0003)	0.0006	(-0.0167, 0.0169)	-0.0032	(-0.0212, 0.007)

Baseline model \* includes age, stage and sex (where relevant). -- Indicates not estimable because of lack of convergence in bootstrapping.

## Comparison of indices using Discrimination slopes and Integrated Discrimination Improvement (IDI)

Figures 12 to 17 show box plots for predicted probabilities (based on the specified covariates) of one-year all-cause mortality from baseline models or baseline models including specified measure of comorbidity for each individual stratified by their observed outcome (1=died; 0=not died) within development cohorts. For these analyses, Cox regression models were fitted, with baseline models including age, sex (where relevant) and stage for each site, or age, stage and site for all sites combined. Similar box plots are provided for non-cancer mortality in Appendix 7. Box plots were also produced for the validation cohorts. These were almost identical to those constructed from development cohort data, so are not provided here (although are available from the author).

In all cases, there is a clear (and expected) difference in the *predicted* probability of one-year death between those who died and those who did not. Patients with breast cancer tended to have considerably lower predicted probabilities of death and those with upper GI cancers considerably higher than other sites, as expected. The slope between the mean predicted probability of death of those who did and did not die is the discrimination slope. The difference between two discrimination slopes is the Integrated Discrimination Improvement (IDI).

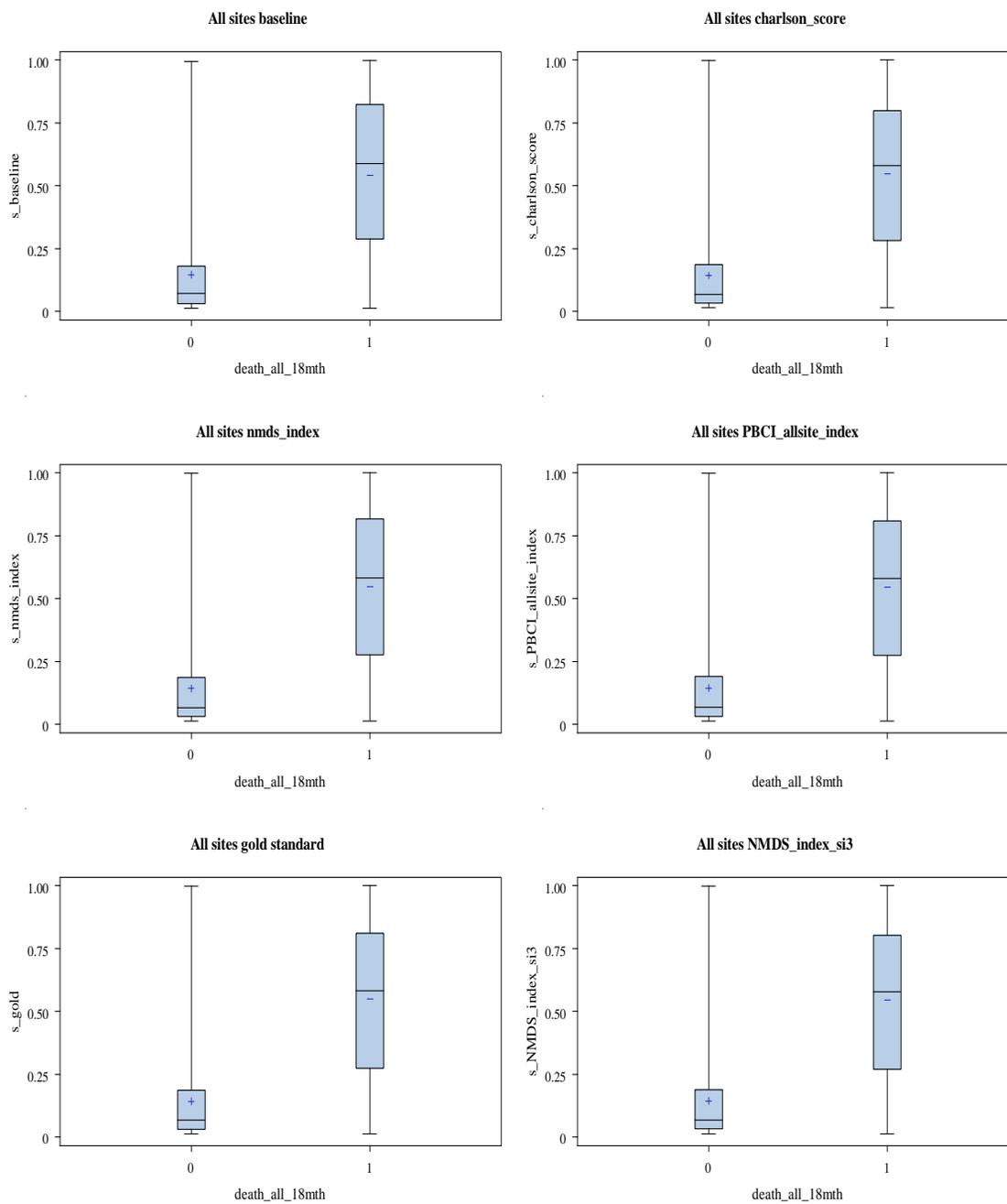
The IDIs give an alternative measure of validity which takes into account improvements in the ability of a model with a 'new' measure of comorbidity to accurately predict those who will die compared with a model with a 'comparison' measure, without adverse impact on the models' ability to accurately predict those who will not die i.e. IDIs take account of both sensitivity and specificity on a model in respect to one-year mortality in this case. Tables 36 and 37 show the Integrated Discrimination Improvement (IDIs) comparing baseline, Charlson and Gold standard approaches to measuring comorbidity with other approaches for each site and all sites combined in validation datasets for all-cause and non-cancer death respectively. Note the p-values have been calculated using the formula provided by Pencina et al (Pencina, D'Agostino et al. 2008); this approach has been criticised as likely

to underestimate standard errors increasing the likelihood of a type I error (Pepe, Feng et al. 2008; Kerr, McClelland et al. 2012), so a more conservative approach of treating a  $p < 0.025$  as significant has been taken for the purposes of this thesis.

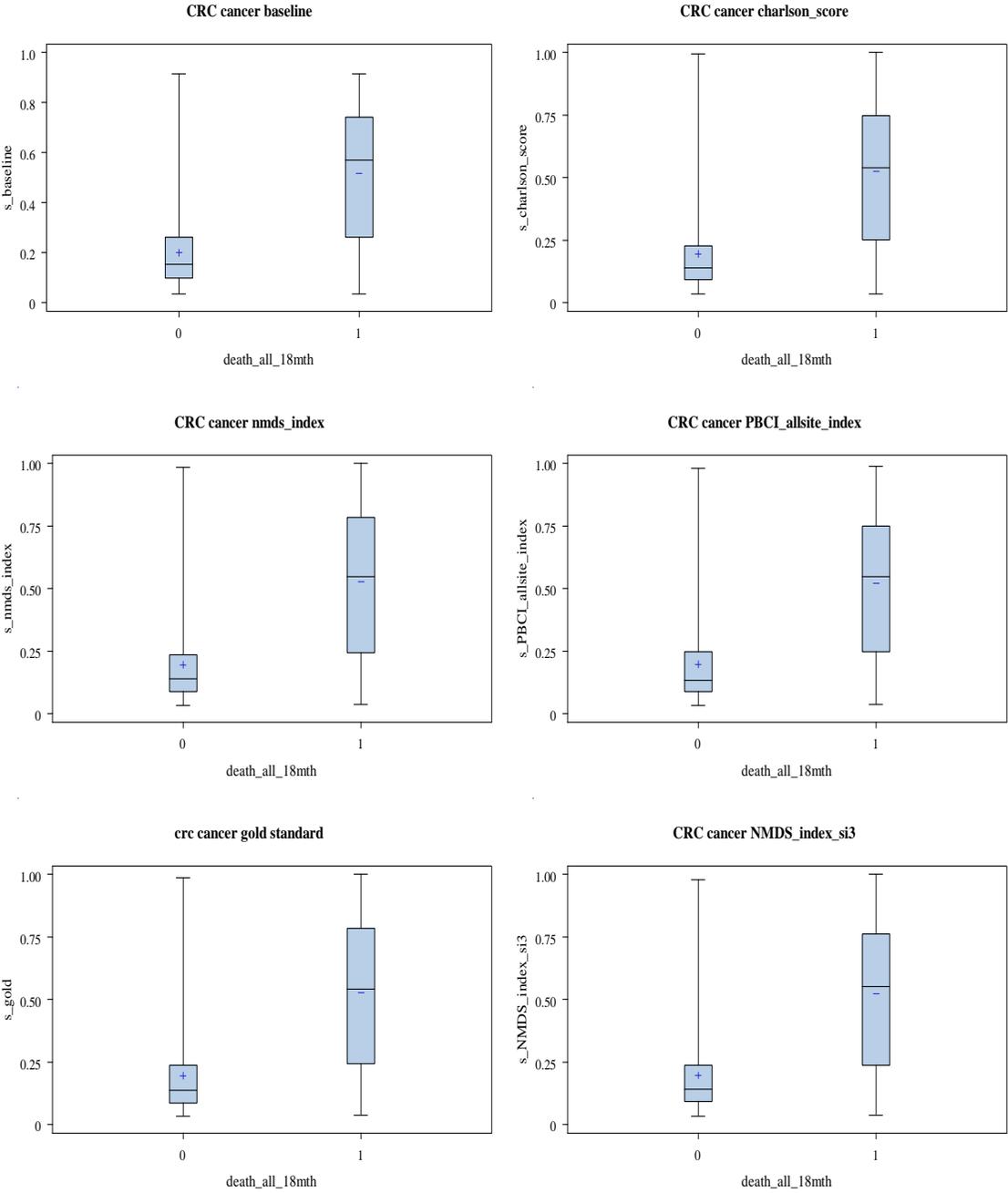
For all-cause mortality, Table 36 shows that, as with previous results, any measure of comorbidity added to the baseline models tended to result in an improvement in IDI, albeit that the differences were not always statistically significant. Compared with the Charlson Index, none of the indices performed consistently better in terms of predicting one-year all-cause mortality. The differences were only significant for colorectal cancer when the Charlson Index was compared with the gold standard, C3 or S11 approaches. Otherwise the only other two statistically significant findings were in relation to PBCI which was found to be worse than the Charlson Index at predicting all-cause death for all sites combined, and gynaecological cancers specifically. The gold standard approach performed better than the simplified indices, but again the differences tended to be small and were not significant for breast, gynaecological (except for S11) or upper GI cancers.

For non-cancer mortality, Table 37, the pattern of results was reasonably similar, with all measures of comorbidity being better than none and the Charlson Index working reasonably well in comparison with other indices, with significant improvements seen only in the colorectal cancer cohort for the gold standard and the simplified indices. While the gold standard approach tended to perform better than the simplified indices, there were no significant differences between them according to IDIs.

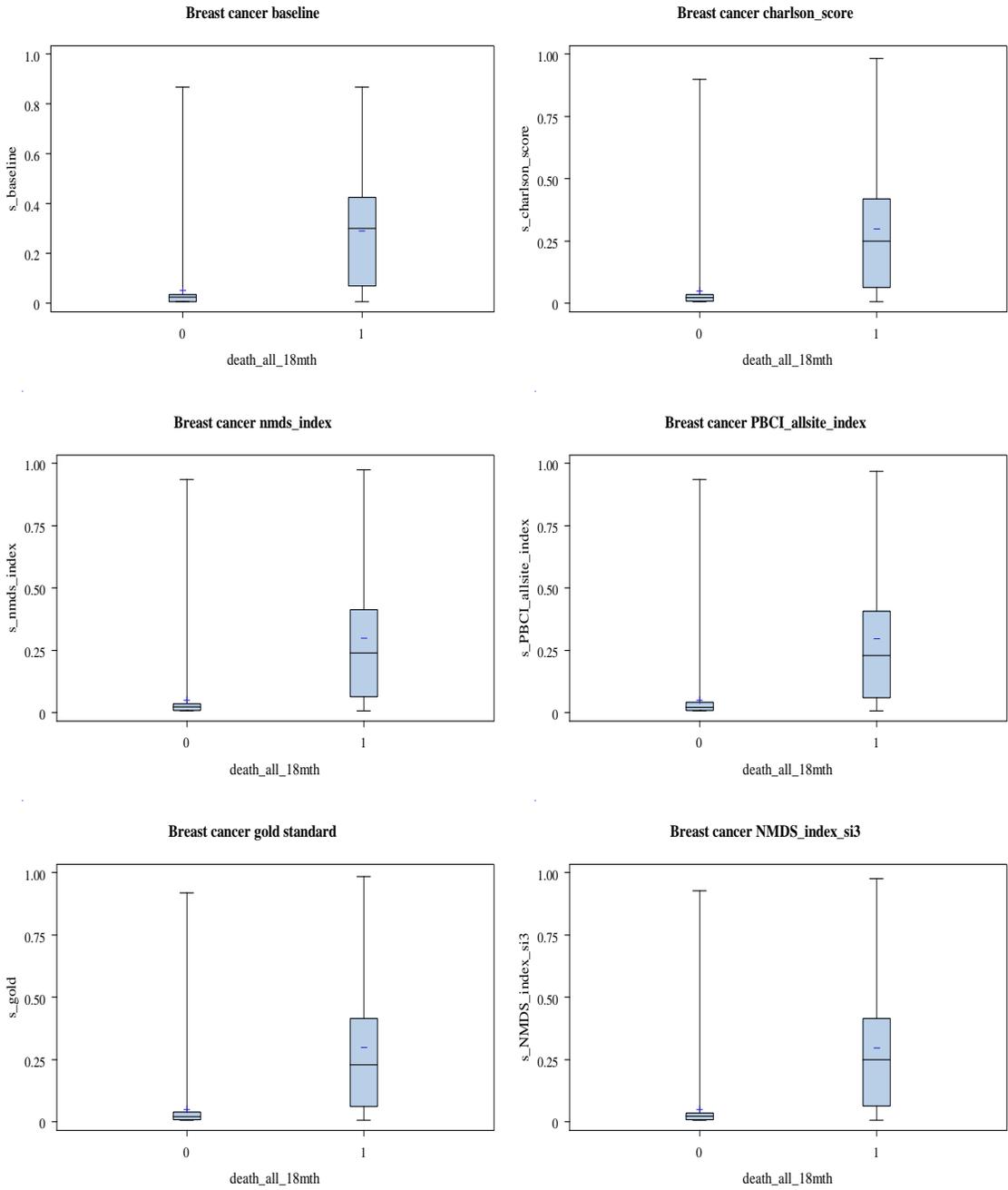
**Figure 12 Boxplots Predicted all-cause death from baseline (age, site and stage) model, and baseline combined with various measures of comorbidity. Development cohort: All sites combined**



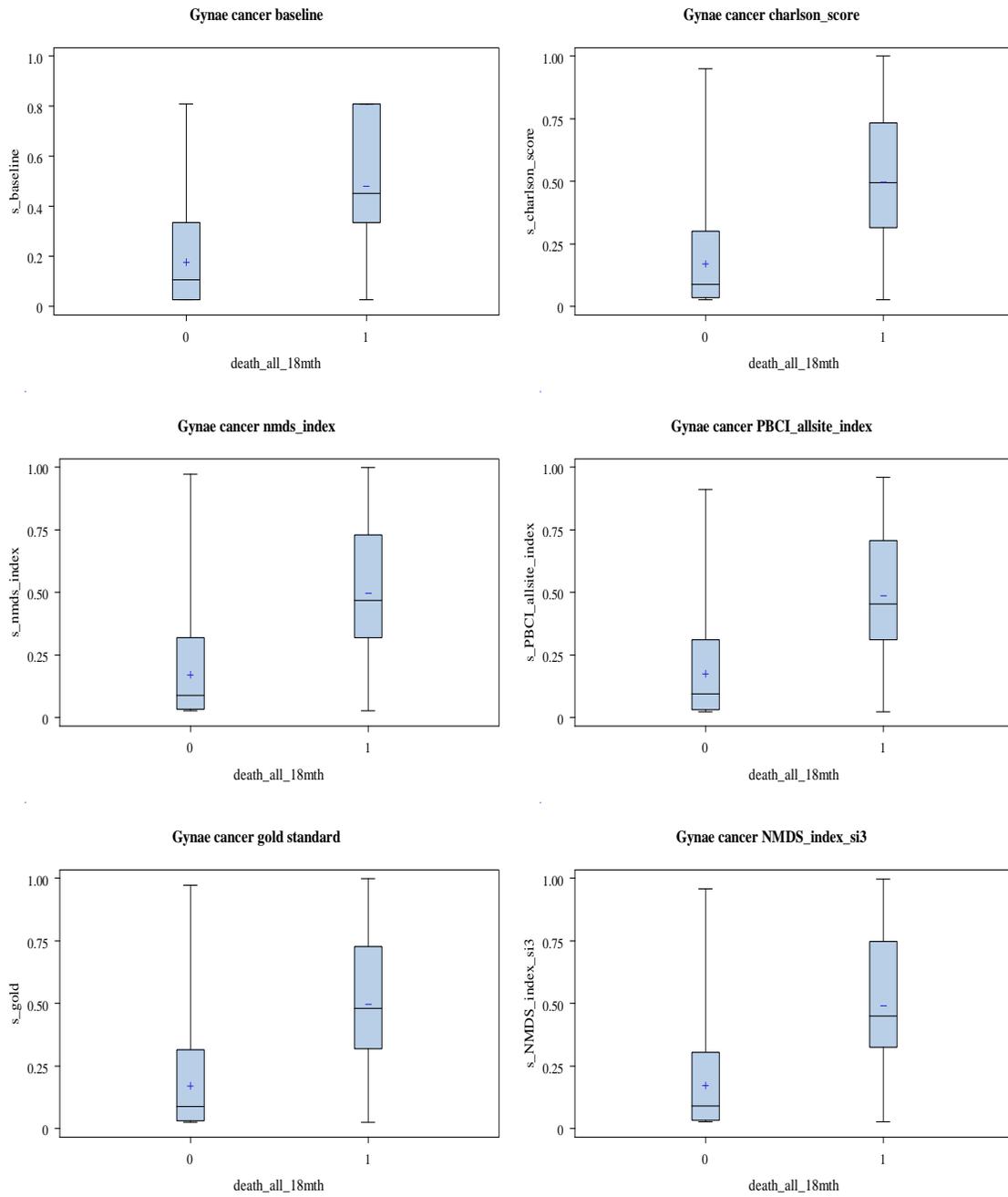
**Figure 13: Boxplots showing predicted all-cause death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: CRC cancer.**



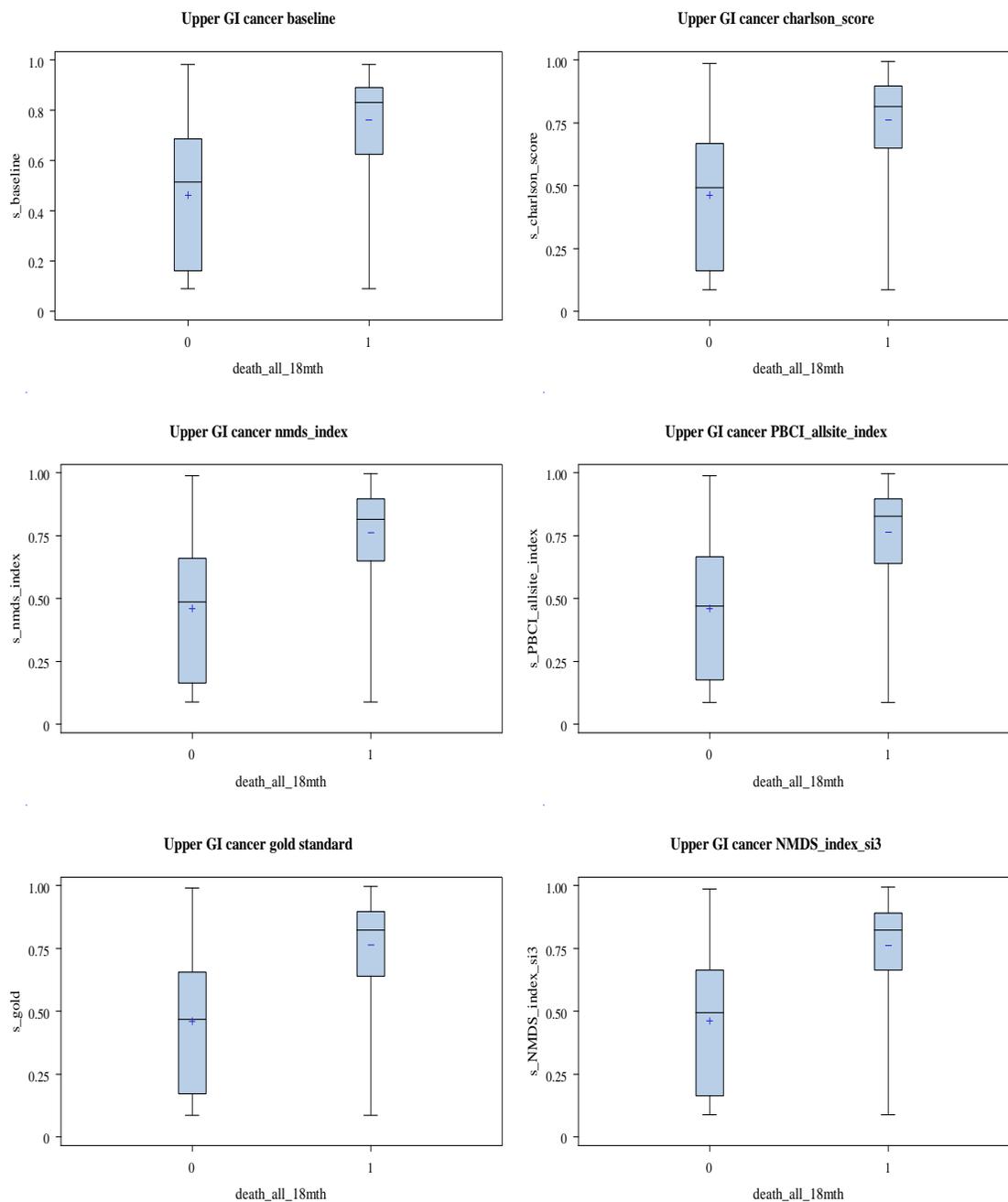
**Figure 14: Boxplots showing predicted all-cause death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Breast cancer**



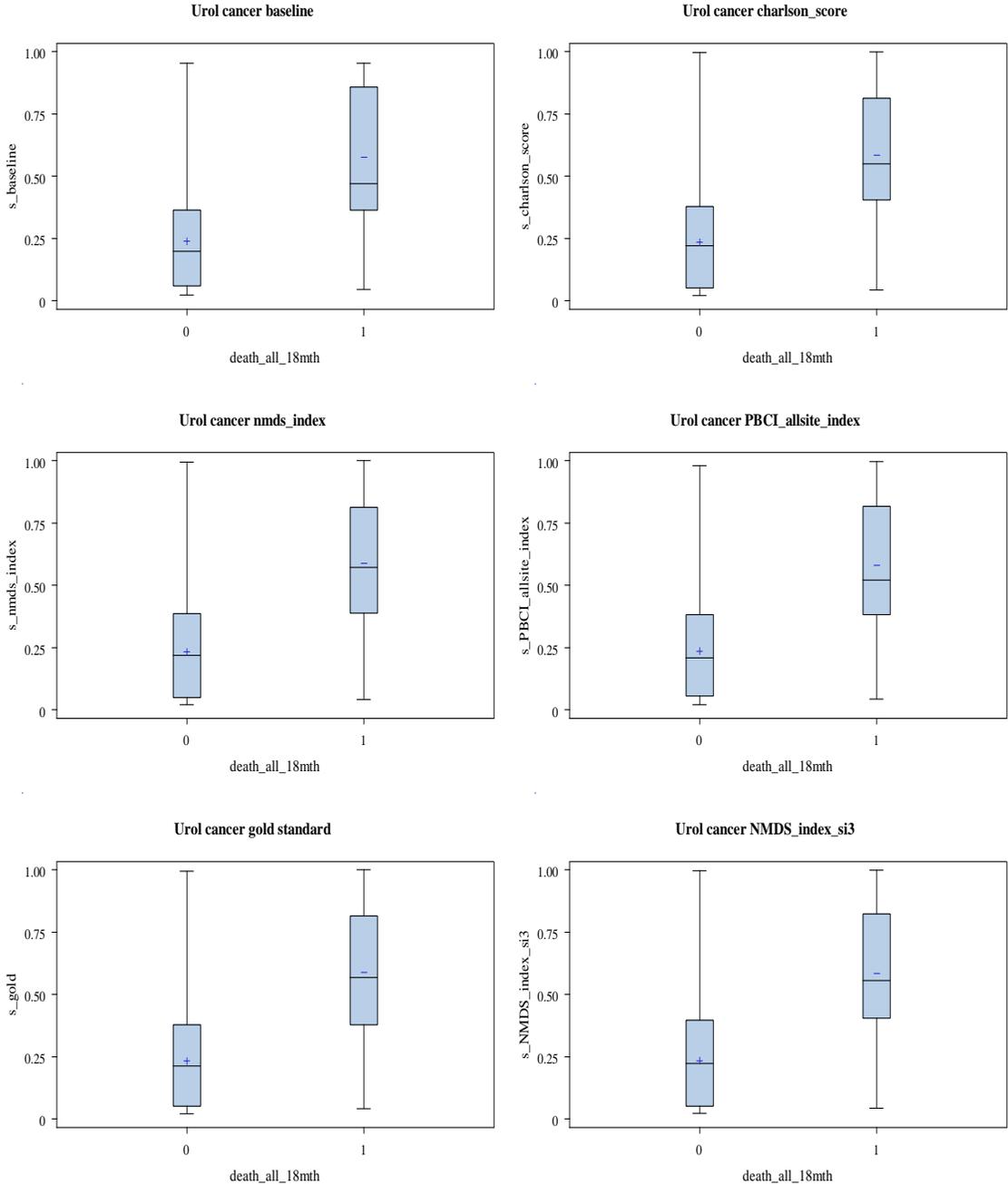
**Figure 15: Boxplots showing predicted all-cause death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Gynaecological cancers**



**Figure 16: Boxplots showing predicted all-cause death from baseline (age, sex and stage) model, and baseline combined with various measures of comorbidity. Development cohort: upper GI cancer**



**Figure 17: Boxplots showing predicted all-cause death from baseline (age, sex and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Urological cancer**



**Table 36 showing Integrated Discrimination Improvement (IDIs) comparing baseline, Charlson and Gold standard approaches to measuring comorbidity with other approaches for each site and all sites combined for all-cause death in validation datasets**

		CRC		Breast		Gynaecological		Upper GI		Urological		All sites	
Comparison		IDI	pvalue	IDI	pvalue	IDI	pvalue	IDI	Pvalue	IDI	pvalue	IDI	pvalue
<b>Baseline</b>	<b>Charlson</b>	0.009	<b>0.000</b>	0.016	<b>0.026</b>	0.027	<b>0.002</b>	0.008	0.073	0.005	0.053	0.008	<b>0.000</b>
	<b>C3</b>	0.014	<b>0.000</b>	0.012	<b>0.049</b>	0.021	<b>0.006</b>	0.003	0.163	0.007	<b>0.012</b>	0.008	<b>0.000</b>
	<b>PBCI</b>	0.010	<b>0.000</b>	0.004	0.441	0.006	0.227	0.004	0.072	0.001	0.515	0.004	<b>0.000</b>
	<b>Si1</b>	0.014	<b>0.000</b>	0.011	0.058	0.026	<b>0.003</b>	0.004	0.145	0.006	<b>0.024</b>	0.009	<b>0.000</b>
	<b>Si2</b>	0.009	<b>0.000</b>	0.010	0.076	0.021	<b>0.007</b>	0.004	0.116	0.003	0.094	0.007	<b>0.000</b>
	<b>Si3</b>	0.009	<b>0.000</b>	0.010	0.067	0.024	<b>0.003</b>	0.004	0.126	0.003	0.105	0.006	<b>0.000</b>
	<b>Gold</b>	0.015	<b>0.000</b>	0.011	0.073	0.021	<b>0.007</b>	0.005	0.078	0.008	<b>0.008</b>	0.009	<b>0.000</b>
<b>Charlson</b>	<b>C3</b>	0.004	<b>0.004</b>	-0.004	0.261	-0.006	0.161	-0.004	0.165	0.002	0.293	0.000	0.734
	<b>PBCI</b>	0.000	0.884	-0.012	0.083	-0.021	<b>0.007</b>	-0.004	0.344	-0.005	0.060	-0.003	<b>0.014</b>
	<b>Si1</b>	0.004	<b>0.003</b>	-0.005	0.207	-0.001	0.773	-0.004	0.203	0.000	0.795	0.001	0.389
	<b>Si2</b>	0.000	0.952	-0.006	0.149	-0.006	0.173	-0.004	0.238	-0.002	0.246	-0.001	0.148
	<b>Si3</b>	0.000	0.730	-0.006	0.143	-0.004	0.392	-0.004	0.212	-0.002	0.183	-0.001	0.094
	<b>Gold</b>	0.006	<b>0.000</b>	-0.005	0.249	-0.006	0.165	-0.003	0.346	0.003	0.197	0.001	0.464
<b>Gold</b>	<b>Si1</b>	-0.002	0.048	0.001	0.814	0.005	<b>0.016</b>	-0.001	0.380	-0.002	<b>0.016</b>	-0.000	0.836
	<b>Si2</b>	-0.006	<b>0.000</b>	-0.001	0.599	0.000	0.971	-0.001	0.567	-0.005	<b>0.003</b>	-0.002	<b>0.000</b>
	<b>Si3</b>	-0.006	<b>0.000</b>	-0.001	0.733	0.003	0.237	-0.001	0.511	-0.005	<b>0.002</b>	-0.002	<b>0.000</b>

Si1; Si2 and Si3= Simplified indices 1, 2 and 3 respectively

IDIs calculated from mean predicted one year all-cause survival calculated from Cox regression models including age, sex (where relevant), stage and site (for all site models). Bolded numbers are significant at a p<0.025 level.

**Table 37 showing Integrated Discrimination Improvement (IDIs) comparing baseline, Charlson and Gold standard approaches to measuring comorbidity with other approaches for each site and all sites combined for non-cancer death in validation datasets**

		CRC		Breast		Gynae		Upper GI		Urol		Allsites	
Comparison		IDI	pvalue	IDI	pvalue	IDI	pvalue	IDI	pvalue	IDI	pvalue	IDI	pvalue
<b>Baseline</b>	<b>Charlson</b>	0.017	<b>0.001</b>	0.068	<b>0.009</b>	0.022	0.517	0.026	0.086	0.027	<b>0.012</b>	0.026	<b>0.000</b>
	<b>C3</b>	0.026	<b>0.000</b>	0.053	<b>0.006</b>	-0.003	0.768	0.030	<b>0.012</b>	0.031	<b>0.005</b>	0.029	<b>0.000</b>
	<b>PBCI</b>	0.018	<b>0.001</b>	0.064	<b>0.006</b>	0.034	0.144	0.018	0.027	0.015	0.044	0.025	<b>0.000</b>
	<b>Si1</b>	0.027	<b>0.000</b>	0.056	<b>0.009</b>	0.013	0.559	0.032	<b>0.011</b>	0.029	<b>0.007</b>	0.032	<b>0.000</b>
	<b>Si2</b>	0.030	<b>0.000</b>	0.041	<b>0.014</b>	-0.002	0.792	0.036	<b>0.005</b>	0.025	<b>0.004</b>	0.031	<b>0.000</b>
	<b>Si3</b>	0.030	<b>0.000</b>	0.048	<b>0.011</b>	-0.001	0.904	0.032	<b>0.008</b>	0.026	<b>0.004</b>	0.031	<b>0.000</b>
	<b>Gold</b>	0.030	<b>0.000</b>	0.072	<b>0.001</b>	0.051	0.148	0.032	<b>0.008</b>	0.032	<b>0.004</b>	0.035	<b>0.000</b>
<b>Charlson</b>	<b>C3</b>	0.008	0.044	-0.015	0.201	-0.025	0.335	0.004	0.772	0.004	0.541	0.003	0.376
	<b>PBCI</b>	0.001	0.866	-0.004	0.896	0.012	0.783	-0.008	0.607	-0.012	0.263	-0.001	0.906
	<b>Si1</b>	0.009	<b>0.021</b>	-0.012	0.249	-0.009	0.702	0.006	0.658	0.003	0.688	0.006	0.080
	<b>Si2</b>	0.012	<b>0.007</b>	-0.027	0.104	-0.025	0.393	0.010	0.427	-0.002	0.809	0.005	0.205
	<b>Si3</b>	0.013	<b>0.003</b>	-0.020	0.210	-0.024	0.361	0.006	0.616	-0.001	0.874	0.006	0.120
	<b>Gold</b>	0.013	<b>0.025</b>	0.004	0.876	0.029	0.612	0.006	0.658	0.005	0.486	0.009	0.048
<b>Gold</b>	<b>Si1</b>	-0.003	0.236	-0.015	0.444	-0.039	0.414	0.000	0.946	-0.002	0.343	-0.003	0.288
	<b>Si2</b>	-0.001	0.871	-0.031	0.097	-0.054	0.171	0.004	0.627	-0.007	0.162	-0.005	0.189
	<b>Si3</b>	-0.000	0.945	-0.024	0.212	-0.053	0.199	0.000	0.956	-0.006	0.228	-0.004	0.313

Si1; Si2 and Si3= Simplified indices 1, 2 and 3 respectively

IDIs calculated from mean predicted one year non-cancer survival calculated from Cox regression models including age, sex (where relevant), stage and site (for all site models). Bolded numbers are significant at a p<0.025 level.

# Summary of Results

The results of this chapter were organised into four Sections:

**Section 1** provided a description of the main development and validation cohorts used in this thesis. There were 14,096 people in the development cohort and 11,014 patients in the validation cohorts, diagnosed with colorectal, breast, gynaecological (ovarian or uterine), upper GI (liver or stomach), or urological (renal or bladder) cancers. The sex and age distributions were largely as expected and similar for the development and validation cohorts. Those with breast and gynaecological cancers tended to be younger, have lower levels of comorbidity and lower mortality than other cancers. Those with upper GI cancers tended to have higher levels of comorbidity, and highest proportions dying of all-cause and non-cancer causes.

**Section 2** provided:

1. Results of the validation of routine hospitalisation data against data collected from a hospital notes review for the purpose of measuring comorbidity;
2. Prevalence and impact of important comorbid conditions identified in the hospitalisation data, and
3. Development and validation of site-specific hospitalisation-based comorbidity (C3) indices.

The results of the data validation showed that among the 569 patients with colon cancer who were included in the validation exercise, there was generally higher comorbidity measured from notes than administrative data, with better comparability with an 8-year lookback period, than one-year. The kappa scores varied by specific comorbid condition, but were generally moderate or good. Regardless of source of data, all measures of comorbidity significantly improved the ability of multivariable models to explain all-cause survival.

After an extensive process, 50 specific conditions were identified from the administrative hospitalisation data, and evaluated in terms of prevalence and impact on survival across each site category and all sites combined. Of the 50 conditions, the most common were hypertension (prevalence 8.0 to 20.9%); cardiac conditions (2.1-

13.5%); and diabetes with (2.3-13.3%) and without (2.9-12.9%) complications. Comorbidity was associated with higher all-cause mortality but the impact varied by condition and across cancer site, with impact less for cancers with poor prognoses. Conditions most consistently associated with adverse outcomes across all cancer sites were renal disease, coagulopathies and congestive heart failure.

Five site (group) specific indices were developed with conditions weighted according to their log hazard ratios from age and stage adjusted Cox regression models with non-cancer death as the outcome. The performance of these indices (the C3 indices) were compared with the Charlson and NCI comorbidity indices. The correlation between the Charlson and C3 index scores ranged between 0.61-0.78. The C3 index outperformed the other indices for colorectal cancer, performing similarly for upper gastrointestinal, urological, breast and gynaecological cancers.

**Section 3** provided:

1. Results of a comparison exercise of conditions identified through administrative pharmaceutical data with those identified through hospital notes review.
2. Prevalence and impact of conditions identified through the pharmaceutical data among cancer patients.
3. Development and validation of pharmaceutical-based comorbidity indices (PBCI).

The prevalence of conditions used in the comparison exercise varied depending on the data source used. Kappa coefficients for conditions identified in notes review compared with pharmaceutical data ranged from 0.83 (diabetes) to 0.26 (anxiety/depression).

Of the nineteen conditions identified using the pharmaceutical data, the most common was hypertension (34-52%). Other common conditions were gastric acid disorders (21-52%), hyperlipidaemia (17-31%), conditions requiring antiplatelet medication (14-26%) and reactive airways disease (13-18%). Conditions tended to be more strongly associated with non-cancer mortality than all-cause mortality and while the impact varied by condition, impacts tended to be reasonably constant across cancer sites. The highest impacts on non-cancer death were for congestive heart failure, psychotic illness and cardiac arrhythmias.

A pharmacy-based comorbidity index (PBCI) was developed with each condition weighted according to its association with non-cancer mortality. Predictive abilities of PBCI were compared with the Charlson and C3 comorbidity indices. Correlation coefficients with Charlson ranged from 0.37-0.45 across cancers. All comorbidity indices were significant predictors of mortality, and differences between models were small. The PBCI outperformed the other indices in predicting non-cancer mortality for breast and possibly gynaecological cancers.

**Section 4** provided results relating to the development and validation of three simplified hospitalisation-based indices, and comparison of their performance with that of the other indices (Charlson, C3, PBCI, and C3 combined with PBCI). The three simplified indices were 1) a single hospitalisation index which included all conditions in the C3 indices, but applied all-site weights rather than site-specific weights; 2) as for the first simplified index, but only the nineteen conditions with prevalence greater than 2% and hazard ratio for non-cancer death (adjusted for age and stage) of at least 1.2 were included; 3) as for second simplified index, but weights were further simplified by dividing by the smallest parameter estimate and rounding to the nearest integer.

The correlations between the simplified indices and the Charlson scores ranged across sites but were similar for each index within a given site. All were within the 0.57 to 0.80 range in all sites and across both development and validation cohorts.

The results in terms of optimal measures of comorbidity were not consistent, and varied across cancer sites and whether the outcome was all-cause or non-cancer death. These results are summarised below.

### **All sites combined**

**All-cause death:** the gold standard approach performed similarly to the C3 and SI1 indices, and these indices outperformed the Charlson, SI2, SI3 and PBC indices. SI2 and SI3 tended to perform similarly to the Charlson index.

**Non-cancer death:** The gold standard had significantly higher c-statistics and lower AIC compared with all other indices, although the IDIs were not significantly different. The simplified indices performed almost equivalently to the full C3 indices (and the PBCI) in terms of both AIC and c-statistics, and clearly better than Charlson on both.

## Colorectal cancer

**All-cause death:** The gold standard, C3 and SI1 indices tended to outperform the others in terms of c-statistics and AIC. These three measures also had significantly better IDIs than the Charlson index.

**Non-cancer death:** The gold standard approach performed only slightly better than the C3 and SI1-3 approaches and, these indices all outperformed the Charlson on all three measures (c-statistics, AIC and IDIs), although the difference in c statistics was only significant for SI1 and the Charlson index.

## Breast cancer

**All-cause death:** The c-statistics were very similar regardless of measure of comorbidity with less than 10 units between AIC scores across all hospitalisation-based indices. There were no significant differences between IDIs.

**Non-cancer death:** The PBCI and gold-standard had higher c-statistics and greater than 10 units lower AIC than the hospitalisation-based indices. The simplified indices performed similarly to the full C3 and Charlson. The IDIs were not significantly different regardless of comparison.

## Gynaecological cancer

**All-cause death:** All hospitalisation-based indices performed similarly, and slightly outperformed PBCI in terms of c-statistics and AIC. PBCI also had a significantly lower IDI than the Charlson index. SI1 had a significantly higher IDI than the gold standard.

**Non-cancer death:** There were relative view non-cancer deaths in this cohort, so results tended to be imprecise, with failure to converge of the bootstrapped non-cancer mortality models. However, the PBCI and gold standard had somewhat higher c-statistics with all other hospitalisation-based indices performing reasonably similarly. The AICs were lower for the PBCI, and IDIs were similar regardless of which comorbidity measure was used.

## Upper GI cancers

**All-cause death:** Adding any measure of comorbidity to the baseline model made very little difference in terms of c-statistic, AIC or IDIs.

**Non-cancer death:** The gold, C3 and simplified indices tended to perform better than the PBCI or Charlson index in terms of c-statistics and AICs. There were no significant differences in IDIs regardless of comparison made.

## **Urological**

**All-cause death:** the c-statistics were all similar and not much better than baseline regardless of measure of comorbidity used. Simplified indices 1, 2 and 3 had significantly lower IDIs than the gold-standard.

**Non-cancer death:** There was little difference between comorbidity measures in terms of c-statistics, AICs or IDIs.



# Chapter 7. Discussion: Strengths and weaknesses of the data and methods used

*Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful.* ~George Edward Pelham Box

The overall Discussion section is divided into two chapters. This chapter (Chapter 7) focuses on identifying the strengths and limitations of the data and methods used. The next chapter (Chapter 8) provides an interpretation of the findings of the thesis and a Discussion relating to the implications of those findings.

Specifically, this Chapter begins with an examination of the strengths and limitations of the data sources used in this work; the Cancer Registry, mortality data, hospitalisation data and pharmaceutical data, as well as identifying alternative data sources that were not used. It then describes considerations relating to the methods used to develop the weighted indices including a discussion of alternative approaches and issues associated with the estimation and combination of weights. Finally, there is a discussion on the approaches used in the validation and comparison of indices developed in this thesis.

## Data sources used

### Cancer Registry data

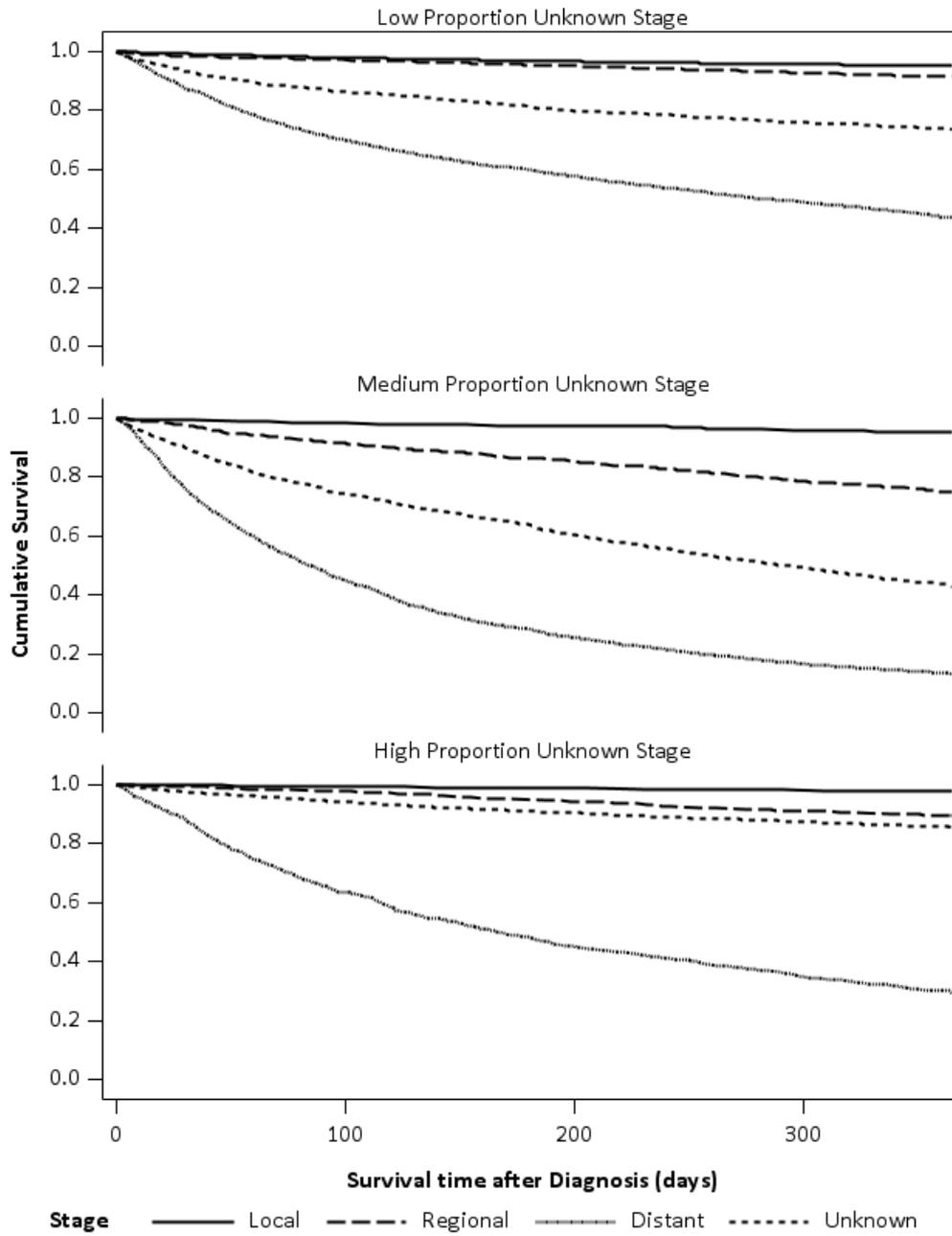
Cancer Registry data were used to identify cancer patients, and to provide some cancer-related information, particularly extent of disease (or stage). The major strength of the NZ Cancer Registry is that it is (theoretically) a registry of all cancer patients diagnosed in New Zealand, except those with basal and squamous cell carcinomas (Ministry of Health 2010). Since 1994 it has been mandated that all newly diagnosed

cancers are notified to the NZ Cancer Registry, and for this reason it is assumed to provide a reasonably complete population of people diagnosed with cancer (Ministry of Health 2010). However, there has been only one evaluation of the completeness of case ascertainment of the NZ Cancer Registry data since mandated reporting commenced. Stevens et al compared lung cancer patients diagnosed in Auckland by reviewing listings of hospital admissions and discharges, thoracic surgery operation schedules, databases of cytohistopathology, radiation oncology, palliative care, and regional hospice services, with a list of lung cancer patients identified by the NZ Cancer Registry. They found 12% of patients were not initially identified in the NZCR, although some of these 'missing' patients were subsequently registered, were living outside the region in which the study took place or had a different date of registration (Stevens, Stevens et al. 2008). This potential under-ascertainment of patients is likely be more marked in cancers for which a pathological diagnosis is less common (such as lung cancer), because pathology laboratories are the primary source of data for cancer registrations, therefore the under-ascertainment of the cancers included in this study is likely to be less than 12%. In order to affect the results of the work presented here, there would have to be a substantially different association between comorbidity and outcomes among the missing patients, which seems unlikely. For these reasons, under-ascertainment of cancer cases is unlikely to have materially affected the results of this thesis.

Data on extent of disease at diagnosis are not complete in the NZCR and patients with missing extent of disease data were included in the study, with a separate category included for 'missing' within the 'extent of disease' variable. This was based on the fact that we found that those with missing extent of disease data had survival probabilities consistently between those of regional and advanced disease in all cancer sites (Figure 18), so it seemed reasonable to treat 'missing' as a meaningful category in its own right. However, both the proportion of missing and the patterns of missingness of extent of disease data varies by cancer type (Gurney, Sarfati et al. 2013) (Table 38). The cancers included in this study can be divided into three groups: low proportion unstaged (ovarian 6%; colon, 10%; breast 10%; uterine 11% and renal cancers 14%); moderate proportion unstaged (rectal 33% and stomach cancers 38%); and high proportion unstaged (liver 67% and bladder cancers 72%). Extent of disease is a critical factor in predicting outcomes from cancer, and will therefore act as a confounder in the associations between comorbidity and outcomes if there is also an association between comorbidity and missing extent of disease data. We investigated

this issue with the developmental data described here (as well as some additional data on other cancers) and found that after adjusting for sex, age and ethnicity, comorbidity was only associated with missing extent of disease data among cancers with a low proportion of missing stage (for example, women with missing data on extent of disease who had uterine or ovarian cancer had approximately four-fold increased odds of having a Charlson score of 3+ compared with women with local disease, and patients with colon, renal or breast cancer a two to three-fold increased odds) (Table 38). The association between comorbidity and missing stage data was not evident for any of the cancers with a moderate or high proportion of missing extent of disease data, except for liver cancer (OR=1.98; 1.2-3.2). This is reassuring, because these missing data are more likely to be an important source of bias where the proportion missing is high, and the association between comorbidity and the missing data is strong. These two criteria were only both met for liver (and to a lesser extent stomach) cancer. This means that there may be particular residual confounding by stage for those with upper GI cancers, which could result in an overestimation of the impact of comorbidity on outcomes. However, the cancer-specific mortality is also particularly high for these cancers, so in fact the relative impact of comorbidity tends to be lower than other cancers anyway.

**Figure 18: Unadjusted Kaplan-Meier curves for one-year survival, by proportion unknown stage group**



(From Gurney J, Sarfati D et al 2013; Cancer Epidemiology 37: 498-504.)

**Table 38: Odds ratios for likelihood of having missing stage (or extent of disease at diagnosis) data by comorbidity category.**

	% missing stage data	Charlson 3+ vs 0	
		Adj OR*	95% C.I.
<i>Ovarian</i>	6	<b>4.02</b>	(1.79 - 9.01)
<i>Breast</i>	10	<b>2.83</b>	(2.08 - 3.86)
<i>Colon</i>	10	<b>2.44</b>	(1.91 - 3.11)
<i>Uterine</i>	11	<b>4.42</b>	(2.50 - 7.83)
<i>Kidney</i>	14	<b>2.91</b>	(1.84 - 4.62)
<i>Rectal</i>	33	0.80	(0.57 - 1.13)
<i>Stomach</i>	38	1.34	(0.92 - 1.96)
<i>Liver</i>	67	<b>1.98</b>	(1.22 - 3.20)
<i>Bladder</i>	72	0.90	(0.55 - 1.48)

\* adjusted for age, sex and ethnicity

(Modified from Gurney J, Sarfati D et al 2013; *Cancer Epidemiology* 37: 498-504.)

## Mortality data

This study used data from the National Mortality database to identify the outcomes for individuals in order to ascertain the relationship between comorbidity and survival (or mortality). Misclassification of mortality data could impact estimates of the strength of this relationship. There are two levels at which misclassification relating to death could occur; the first is the fact of death, and the second is misclassification of the cause of death (Dignam, Huang et al. 2009; Howlader, Ries et al. 2010).

Survival estimates were ascertained by linking individuals to the mortality database; those without a record on this database were assumed to be still alive at the end of study follow-up. It is very unlikely that a person who is still alive would be falsely recorded as having died, and whilst the possibility that someone has died without having their death recorded is slightly more possible, the risk of this is considered negligible (Ministry of Health 2009). Deaths may be missed if study subjects died outside New Zealand. This is likely to be extremely uncommon among those recently diagnosed with cancer. For these reasons, misclassification as to the fact of death is unlikely to be a major source of error in this study.

Cause of death is assigned by registrars at the Ministry of Health, and based on an extensive process of checking (involving death certificates, coroners reports, review of hospital records etc) (Ministry of Health 2009). However, it is possible that some patients who were identified as having died of non-cancer causes, in fact died of cancer causes. This source of error will not affect all-cause survival estimates, but may result in biased estimates of hazard ratios for non-cancer specific survival. A few studies have attempted to determine the sensitivity and specificity of routine death data. However this is complicated by the fact that accuracy of death data varies depending on a range of factors such as the level of diagnostic detail, the 'gold standard' against which death certificate data are measured and hence cancer-specific death defined (for example, autopsy or medical notes review), and the level of clinical certainty underlying specific diagnoses. The quality of data is also likely to vary over time, place and possibly social grouping (Percy, Stanek et al. 1981; Samphier, Robertson et al. 1988). Several authors have shown that death certificate classification of cause of death may be more accurate for cancer than for some other causes of death, at least at a major diagnostic grouping level (Samphier, Robertson et al. 1988; Goldacre 1993; Albertsen, Walters et al. 2000). For this reason, in this study cancer-specific deaths were defined as deaths from any cancer (not only the site of cancer that had been diagnosed). Also somewhat reassuringly, recent studies have suggested that the estimates of cause-specific mortality based on death certificate data are generally not substantially biased (Dignam, Huang et al. 2009; Howlader, Ries et al. 2010).

Misclassification of deaths as being due to non-cancer causes when they are, in fact, due to cancer causes is particularly important in terms of its ability to cause substantial bias to the hazard ratio estimate if the misclassification is differential. If the misclassification is independent of whether or not an individual has a particular comorbidity, then the hazard ratios will be biased, somewhat, to the null. However, it is not unreasonable to think that those with comorbidity may be more likely to be classified as having died of non-cancer causes because of their comorbidity than those without, even if they did, in fact die from a cancer cause. In this case, those with comorbidity will have higher non-cancer hazard estimates than they would have done in the absence of comorbidity, and thus the hazard ratio will be biased away from the null. In other words, it is possible that the estimates of the impact of comorbid conditions on non-cancer mortality may be overestimated.

Misclassification of non-cancer deaths as being due to cancer will decrease the non-cancer hazard estimates. Given that those with comorbidity are more likely to, in fact, die of non-cancer causes, it is possible that this bias will be greater for them. In other words, those with comorbidity may be more likely to die (of any cause) and for the cause of death to be recorded as being cancer-related even when it was, in fact, due to other causes. In this situation, the non-cancer hazard estimates would be underestimated for those with comorbidity, and the hazard ratio would be underestimated.

It is difficult to know the extent to which these biases might be operating in this study, but many more deaths are due to cancer than non-cancer in these populations, even among those with comorbidity, thus numerically the first bias is likely to be more important than the second. This means that the estimated impact of comorbidity in non-cancer mortality may be somewhat overestimated, and the extent of this will depend of the unknown extent of misclassification of cause of death between those with and without comorbidity, and may vary across comorbid conditions. However, given the two opposing biases above, it is unlikely that this bias will be substantial.

## **Hospitalisation data**

The aim of this study was to develop optimal comorbidity indices using administrative data. The primary source of comorbidity data used in this study was administrative hospitalisation data. The major strengths of these data are that they are relatively easy to obtain and available at a population level, making them useful for measuring comorbidity in a practical way for a large population. However, data are not collected for research purposes. They may be incomplete or missing, incorrect diagnosis codes may be applied and they may be biased towards more severe conditions or those that attract higher levels of funding (Elixhauser, Steiner et al. 1998; Mnatzaganian, Ryan et al. 2012). As a general rule in New Zealand, comorbidities are only coded in administrative data if they co-exist or arise during a given episode of care and if they affect patient management in a way which might extend length of hospital stay. This approach is likely to result in an emphasis on the most active and clinically important conditions, and will explain some of the difference between notes and administrative comorbidity data. It is difficult to identify complications from pre-existing diagnoses using administrative data. As a result, in this study, some conditions (such as congestive heart failure, pulmonary embolism and myocardial infarction) were excluded

if they were **only** identified at the index admission to exclude apparent comorbidities that were, in fact, complications of the cancer or its treatment. However, some of these excluded conditions would have been genuine comorbid conditions, and their exclusion would result in an underestimate of the prevalence of those conditions, and of comorbidity in general. Finally, administrative databases are often large and unwieldy and require expertise to manage and manipulate them.

A comparison of New Zealand administrative hospitalisation data with manual clinical notes review data was carried out early in the thesis process in order to ensure these data were adequate for the purpose of measuring comorbidity. Clinical notes review often results in higher ascertainment of comorbidity than data abstraction from routinely collected hospitalisation data (Romano, Roos et al. 1993; Malenka, McLerran et al. 1994; Newschaffer, Bush et al. 1997; Kieszak, Flanders et al. 1999; van Doorn, Bogardus et al. 2001; Sharabiani, Aylin et al. 2012). Where clinical and administrative data sources have been directly compared, the findings tend to show that the correlation between individual conditions is moderate at best, and varies depending on the quality of the administrative data, and on the nature of the individual condition (Malenka, McLerran et al. 1994; Newschaffer, Bush et al. 1997; Kieszak, Flanders et al. 1999; van Doorn, Bogardus et al. 2001; Parker, Li et al. 2006). The comparison between administrative and manually collected hospitalisation data presented here similarly found a range of kappa coefficients for individual conditions although, reassuringly, all but two conditions showed moderate or high correlation with the longer lookback period.

Despite the lack of correlation between individual conditions, where comorbidity was included as a covariate, both sources of data were found to improve multivariable model fit, compared with using none, to a similar degree, and both sources of data combined were better than either alone. These findings are consistent with other studies which have carried out similar comparisons (van Doorn, Bogardus et al. 2001; Aylin, Bottle et al. 2007; Klabunde, Legler et al. 2007). These comparison studies tend to show that administrative comorbidity data are not a subset of medical notes data, and it is likely that combining datasets provides less misclassification of comorbidity than either source alone (Malenka, McLerran et al. 1994; Newschaffer, Bush et al. 1997; van Doorn, Bogardus et al. 2001). This is, of course, rarely possible. Given that both sources result in misclassification of the (immeasurable) underlying construct of 'true' comorbidity, it is also possible, or even likely, that each of the sources of data

correlates more strongly with this third measure than they do with each other, assuming that the misclassification errors in administrative and notes review data are independent of each other.

For the data validation exercise, only patients with colon cancer were included because of the accessibility of previously collected clinical notes review data. While patients with other primary conditions may have somewhat different patterns of comorbidity, it seems unlikely that this will affect the quality of the recording of their comorbidity data. In that respect, it seems reasonable to be able to generalise the findings of this comparison to hospital-based comorbidity data in New Zealand in general.

For the validation, the coding recommended by Deyo et al was used (Deyo, Cherkin et al. 1992). This was because, as mentioned, the validation was done prior to any of the other work done for this thesis, and the comparison cohort for which we had clinical notes review data included patients diagnosed from 1996 at which time ICD-9 coding was standard. However, it is not entirely clear how one should map conditions from clinical notes to ICD codes, and there has been dissent expressed on this in the literature (Deyo, Cherkin et al. 1992; Charlson 1993; Deyo 1993; Romano, Roos et al. 1993; Romano, Roos et al. 1993; Quan, Sundararajan et al. 2005). No gold standard mapping approach has been established, so considerable care was taken to optimise the coding of the comorbid conditions included in the indices. All coding relating to the initial 50 included conditions was checked, again with input from clinicians to ensure that only the specific conditions that they considered relevant to function or length of life were included in these categories. While the validation exercise was not carried out on these re-coded conditions, in most cases where conditions had been compared, any coding changes to those conditions were minor so would be unlikely to substantially change the findings. However, there were also some conditions that were included in the full study that were not part of the validation exercise.

Despite these efforts, there is no way of eliminating measurement error of individual conditions, and of comorbidity as a construct when using administrative hospitalisation data. The discussion here will focus on the first issue (misclassification of individual conditions), with a discussion in the next chapter about issues relating to misclassification of comorbidity more generally.

Misclassification of individual conditions will impact estimates of prevalence of specified conditions, as well as hazard ratios that estimate the impact of conditions on outcomes. There are two possibilities with regard to misclassification of conditions; first it is possible that some of those identified as having the condition, in fact do not have the condition. Alternatively, not all those with the condition may have been identified as such; all individuals without mention of a given condition are assumed not to have it. The latter of these possibilities is likely to be both more common and more important. Assuming this error is non-differential with regards to the outcome (in other words those with the condition who have not been identified have, on average, similar survival patterns as those with the condition who have been identified), then the effect will be to bias the hazard ratios (slightly) to the null. However, if the misclassification is differential with regards to outcome, then the hazard ratios could be biased in either direction. For example, if those with less severe disease are less likely to be identified in the hospitalisation data, and these individuals have a better survival probability than those who have been identified, then the hazard ratio will be biased away from the null.

## **Pharmaceutical data**

Pharmacy-based instruments provide an alternative approach that addresses some of the known weaknesses of hospitalisation-based indices. In addition to the limitations of administrative hospitalisation data relating to inaccurate or incomplete ascertainment of conditions, and variations in coding, there is also the issue that they will only identify conditions that are recorded within hospitalisations. People who have not been hospitalised or hospitalised infrequently may still have substantial comorbidity which may be underestimated in hospitalisation-based indices (Fortin, Bravo et al. 2005). Pharmaceutical data allows the identification of conditions for which medication has been prescribed, and the prescription filled. They will therefore allow the identification of conditions even among those who are not hospitalised. Prescription records will identify chronic conditions for which medications are regularly prescribed. Assuming complete data, all actively treated medical conditions for which prescriptions are filled will be identified regardless of the primary condition or funding arrangements that encourage the recording of one diagnosis over another.

However, there are limitations in using pharmaceutical data to measure comorbidity, One of the disadvantages of pharmacy-based indices is that disease categories are based predominantly on drug-class-level, and misclassification of illness may occur when medications are used for conditions other than their major indication (Lu, Barratt

et al. 2011). Additionally, pharmacy-based indices will under-count chronic illnesses not treated by prescriptions such as diabetes treated by diet only (Vitry, Wong et al. 2009). Conditions will also only be identified if patients fill their prescriptions which may not always occur, and may be more important for some population groups than others (Iezzoni 1997). Another limitation is related to the fact that pharmaceutical data are often collected for funding reimbursement purposes, which may impact on the data collected. In New Zealand, data are only collected on medications for which a subsidy or reimbursement is required. Because the cost of medications in New Zealand is almost always more than what the patient pays, this has been estimated to result in only a minor loss of data (e.g. about 0.5% of prescriptions in 2011/12) (Personal communication: Hew Norris, Senior Analyst, Pharmac NZ, 6 November 2012), but is an issue that should be considered.

Where pharmaceutical and hospitalisation-based indices have been compared, generally both are found to be valid measures (Vitry, Wong et al. ; Schneeweiss and Maclure 2000; Perkins, Kroenke et al. 2004; Dominick, Dudley et al. 2005; Baser, Palmer et al. 2008; Lu, Barratt et al. 2011). For example, Lu et al. (Lu, Barratt et al. 2011) reported that the Charlson index and Rx-Risk model are both valid comorbidity measures for predicting deaths but there were substantial differences between the two indices in identifying specific chronic illnesses. Two comparison studies showed that the Rx-Risk model performed as well as the hospitalisation-based comorbidity measures in predicting overall health care use but there were differences in their ability to predict specific health service variables such as physician visits, prescription drugs and hospitalisation (Perkins, Kroenke et al. 2004; Dominick, Dudley et al. 2005). The Rx-Risk model, not surprisingly, was a stronger predictor of prescription medication use compared with Elixhauser or Charlson approaches, while the Elixhauser method outperformed the Charlson index and the Rx-Risk model in predicting physician visits. However the differences in predictive ability among the models were small, indicating no clear advantage for using any of the measures (Dominick, Dudley et al. 2005). Additionally, the findings from Johnson et al. (Johnson, El-Serag et al. 2006) showed that an extended-version of the Rx-Risk model outperformed a diagnostic-based comorbidity measure (i.e., Deyo score) in outpatients from the Department of Veteran Affairs. In contrast, some studies have found that hospitalisation-based indices are slightly superior to pharmaceutical ones in terms of predicting mortality, particularly in elderly populations (Schneeweiss, Seeger et al. 2001; Perkins, Kroenke et al. 2004; Schneeweiss, Wang et al. 2004; Belosesky, Weiss et al. 2011; Lu, Barratt et al.

2011). Similarly the findings specifically among cancer patient populations have been mixed, with some studies showing that pharmaceutical indices provide a poor measure of comorbidity among these patients (Hall, Rochon et al. 2002). This may be because pharmaceutical-based indices that have been previously used have not been specifically designed for use among cancer populations. For example, they are likely to include some conditions such as anaemia that are complications of the cancer itself or its treatment, and may include some short term conditions such as pain and inflammation which may not be important in term of survival from cancer (Sloan, Sales et al. 2003; Johnson, El-Serag et al. 2006). To address this, in this work, conditions included in the PBCI were reviewed by clinicians and pharmacists to ensure both their relevance to cancer, and that the medications included were relevant and correct.

These pharmaceutical data were validated against clinical notes review data. As previously discussed, it is reasonable to expect differences between conditions identified through these two mechanisms, because each is measuring slightly different aspects of comorbidity. The comparison of these two data sources in this study found that the correlations between conditions, as measured by kappa scores, were not high for many conditions, a finding similar to other studies (George, Vuong et al. 2006; Beloosesky, Weiss et al. 2011; Lu, Barratt et al. 2011). However, those that had low kappas were those that might be expected to have low correlations. For example, the two conditions with the lowest kappa scores, namely anxiety and depression (kappa=0.26) and peptic ulcer disease (kappa=0.30), were both more commonly identified in pharmaceutical data. These are both very common conditions in the community, may be considered mild conditions for many and are therefore less likely to be recorded in hospital notes. The correlations of overall PBCI with the Charlson index were very similar to those reported by other authors using pharmaceutical data to measure comorbidity (Beloosesky, Weiss et al. 2011; Lu, Barratt et al. 2011). Again, the validation exercise was carried out on patients with a subset of cancer types (rectal, liver and stomach), so it is possible that the errors inherent in pharmaceutical data are somehow systematically different for people with different cancers. While this is possible, it is unlikely that this is a major effect, and it is reasonable to generalise these validation findings to patients with cancer more broadly.

## **Alternative approaches to measuring comorbidity among cancer populations in New Zealand**

For this work, comorbid conditions were identified separately from administrative hospitalisation and pharmaceutical datasets. There were alternative (or additional) approaches that could have been used to measure comorbidity using routine data. For example, the recently published New Zealand Burden of Disease study (Ministry of Health 2012) identified individual conditions by linking multiple data sources including laboratory claims data, routine mental health data and outpatient data from the National Non-admitted Patient Collection. There are two main reasons why this approach was not used here. First, the aim of the thesis was to develop practical and useful comorbidity indices for researchers, health service planners and others. It is considerably less practical for researchers to link multiple datasets within New Zealand, and often impossible in many other countries. The second reason this approach was not used in this thesis is that there are substantial problems with these additional datasets. For example, the laboratory dataset only provides data on the fact of a test, not the result; and the outpatient dataset does not provide diagnosis codes. For this reason, only a very small subset of conditions, including diabetes, are likely to benefit from including information from other datasets. Reassuringly, if we compare our prevalence estimates of diabetes calculated from the hospitalisation data with those reported in the New Zealand Health Survey, it seems that our estimates are reasonably comparable. For example, among women over 55 years, the prevalence of self-reported diagnosed diabetes ranged between 6-12% in the Health Survey (Ministry of Health 2004). The estimates of diabetes prevalence for women with breast, ovarian and uterine cancers respectively were 5.2%, 8.9% and 16.1%.

A very useful alternative source of comorbidity data would be those collected in the primary care sector. Currently standard national-level primary care data are not available in New Zealand, but this may be an avenue for future exploration.

As discussed earlier, obtaining data on comorbidity directly from patients' clinical notes is considered gold standard, however it is not without its problems. It is time-consuming and expensive to collect such data, data abstractors must be trained and such data are generally not available at the population level. Nevertheless, these data are usually collected for a specific study purpose, and therefore can provide necessary detail such as the timing, and severity of conditions and can differentiate complications

from pre-existing disease. They also most closely reflect the clinical information available to clinicians at the time of diagnosis which is very useful especially if the aim of the research is to assess the impact of comorbidity on clinical decision-making (Lash, Mor et al. 2004).

Collecting data from patients themselves can be less resource intensive than reviewing clinical notes, and these data generally correlate well with quality of life and functional status (Crabtree, Gray et al. 2000; Ogle, Swanson et al. 2000; Byles, D'Este et al. 2005; Groll, To et al. 2005; Bayliss, Ellis et al. 2009), and reasonably with mortality and health service use (Fan, Au et al. 2002; Susser, McCusker et al. 2008). Self-report measures of comorbidity tend to identify higher levels of comorbidity than either notes review or administrative data sources (Katz, Chang et al. 1996; Crabtree, Gray et al. 2000; Byles, D'Este et al. 2005). For example, Katz et al found that when they converted the Charlson index into a patient report instrument, scores based on self-report tended to be higher than scores based on clinical notes review, but there were reasonable correlations between the two sources and the distributions were similar (Katz, Chang et al. 1996). A major disadvantage of self-reported data is that patient recall may result in error which may be related to other variables in the study, either if data on other variables are also collected from patients or through other mechanisms resulting in dependent error. For example, Katz et al found that correlations between conditions identified through clinical notes review and patient report were higher for those with higher levels of education (Katz, Chang et al. 1996). The implication of this is that education and comorbidity will become associated in part because of differential comorbidity reporting practices by education strata. Studies have also found that the accuracy of self-report varies considerably between specific conditions (Merkin, Cavanaugh et al. 2007; Cavanaugh, Merkin et al. 2008). For example, Merkin et al found that among a cohort of patients with end stage renal failure, there was high agreement between patients and medical records for diabetes ( $\kappa=0.93$ ), but low agreement for chronic obstructive airways disease ( $\kappa=0.20$ ) (Merkin, Cavanaugh et al. 2007). Furthermore, in retrospective studies of cancer outcomes, some patients may no longer be available either because they have died or cannot be contacted for other reasons.

Given that most research suggests that each source of data provides somewhat different information about the underlying construct of comorbidity, each is only moderately correlated with the others and models containing data from several sources

often perform better than models with data from a single source, Lash et al have suggested an approach which combines different sources of data into a single model (Lash, Thwin et al. 2003). This approach uses a latent variable approach which allows separate logistic regression models for each measurement method to be merged into a single regression equation (Horton, Laird et al. 1999). This allows an overall assessment of the impact of comorbidity on the outcome of interest, and the roles of each individual index. Lash et al combined five comorbidity indices (Charlson Comorbidity Index, ICED, ASA, and an overall clinical measure of comorbidity) to assess the role of comorbidity on receipt of treatment for breast cancer among a cohort of elderly breast cancer patients. They found that likelihood of discussing treatment was inversely related to comorbidity, and that the multiple informants approach provided more precise estimates (narrower confidence intervals) than traditional regression methods. However, they concluded that “*when a single comorbidity index applies directly to a research question, or such an index can be developed, then that single index should be given preference [over multiple informants approaches].*”

## Strengths and limitations of using weighted index to measure comorbidity

### Why develop a weighted index?

The indices presented in this thesis are all weighted indices. Other approaches that have been previously used are less likely than a weighted index approach to fulfil the requirements of a simple, administrative data-based comorbidity index for cancer, which was the aim of the thesis.

Alternative possibilities that were considered were as follows:

**Case-mix approaches** (such as ACGs, and DCGs) and approaches based on **clinical judgement** (such as the global American Society of Anesthesiologists’ class (ASA)) were considered. Case-mix approaches are designed to be based on administrative data so they can be applied to large populations relatively easily. In this respect, they meet the requirements of this thesis. However, the main focus of these systems is to predict health service resource use. For this reason, they include disease and patient factors (such as sex and age) in their groupings of conditions which relate to each

other in terms of quanta of healthcare resources used. This type of approach was not considered appropriate for this work. Approaches based on overall clinical judgement are overly simplistic and require clinical assessment (or access to clinical notes).

**Organ or systems-based approaches** assess the impact of comorbidity on the function (or dysfunction) of body organs or systems (such as the respiratory, cardiovascular, gastrointestinal and renal systems). The resulting ordinal indices are based on highly simplifying assumptions, such as for the Kaplan-Feinstein Index (KFI) and ACE-27 approaches for which an overall ranking is (generally) assigned based on the severity of the single most severe condition (Kaplan and Feinstein 1974; Piccirillo 2000; Piccirillo, Costas et al. 2003; Piccirillo, Tierney et al. 2004). Some of these approaches (for example, Index of Coexistent Disease (ICED) and Total Illness Burden Index (TIBI)) have also combined measures of comorbidity with functional status (Greenfield, Apolone et al. 1993; Greenfield, Sullivan et al. 1995). This has two impacts. First, this means that these measures are not 'purely' measuring comorbidity, but rather conflate comorbidity with functional status. Second, and perhaps more importantly, the functional status element cannot be ascertained from administrative data (in New Zealand, at least).

The ACE-27 approach was designed assuming access to clinical notes, but it has recently been converted into a claims-based index among patients with breast or prostate cancer (Fleming, Sabatino et al. 2011). This work involved making an assessment of the severity of each condition included in ACE-27 identified from ICD-10 codes in claims data from up to one year prior to diagnosis from cancer. Each condition was categorised as resulting in mild, moderate or severe decompensation, although some categories had to be collapsed because of lack of detail in the administrative data. These authors compared the results from claims-based data to those from clinical review. They found that for the overall index, the agreement between the two sources of data was fair (k statistics 0.21-0.40), and there was generally modest agreement between the two data sources for most individual conditions (k statistics 0.41-0.60). They did not assess the predictive ability of the claims-based index in this paper. The advantage of this approach is that it allows an estimation of severity within a specific condition category, however the key disadvantage relates to the simplifying assumptions in terms of overall comorbidity categorisation of individuals. This may be more important for the claims-based version, because it may be more difficult to accurately categorise the severity of disease, or to differentiate between comorbid disease and complications of the disease or its

treatment (which is a focus of the ACE-27 approach) (Piccirillo, Lacy et al. 2002; Piccirillo, Tierney et al. 2004). For these reasons, this approach, whilst interesting, was not pursued.

**Counts of conditions** have been used successfully by a number of authors, and this approach is not necessarily simple (or simplistic). For example, the Multipurpose Australian Comorbidity Scoring System (MACSS) included 102 separate conditions and included a hierarchical approach so that additional terms were added for each ICD-9 chapter as well as each individual condition (Holman, Preen et al. 2005). Tammemagi et al used individual conditions and counts of comorbidity in their work to ascertain interacting influences of different comorbid conditions, treatment and outcomes (Tammemagi, Neslund-Dudas et al. 2003; Tammemagi, Nerenz et al. 2005). The inclusion of individual conditions in a model (such as in the MACSS approach) may allow good adjustment for confounding or mediation through comorbidity (discussed more below) but it does not allow for an estimation of the level or overall distribution of comorbidity within or between populations, nor does it allow an estimation of the effect of comorbidity itself on outcomes. Comorbidity counts require the simplifying assumption that all conditions have an equal impact on outcomes. Whilst this assumption is clearly not met, in reality it may not have a substantial impact on the functioning of an index; the inclusion of a given condition is more important than any weight assigned to it especially when there is a large number of conditions (Streiner and Norman 2008).

**Weighted indices** have been used in the context of cancer by many authors. Whilst the Charlson index was conceptualised as a general index of comorbidity, most others have been developed for one (or a couple of) specific cancer sites (Charlson, Pompei et al. 1987; Fleming, Rastogi et al. 1999; Piccirillo, Lacy et al. 2002; Fleming, Pearce et al. 2003; Colinet, Jacot et al. 2005; Klabunde, Legler et al. 2007; van Walraven, Austin et al. 2009). The advantages of weighted indices are that they can be easily used with administrative data and they take account both of the number and the severity of individual conditions. For these reasons, this was the approach that was taken here. However, there are still simplifying assumptions, the most notable being that the impact of multiple conditions is reflected in the sum of weights each of which relates to the impact of the condition on a particular outcome. Clearly this is unlikely to be true in reality. For example, Gross et al (2006) found the effects of combinations of comorbidities on survival among colon cancer patients were complex and difficult to predict (Gross, Guo et al. 2006). Diabetes, CHF and chronic respiratory disease all exerted strong independent effects on survival. Patients with both CHF and diabetes

had considerably worse survival than those with either condition individually; whereas those with chronic respiratory disease had similar survival rates whether or not they also had diabetes.

The final point is that the reduction of data on (potentially) multiple comorbid conditions to a single metric inevitably results in loss of data for any approach that seeks to do this. For this reason, if optimal adjustment for comorbidity (as a confounder or a mediator) is required and there is both a sufficiently large sample size, and data available on individual conditions, then consideration should be given to including each condition in the model separately (Sarfati, Hill et al. 2009).

# **Strengths and weaknesses of the specific methods used in developing the weighted indices (C3, PBCI and simplified indices)**

## **Identification of conditions**

The first issue to consider in relation to whether the process of identification of conditions was appropriate is to consider what an index is (and what it isn't). More specifically, one must consider what role each comorbid condition plays in the construction of a comorbidity index. An index is a summary of a set of factors that have a common effect, but do not necessarily have a common cause (Devellis 2012). There is an assumed correlation with the common cause but no assumption of correlation between items. That is, presence of any of the comorbid conditions results in an increase in the underlying construct of 'comorbidity', but the converse is not necessarily true (for example, if an individual has diabetes, then by definition they have some level of 'comorbidity', however an individual may have a high level of comorbidity, and yet not have diabetes at all). In contrast, a measurement 'scale' consists of items whose values have a common cause, creating, by definition, correlations between them (Devellis 2012). For example, a scale used to measure depression might include items relating to feeling unhappy, change in appetite, change in sleep patterns, feelings of isolation etc. Each of these is likely to be caused by the underlying construct of 'being depressed', and so there is likely to be relationships between them. This is an important distinction because the process through which items are best identified is quite different for an index compared with a scale. In order to optimise the items for inclusion in a scale, they are usually evaluated within a development cohort, and only those items that add meaningful information are included. Often parsimonious choices relating to which items should be retained will be made after analytical approaches such as factor analysis or principle components analysis, which identify items or sets of items that most strongly correlate with the underlying construct of interest (Devellis 2012).

In contrast, for indices where there is no reason to assume that there are correlations between items, it is not appropriate to use statistics based on homogeneity such as factor analysis and principal components analysis (Streiner and Norman 2008). In this situation, it is important to be inclusive of conditions rather than to try and reduce them as is the case in a measurement scale (Streiner and Norman 2008; Devellis 2012). Three approaches to identifying items to be included in an index are possible: 1) based on the theoretical underpinnings of the construct; 2) based on previous research and 3) based on expert opinion (Streiner and Norman 2008). All three of these approaches were used in the identification of conditions included in the C3 and PBCI indices. There were extensive iterative processes that involved reviewing the conditions that have been included in previous indices, reviewing ICD-10 codes or pharmaceutical codes and consultation with cancer clinicians to identify those conditions that they thought would have an impact on the quality or quantity of cancer patients' lives. This process was a strength of this work relative to other work which has tended to focus improvements on reweighting conditions included in the Charlson index rather than considering whether the appropriate conditions have been included (Klabunde, Legler et al. 2007; Quan, Li et al. 2011) .

Despite the effort that went in to identifying all important conditions, there is no doubt that not all such conditions will have been identified either in the C3 indices or the PBCI. First, some conditions will not have been identified because of missing data or errors in coding. This issue of data quality has been discussed above. Second, some conditions were excluded because of very low prevalence meaning that it was difficult to calculate a weight for them. Whilst each individual rare condition is, by definition, uncommon, the cumulative effect of many (missing) rare conditions might be quite large. Third, arguably it would have been useful to subdivide conditions according to severity as Fleming et al did when they converted the ACE-27 approach into a claims-based approach (Fleming, Sabatino et al. 2011). In other words, the binary variables included in the index are not necessarily truly binary in the underlying construct that they represent (Streiner and Norman 2008). This was not attempted largely because of the desire to balance accuracy of the indices with pragmatism, as well as a lack of evaluation of the usefulness of this approach. While not all conditions are likely to have been identified, because of the process above, it may be reasonable to assume that most 'important' conditions have been. Furthermore, when the full indices were compared with the simplified indices (and Charlson) both of which included considerably fewer conditions, the impact on the validity was measureable, but not

large. Thus lack of identification of conditions is unlikely to be a major source of error in this study.

## **Strengths and weakness of weights and weighting procedures**

Weights were applied to each condition with weights empirically based on the (age and stage adjusted) impact of conditions on non-cancer mortality. This approach means that conditions with a stronger association with non-cancer death, and therefore by implication a greater impact on the underlying construct of comorbidity, were given greater weight than those with weaker associations. This empirical approach is a strength of this work. However, there are two levels of error to consider in relation to the weights. The first relates to the validity of a specific weight assigned to a particular condition. This depends on whether it was reasonable to use Cox regression models, whether adjustment was done appropriately and whether non-cancer death was a reasonable outcome. The second level of error to consider is whether the way the weights were combined was reasonable. I will consider each of these below.

## **Use of Cox regression models**

Cox regression models are commonly used to assess survival (or more accurately mortality hazards) among patients with cancer. One of the key assumptions underlying the Cox proportional hazards approach is proportionality of the covariates. In other words, it is assumed that the ratio of the hazards in two (or more) categories of a covariate are proportional over time (Therneau and Grambsch 2000; Kirkwood and Sterne 2003). This assumption was examined graphically and by checking for interactions between each variable in the age and stage adjusted models with log(survival time) (Therneau and Grambsch 2000). In the few instances where the proportionality criterion was not met, the impact was assessed using stratified Cox regression models. In all cases, the impact was negligible.

Cox regression models are also based on the assumption of independence of causes of death. In other words, it is assumed (in this case) that those who died from cancer would have had the same risk of non-cancer death had they not died (from cancer). If, for example, people with comorbidity are more likely to die both from cancer and from

non-cancer causes, then censoring them after their cancer death will introduce bias to the estimates of the association between comorbidity and mortality by underestimating the hazards of non-cancer death among those with comorbidity (Satagopan, Ben-Porat et al. 2004; Andersen, Geskus et al. 2012). This bias is particularly important when the competing cause (in this case, cancer death) is common, so will be particularly important for highly aggressive cancers (Kendal 2008). For this reason, in studies investigating cause-specific survival, approaches that use competing causes analysis are being increasingly used (Fine and Gray 1999; Du, Fox et al. 2008; Kendal 2008; Rose, Jeong et al. 2011; Kutikov, Egleston et al. 2012; Cho, Mariotto et al. 2013; Dasgupta, Youlden et al. 2013). This approach uses cumulative probability functions of the hazards of all competing events, and models the covariate effects directly on them (Fine and Gray 1999). In other words, it takes account of the impact of covariates on both cancer and non-cancer death, reducing the bias from competing causes. However, where the two methods have been compared, even where the magnitude of this bias has been more substantial, the relative impacts across categories of covariates (including comorbidities) are similar (Dasgupta, Youlden et al. 2013). This means the relative weighting of conditions are not greatly impacted. For example, using a 'usual' Cox regression approach Dasgupta et al (2013) found that patients with colorectal cancer and diabetes had a 16% cumulative probability of death (13.8-18.5) after five years, compared with 6.3% (5.8-6.7) for those without diabetes (Dasgupta, Youlden et al. 2013). The equivalent estimates using competing risk analysis were 12.4% (10.6-14.3) for those with diabetes and 5.0% (4.6-5.4) for those without. The relative impact for those with and without diabetes for both approaches was therefore 2.5 (and for all comorbidities combined, the relative impact for those with and without comorbidity on 5-year non-cancer mortality was 3.3 for Cox regression and 3.0 for competing risk analysis) (Dasgupta, Youlden et al. 2013). This, then, is unlikely to be a major source of bias in the analyses presented here.

## **Misclassification of variables**

Additional sources of bias relate to misclassification of the exposures (individual conditions), outcome (non-cancer mortality) or confounders (most importantly stage). These issues have been largely addressed above. One remaining issue is whether age should have been treated as a continuous or categorical variable in the Cox regression models. In the results presented here, age was categorised, which may result in residual confounding given the relative coarseness of the age groups

(compared with age as a continuous variable). The reason for this was that the relationship between both age and comorbidity, and age and mortality was not linear (with little association at younger ages, but almost exponential at older ages). To check that residual confounding was not a major issue, the models were also run treating age as a continuous variable, and the results were found to be almost identical.

## **Choice of outcome variable**

Non-cancer mortality was used as an outcome because both cancer-specific and all-cause mortality are largely driven by cancer-related factors, particularly stage of disease, and therefore are less affected by comorbidity. Furthermore, other authors have used non-cancer mortality as their primary outcome in the development of comorbidity indices (Charlson, Pompei et al. 1987; Malenka, McLerran et al. 1994; Klabunde, Legler et al. 2007; Cho, Mariotto et al. 2013). However, relatively few patients died of non-cancer causes in our cohorts which meant that the calculated weights may be somewhat imprecise, and that weights for some conditions needed to be 'imputed' in some site specific indices.

## **Impact of multiple conditions**

Those with comorbidity often have more than one additional condition (Byles, D'Este et al. 2005; Valderas, Starfield et al. 2007; Britt, Harrison et al. 2008; Tooth, Hockey et al. 2008; Sarfati, Hill et al. 2010). In fact, Britt et al found that in Australia among those over 60 years, multimorbidity was more common than any single condition (Britt, Harrison et al. 2008). The effects of two or more conditions that coexist are unpredictable (Fleming, Pearce et al. 2003; Gross, Guo et al. 2006). However, it is unlikely to be feasible to add every possible combination of conditions in models assessing the impact of comorbidity. For example, if there are 20 conditions, then there will be 380 ( $[20 \times (20-1)]/2$ ) possible two condition pairs, and 1140 ( $[20 \times (20-1)(20-2)]/[3 \times 2]$ ) possible three condition pairs. Most measures of comorbidity ignore this issue altogether, although a few have attempted to address it. For example, Fleming et al (2003) developed a comorbidity index for men with prostate cancer that included 27 comorbidity categories. They calculated five sets of weights all derived from Cox regression models of all-cause mortality, but varying in the extent to which they included all conditions, and two-way, three-way and four-way interactions (with

prevalence of >3%). They found that hazard ratios for individual conditions were reasonably stable across models. They found that the best fitting model was one that included all possible two-way interactions, but the difference between the models was not great. They also found that using an index that took account of the number of diagnoses that an individual had within a particular comorbidity category was slightly better at distinguishing those with comorbidity, but again differences were not great.

This issue was explored here to assess whether or not the impact of other conditions on the weights calculated for each condition would have an impact on the performance of the C3 indices (see Appendix 4 for detail). The findings suggested that, for colorectal cancer at least, attempting to account for interactions with other conditions made almost no difference to the functioning of the index. For this reason, the more simple approach to weighting conditions was used.

## **Impact of error in estimation of weights**

There are both good theoretical reasons and empirical evidence to suggest that the specific weighting given to conditions is relatively unimportant compared with the inclusion of all relevant conditions within an index (Baldwin, Klabunde et al. 2006; Klabunde, Legler et al. 2007; Streiner and Norman 2008). For example, Klabunde et al. found that their NCI indices performed better than Charlson, but acknowledged that they had excluded a number of conditions in their calculation of Charlson which were included in the NCI indices (Klabunde, Legler et al. 2007). They noted that a simple count of the NCI conditions performed nearly as well as the weighted index. Similarly, Baldwin et al. found that unweighted and weighted indices had similar predictive ability in a cohort of patients with colorectal cancer (Baldwin, Klabunde et al. 2006). I also tested other weighting approaches (including parameter estimates from models using all-cause mortality as outcome, and hazard ratios rather than parameter estimates). The results were similar regardless of the weights used. For these reasons, it seems reasonable to assume that even if there was bias in the estimates of non-cancer mortality for individual conditions, it would be unlikely to result in major error in relation to the indices themselves.

## Combining weights into an index

The weights were simply added together to create an index. This assumes that each condition has an impact that is independent of all others, and that there are no interactions between them. The reality is likely to be considerably more complex than this, of course. A perfect comorbidity index would take account of the way that specific combinations of conditions impact outcomes. However, for the reasons discussed above, this would add considerably to the complexity of the index, and may not have a substantial impact on the validity of it.

## Strengths and weaknesses of the validation approaches used

An assessment of the validity of the indices developed in this thesis is provided in the next chapter. Here, a brief discussion on the methods used to assess particularly criterion validity is provided. Criterion validity can refer either to how an index correlates with another measure taken at the same time (concurrent validity), or the extent to which the measure is able to predict future outcomes of interest (Streiner and Norman 2008). Content and face validity relate to whether an index appears to be designed appropriately for its purpose (Streiner and Norman 2008). These are qualitative assessments and are discussed in the next chapter. There are many approaches to quantitatively evaluate the validity of a new index and all seek to answer hypotheses about the extent to which we can infer something from the index, however there is no consensus about which approach(es) to measure validity is optimal (Cook 2007; Streiner and Norman 2008; Steyerberg, Vickers et al. 2010; Kerr, McClelland et al. 2012).

The methods used to assess validity of the indices presented in this thesis were:

1. **Measuring concurrent validity: Spearman's rank correlation coefficient.**

This provides an assessment of concurrent validity and measures the extent to which an index correlates with another index taken at the same time. In this case the Charlson index was used. Because the Charlson index is not, itself, a gold standard measure of comorbidity, the aim was not perfect correlation but a correlation within the range 0.4 to 0.8. The extent to which two indices correlate

with each other depends on how well each is correlated to the underlying construct of comorbidity (which is unknown), but also the extent to which any mismeasurement of that construct is correlated within the two measures (Streiner and Norman 2008). Any measures that are based on similar assumptions, data and/or methods are likely to have higher correlations than those that are not. For this reason, it is not surprising that we found higher correlations between indices that were both based on hospitalisation data (such as Charlson and the C3 indices), than indices where one was based on hospitalisation data and the other on pharmaceutical data (PBCI). However, in the results presented here, all indices correlated with the Charlson index and all but one correlation coefficient were within the 0.4-0.8 range. Assuming that the Charlson index is in fact measuring comorbidity, this provides reassurance that the indices here are all also measuring aspects of this same underlying construct. However this does not give any indication of which index is measuring comorbidity better.

2. **Measuring predictive validity: Measures of discrimination.** A good comorbidity index will accurately discriminate between those who will, and those who will not, die from non-cancer causes. Three main measures were used to assess this: the Akaike Information Criterion (AIC), concordance (c) statistics and Integrated Discrimination Indices (IDIs).
  - a. AICs provide a measure of goodness of fit of models which are not required to be nested, based on the log likelihood with a penalty for the number of variables included in the model (Hosmer and Lemeshow 2000). A lower number indicates better fit. It is closely related to the  $-2\log$  likelihood ratio which does not include a penalty for additional variables in a model and to the Bayesian Information Criterion (BIC) which includes a somewhat greater penalty than the AIC, but is otherwise very similar (Hosmer and Lemeshow 2000; Cook 2007). Arguably any (or all) of these measures could have been used in this thesis. In fact all were calculated and demonstrated very similar patterns to the AICs provided here.
  - b. A c-statistic provides a rank correlation measure of goodness of fit. It is determined by taking all possible pairs of individuals, one who died and one who did not, and calculating the proportion of these pairs in which a given model calculates a higher predicted probability of death to the one who died (Hosmer and Lemeshow 2000; Pencina, D'Agostino et al.

2008; Steyerberg 2009). The higher the c-statistic, the better the ability of the model to discriminate between those who died and those who did not. These measures are useful and are very commonly used in this context (Cook 2007; Steyerberg, Vickers et al. 2010). The main problem with their use in the context of comorbidity and cancer, is that for all-cause, cancer-specific and even non-cancer death, models that include age and stage of disease are good at discriminating those with from those without the outcome. For this reason, there is not much 'room' to improve the discriminatory ability of models even with a very good measure of comorbidity. Some authors argue that in circumstances where a baseline model has good discriminatory ability, even a new measure with a very strong association with the outcome of interest is unlikely to result in much of a shift in the c-statistic (Pencina, D'Agostino et al. 2008; Ware and Cai 2008). Indeed, the results presented here show modest changes in c-statistics only.

- c. IDIs were developed, in part, in response to the concerns raised above (Cook 2007; Pencina, D'Agostino et al. 2008; Steyerberg, Vickers et al. 2010). IDIs are related to net classification improvement, with both assessing the extent to which those who die shift to a higher prediction (or predicted category) of risk, compared to the extent to which those who do not die shift downwards. Net classification improvement requires meaningful risk categories to be pre-specified and the performance of this measure depends on the choice of categories (Cook 2007; Kerr, McClelland et al. 2012). Therefore IDIs may be useful in the situation where no clearly defined meaningful risk categories exist (Pencina, D'Agostino et al. 2008; Kerr, McClelland et al. 2012). The IDI is equivalent to an integrated difference in Youden's index which is often used in the assessment of diagnostic tests (Chi and Zhou 2008). Like the Youden's index, the IDI places equal weight on sensitivity (the ability of the model to accurately predict those with the outcome) and specificity (the ability to accurately predict those without the outcome) (Chi and Zhou 2008). This may, of course, be a weakness if the implications of a low sensitivity are more or less severe than those for a low specificity. Cook (2007) makes the point that differences in mean predicted probabilities are unlikely to be large, so IDIs will consequently tend to be small, and possibly difficult to interpret

(Cook 2008). In the results presented here, the differences between IDIs were indeed very small, and not always consistent with the other measures of predictive validity, so our experience would be consistent with this concern. Furthermore, if a difference exists, it is not possible to distinguish whether the difference is due to a smaller number of large shifts in predicted probabilities, or a larger number of small ones (Pepe, Feng et al. 2008). The p-values calculated by the method provided by Pencina et al (2008) have been shown to be underestimated (Pepe, Feng et al. 2008; Kerr, McClelland et al. 2012). For this reason, a lower threshold of 0.025 was used to define statistical significance. However, this is a reasonably arbitrary cut-off based on findings of a modelling exercise by Kerr et al which showed that the standard errors tended to be underestimated by a factor of about 2 (on average) (Kerr, McClelland et al. 2012). Bootstrapping is also not recommended when IDIs are close to zero because the estimated confidence intervals are likely to be biased positively away from the null (Kerr, McClelland et al. 2012).

## **Summary of strengths and weaknesses**

The main strengths of the data sources were that they were population-based, which meant that all (or nearly all) patients diagnosed with the specified cancers in New Zealand over the period of the study were included. More than one source of comorbidity data was used, and administrative data were validated against clinical notes data. These data are relatively easily accessible and applicable to large populations. The key weaknesses are those inherent in administrative data generally; data may be incomplete or missing, there may be coding inaccuracies, and these databases can be somewhat unwieldy to manage. The strengths of the index development work were that there was an extensive process to ensure the most important and relevant conditions were included, indices based on different data sources were developed, and a range of alternative indices using different condition inclusion and weighting procedures were developed and compared against each other and external measures. The weaknesses related to the necessary reduction of data inherent in the process of index development, the fact that not all conditions were

included and that while the weighting procedures were reasonably robust, the weights were based on some simplifying assumptions and were in some cases imprecise. Reassuringly for both empirical and theoretical reasons, these issues are unlikely to have substantially impacted the performance of the indices. The strengths of the validation work were that several measures were used to assess and compare the validity of the various indices produced in this thesis. Whilst none of these tests are perfect, they all provide useful information, and in combination are likely to address, to the extent possible, important aspects of construct validity. Whilst other measures of validity are also possible, a balance between being inclusive of all possible measures and a thorough but parsimonious assessment of multiple indices was required. A second important strength of this work is that the validation and comparison of indices was performed on separate data to those in which the indices were developed (Steyerberg 2009).



# Chapter 8. Discussion:

## Interpretation and implications of results

*Measurement is the first step that leads to control and eventually to improvement. If you can't measure something, you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it. ~H. James Harrington*

### Summary of key findings

The key findings from this study are as follows:

- Both administrative hospitalisation and pharmaceutical data in New Zealand can be used to measure comorbidity in the context of cancer.
- Comorbidity is common among people diagnosed with cancer, and tends to be associated with poorer survival.
- Site-specific comorbidity indices developed for a range of cancer sites using administrative hospitalisation data were demonstrated to be valid. The same index without site-specific weights, but weights taken from all the sites combined resulted in an almost identical level of discrimination as the site-specific indices, suggesting that site-specific indices may be unnecessary.
- A pharmaceutical data-based index was also found to be valid in this context. Its ability to discriminate between those who died, and those who did not tended to be less than the new hospitalisation-based indices for colorectal, upper GI and urological cancers. For gynaecological and breast cancers the PBCI tended to outperform the hospitalisation-based indices for non-cancer mortality.
- Simple indices that included fewer conditions (20 or less) including Charlson, PBCI and two abbreviated versions of the C3 indices tended to perform adequately in many situations. For all-sites combined, colorectal and upper GI cancers, the C3-derived simplified indices outperformed the Charlson index, while PBCI outperformed the others for breast and gynaecological cancers for non-cancer mortality. For urological cancers, the Charlson and the C3-derived simplified indices performed similarly.

This chapter provides a discussion of these key findings, makes recommendations about how comorbidity should be measured in the contexts explored within this thesis, and considers the extent to which the findings can be generalised. It finishes with a concluding statement and a summary of recommendations.

## **Prevalence and impact of comorbidity among cancer populations**

### **Patterns of comorbidity**

This investigation has demonstrated that comorbidity is common among people diagnosed with cancer. The general pattern of our findings are consistent with other studies, with hypertension, cardiovascular disease, other cancers, respiratory disease and diabetes consistently being among the most common co-existent conditions among cancer patients regardless of whether they were measured using hospitalisation or pharmaceutical data (Yancik, Havlik et al. 1996; Coebergh, Janssen-Heijnen et al. 1998; Coebergh, Janssen-Heijnen et al. 1999; Janssen-Heijnen, Houterman et al. 2005; Klabunde, Legler et al. 2007; Piccirillo, Vlahiotis et al. 2008; Zeber, Copeland et al. 2008). Other studies have also confirmed the high levels of comorbidity among those with urological, liver, stomach and colorectal cancers demonstrated here (Coebergh, Janssen-Heijnen et al. 1999; Ogle, Swanson et al. 2000; Piccirillo, Tierney et al. 2004; Janssen-Heijnen, Houterman et al. 2005). Many factors that increase the risk of these cancers such as smoking, alcohol, poor diet, and obesity also increase the risk of other serious chronic disease (Silva 1999; Wolin, Dart et al. 2013). In contrast, there were lower levels of comorbidity among those with breast cancer which was only partially explained by age and sex differences. This finding is consistent with recent findings from Cho et al (2013), who found that women with breast cancer had better non-cancer survival than similar women without breast cancer, particularly those with early stage disease. There are a number of potential reasons for this, including the possibility that women with breast cancer are more likely to have accessed screening, and therefore may have better access to health care in general; breast cancer is more

common among women in higher socioeconomic groups who tend to have lower levels of comorbidity; and some of the hormonal risk factors for breast cancer may be protective against cardiovascular disease in particular (Cho, Mariotto et al. 2013).

There is marked variation in prevalence estimates of particular conditions in cancer populations presented in the literature. For example, estimates of diabetes prevalence among colorectal cancer patients range between 6 and 18%, of congestive heart failure (CHF) between 4 and 19% and of chronic respiratory disease between 5 and 22% (Ogle, Swanson et al. 2000; Janssen-Heijnen, Houterman et al. 2005; Gross, Guo et al. 2006; Klabunde, Legler et al. 2007; Piccirillo, Vlahiotis et al. 2008; Sarfati, Hill et al. 2009). The estimates presented here were within these ranges (for hospitalisation and pharmaceutical data respectively: 10.3% and 9.8% for diabetes, 5.2% and 11.9% for CHF, and 6.1% and 15.0% for chronic respiratory disease). These variations are a function of the study populations (for example several studies focus only on older patients among whom comorbidity will be more common (Janssen-Heijnen, Houterman et al. 2005; Gross, Guo et al. 2006; Klabunde, Legler et al. 2007)), the data collected (studies using notes review data often report higher levels of comorbidity than those using administrative data (Kieszak, Flanders et al. 1999)), and the definitions used for specific comorbid conditions. For example, unlike previous studies, we excluded all ICD-10 codes pertaining to 'diseases classified elsewhere', in order to avoid double-counting of comorbid conditions.

Some 'conditions' identified using pharmaceutical data are more accurately considered risk factors for future ill health, rather than chronic diseases in their own right. Lipid lowering and antiplatelet medications, for example, are largely prescribed to reduce the risk of future cardiovascular disease (Mangin, Sweeney et al. 2007). Hypertension and diabetes without complications can also be thought of as 'conditions as risk factors', and were identified in both data sources. Not surprisingly, all these conditions tended not to be associated with adverse impacts on survival, with the exception of hypertension identified in hospitalisation data. Furthermore, the apparent relatively positive effect of uncomplicated diabetes on survival may in part reflect the use of metformin, a medication used to treat type II diabetes, that has been found to inhibit cancer growth (Evans, Donnelly et al. 2005; Libby, Donnelly et al. 2009; Landman, Kleefstra et al. 2010)

This investigation has demonstrated that different patterns of comorbidity exist for different cancer sites, and such differences tend to be related to the co-existence of risk factors for specific conditions and certain cancers. An example of this is the much higher levels of diabetes and obesity among those with uterine and liver cancer compared with other cancer sites. Diabetes and obesity are known risk factors for these two cancers and these findings are consistent with other studies that have investigated this (Coebergh, Janssen-Heijnen et al. 1999; Janssen-Heijnen, Houterman et al. 2005). For example Janssen-Heijnen et al (2005) found in their study from the Eindhoven Cancer Registry in the Netherlands, that 22% of women aged 65-79 years with uterine cancer had been diagnosed with diabetes compared with 12-13% of women in this age group with ovarian or breast cancers (Janssen-Heijnen, Houterman et al. 2005). There is also a very high prevalence of chronic viral hepatitis infection among those with liver cancer (44.1%), consistent with its causal association with hepatocellular carcinoma.

## **Impact of comorbidity on survival**

Like many other studies, this investigation confirms that the presence of comorbidity adversely affects survival outcomes. The impact of comorbidity is, in general, greater for total or non-cancer survival than cancer specific survival, but is demonstrable for all measures of survival (Albertsen, Fryback et al. 1996; Sarfati, Hill et al. 2009). In general, conditions that are known to be serious and have a substantial impact on mortality were found to indeed have a major impact on all-cause and non-cancer survival. For example, congestive heart failure, dementia and other neurological conditions all had substantial negative impacts on outcomes across all sites. However, there were a few conditions that had perhaps less intuitively obvious impacts. In particular, sleep disorders and epilepsy were strongly associated with high all-cause and non-cancer mortality. In cancer patients, the most common sleep disorders are excessive fatigue and leg restlessness which are both associated with aggressive and/or advanced disease and poor outcomes (Davidson, MacLean et al. 2002). Sleep disorders are known to be associated with other serious conditions such as severe lung disease, renal disease and obesity, all of which are likely to have an adverse impact on survival (Palesh, Roscoe et al. 2010; Irwin, Olmstead et al. 2013). Because of relatively small numbers of non-cancer deaths, it was not possible to adjust each condition for the impact of all other conditions. This means that the impact of some

conditions might be mediated by the impact of others; sleep disorders may be a good example of this. Finally, sleep disorders themselves have been shown to be associated with higher all-cause mortality even among people with no serious comorbidity (Dew, Hoch et al. 2003). Similarly, epileptic seizures can be associated with brain metastases from (sometimes as yet undiagnosed) cancer, and from other serious medical conditions including neurological conditions, stroke and conditions causing major metabolic abnormalities (Weller, Stupp et al. 2012). While epileptic seizures are not, strictly speaking, epilepsy, they are likely to be identified as such in the ICD-10 coding algorithms used here.

## **Interpretation of the index results:**

### **Content and face validity**

All three sets of indices (C3, PBCI and simplified indices) were designed specifically to measure the impact of comorbidity among patients with cancer. As such they are likely to have a relatively high level of content and face validity in this context. In all three cases the process of selecting conditions was based both on empirical analysis and expert input, however there were differences. For the C3 site-specific indices all or nearly all important conditions were likely to have been included. In contrast, there were many conditions not included in the PBCI that were included in the C3 indices because these conditions are often not treated pharmaceutically. These included major diseases such as renal, liver, cerebrovascular, neurological and cardiac valve disease. This may reduce the content validity of the PBCI to some extent relative to the C3 indices. For two of the three simplified indices (SI2 and SI3), the number of conditions included was reduced to those that had a prevalence of 2% and an association with non-cancer mortality (hazard ratio greater than 1.2). This may also have an impact on content validity because, particularly in combination, the excluded conditions may have an impact on cancer treatment and outcomes. However, the 19 conditions that were included in these indices are likely to be those that have the greatest impact in the cancer context, and therefore the content and face validity, given their simplicity, is likely to remain reasonable.

The likely different impact between conditions in all indices was accounted for by weighting according to their individual associations with non-cancer death. For the C3

indices, both the conditions included and the weighting of conditions were allowed to vary between sites. For the other indices, standard weights were used across sites, consistent with the assumption that the impact of conditions on non-cancer death is reasonably consistent regardless of the primary disease. Whilst this is not always true, in many instances the relative impact of conditions was found to be at least reasonably consistent between sites. Furthermore, empirical analysis of indices based on site-specific compared with all-site weights showed that there was little difference in their performance. The most simplified index (SI3) used a more basic approach to weighting where each weight was divided by the smallest parameter estimate and rounded to the nearest whole number. The advantages of this are that it is generally simpler, and the weights become interpretable in their own right. A weight of two implies that a condition has approximately double the impact on non-cancer death than a condition with a weight of one, and half that of a condition with a weight of four (van Walraven, Austin et al. 2009). However this simplification may have a theoretical impact on content validity. In reality the performance of simplified indices 2 (where original weights were retained) and 3 is almost identical, so this theoretical concern is unlikely to be important. A measure of the severity *within* a particular comorbid condition category was not included in any of the indices, with the exception of diabetes where there were two categories (diabetes with and without complications).

As discussed in the last chapter, indices were constructed by adding together the weights for all conditions recorded for each individual. This means that those with either (or both) more comorbid conditions or more severe conditions were likely to have higher scores than those without. This seems a reasonable assumption. However, this approach does require a simplification of reality in that it assumes that the impact of multiple conditions can be captured by adding together their parameter estimates (equivalent to multiplying their hazard ratios). The reality is likely to be considerably more complex, given probable interactions between conditions. However, the performance of indices that included interaction effects between conditions was almost identical to those that did not (see Appendix 4), so this simplification seems reasonable and probably without a great threat to content and face validity of the indices.

## Concurrent criterion validity

We found that all the correlation coefficients between all indices and the Charlson index were between 0.40 and 0.80, with the exception of the PBCI in the gynaecological cancers cohort, for which the correlation coefficient was 0.37. As discussed previously, this is within the desired range and consistent with the indices having concurrent validity. As expected, the correlations between the PBCI and the Charlson index were generally lower, consistent with the fact that their derivations are more different than the other comparisons made. This has (at least) two possible, and not mutually exclusive, interpretations: 1) assuming the Charlson index is a good measure of comorbidity, the PBCI is a less accurate measure of the underlying construct than the other indices, and/or 2) both indices are mismeasuring the underlying construct, and it is possible that each are measuring somewhat different aspects of it. In the latter case, it is not possible to conclude which index is better or worse in this context.

## Predictive criterion validity

When the C3 and PBC indices are categorised it is clear that higher scores are generally related to higher risk of all-cause, cancer-specific and non-cancer mortality. For example, for the C3 indices, compared to those with a score of 0 or below, those with a score greater than 2 had hazard ratios ranging from 1.4-2.3 for all-cause mortality, 1.3-1.5 for cancer-specific mortality and 4.2-5.8 for non-cancer mortality across the five site groups. The results were similar for those with a PBCI score of 2 or more compared to those with the lowest score (Appendix 5).

The exact results will, of course, depend how the indices are categorised, but the critical issue in relation to predicative validity is not so much whether an index has predictive validity per se, but whether the new indices are better in terms of their predictive abilities compared with the existing ones. When all sites were combined, the gold standard approach to measuring comorbidity outperformed all other approaches in terms of its ability to discriminate between those who died particularly from non-cancer death with higher c-statistics and lower AIC, albeit that the IDIs were not significantly different. Furthermore, the site-specific C3 indices, all three simplified indices and PBCI clearly outperformed Charlson again with higher c-statistics and lower AICs for non-cancer death. All comorbidity indices resulted in a significant improvement in IDIs

in relation to predicting non-cancer death compared with no comorbidity measure, but there were no significant differences between any of the new measures and the Charlson index or between the gold standard approach and the simplified indices using this measure. There was a similar pattern seen within the colorectal and upper GI cancer cohorts with the C3 and simplified indices tending to outperform Charlson in discriminating those who did and did not die from non-cancer death, including significantly improved IDIs for all three simplified indices relative to the Charlson index for colorectal cancer. The differences were less clear for the other cancers, but the C3 and simplified indices performed as well as Charlson in all cases and sometimes better. The performance of PBCI was also generally at least as good as the Charlson index. It performed better than any other index in discriminating between those who died of non-cancer caused among women with breast or gynaecological cancers.

These results taken together clearly support the predictive validity of the C3, PBCI and simplified indices for the cancers included in this study. The implications of these results show that the C3, PBCI and simplified indices are all valid choices for measuring comorbidity in the context of cancer. They all tended to perform as well as the Charlson index, and in many cases better. That said, the differences between the indices were not large in most cases so the most valid conclusion is that the fact of choosing a measure of comorbidity is considerably more important than the specific measure chosen.

## Reliability

Reliability is defined as is "*the extent to which repeated measurements of a stable phenomenon-by different people at different times and places get similar results*" (Hall 2006). All the indices were designed to be used with administrative data, either hospitalisation or pharmaceutical. This means that for a given population with comorbidity defined over a specified period, and assuming correct data access, data management and coding practices, the measurement of comorbidity should be the same for a given individual with a given index regardless of who is measuring it or when the measurement is done. In other words, the reliability of these measures should be close to 100%. These data are relatively quick and easy to access and easily available at population level. However, to reiterate, there are many inherent weaknesses with administrative data. For this reason, while the reliability of these

indices in terms of its definition above may be close to perfect, this is not the same as saying that the indices are reliably correct.

## **Feasibility**

Because the indices are based on administrative data, they are relatively straightforward to implement and use even with very large population-based samples. However, specialist data management skills are required, and should not be underestimated. The site-specific C3 indices require a separate set of conditions and weights for each cancer site, adding to their complexity (but arguably increasing their face validity). In contrast, the simplified indices are more straightforward to implement, particularly simplified indices 2 and 3 that only include 19 conditions.

## **Implications of (mis)measuring comorbidity**

*“Given the complexity and heterogeneity involved in comorbidity, however, no single definition or measure would serve all research or clinical purposes. Rather, definition and measurement of comorbidity approaches may vary depending on practice or research objectives (e.g. clinical, epidemiological, health service) and outcomes of interest (i.e. patient physical function, public health needs, mortality).” (Yancik 2007).*

Earlier chapters in this thesis have discussed why comorbidity is an important factor to consider in epidemiological studies. In an ideal world, we would be able to perfectly measure the underlying construct of ‘comorbidity’ for every individual in a study. However, because of the complexities of comorbidity we are only ever going to be able to estimate a measure of this concept. In other words, there will always be some mismeasurement of comorbidity. The effect of mismeasurement will tend to depend on how the variable is operationalised, particularly whether or not it is a continuous variable or categorised into a dichotomous or multichotomous variable. The effect will also depend on whether any mismeasurement is differential or non-differential; and dependent or non-dependent.

Differential misclassification error refers to that which '*depends on the actual values of other variables*' (Rothman, Greenland et al. 2008). Differential misclassification bias might occur when, for example, more comorbidity data are available for those who have had poorer outcomes, simply because they have tended to have been admitted to hospital more frequently where data on comorbidity are collected. These patients are then more likely to have comorbidity identified and recorded than those with better outcomes, even if the background levels of comorbidity are the same. This may result in an erroneous strengthening of the association between poor outcomes and higher levels of comorbidity.

Dependent misclassification error is that which *depends on the errors in measuring or classifying other variables* (Rothman, Greenland et al. 2008). Dependent misclassification might be expected to occur when data on comorbidity and outcome variables are collected from the same source. For example, if data are collected from a survey, some individuals may be more (or less) likely to report poor health, regardless of the objective reality. This creates a correlation between self-reported comorbidity and self-reported poor health outcomes potentially resulting in an erroneous strengthening of the association between high levels of comorbidity and poor outcomes.

This section considers the impact of measurement error in comorbidity and the impact that might have depending on what variable axis comorbidity is on.

By way of background, if comorbidity is dichotomised (for example, differentiating those who have comorbidity from those who have not), we can calculate a number of useful measures depending on the actual compared with the measured exposure status of an individual (Steyerberg 2009). These measures are most easily represented using a two-by-two table. Some of these terms will be used in the discussion below.

	Truly exposed	Truly unexposed
Measured exposed	a (True positives)	b (False positives)
Measured unexposed	c (False negatives)	d (True negatives)

<b>Sensitivity</b>	The proportion of those truly exposed who are measured as exposed. $a/a+c$
<b>Specificity</b>	The proportion of those truly unexposed who are measured as unexposed. $d/b+d$
<b>Positive predictive value</b>	The proportion of those measured as exposed who are truly exposed. $a/a+b$
<b>Negative predictive value</b>	The proportion of those measured as unexposed who are truly unexposed. $d/c+d$

## Comorbidity as an exposure variable

There are many examples of research questions where comorbidity is treated as an exposure (or independent) variable; what is the effect of comorbidity on cancer survival? Does comorbidity affect the receipt of definitive treatment? Is comorbidity associated with longer length of stay?

The effect of measurement error when comorbidity is considered an independent, explanatory variable in an analysis depends on whether it is categorised as a dichotomous or as a multichotomous or continuous variable. Misclassification of a dichotomous independent variable results in a shift of the effect estimate towards the null as long as the misclassification is both non-differential and non-dependent. In this situation mismeasurement will result in underestimation of the effect of comorbidity (Lash, Mor et al. 2004; Rothman, Greenland et al. 2008). However, in most studies comorbidity is measured as a multichotomous or continuous variable. In this situation, the impact of misclassification is less predictable, even if the misclassification is both non-differential and independent. Nevertheless, in most situations, this type of error will tend to reduce the association towards the null, unless the error in the measurement of the exposure is negatively correlated with the true value (Wacholder 1995; Lash, Mor et al. 2004; Hutcheon, Chiolero et al. 2010). This is unlikely in most

situations. Furthermore, as long as the mean *measured* exposure increases with the mean *true* underlying exposure, such bias will not reverse a trend estimate for a multichotomous variable (Rothman, Greenland et al. 2008).

If misclassification of an independent variable is differential and/or dependent, the expected direction of the bias will entirely depend on the nature of the differentiability or dependence (Lash, Mor et al. 2004).

In relation to the indices presented here, this means that the index with the least measurement error will result, unsurprisingly, in the least biased estimates of associations between comorbidity and specified outcomes. If comorbidity is of substantive concern in a research project where it is being treated as the primary exposure variable, it may therefore be reasonable to consider using the index with the highest validity. Site-specific or all-sites versions of the C3 indices may be optimal in this context given their high content and face validity and generally good performance relative to the other indices; however the choice will depend on the study question (for example, what cancers are being studied). Furthermore, it is important to note that regardless of the choice made, there will always be measurement error in relation to the underlying construct of comorbidity. Also, consideration needs to be given as to how an index is treated, for example as a continuous variable, or categorised.

## **Comorbidity as an outcome variable**

There are fewer studies where comorbidity is an outcome (dependent) variable where the focus is to measure the causes or predictors of comorbidity. Again the impact of misclassification depends on whether comorbidity is categorised as a dichotomous variable or not. If it is dichotomous, and the specificity of the comorbidity measure is perfect then the ratio measure of effect will be unbiased even if the sensitivity of the comorbidity measure is not perfect, as long as any measurement error is independent (Lash, Mor et al. 2004). Put another way, as long as *only* those with comorbidity are identified as having comorbidity the ratio measure of effect will not be biased regardless of whether *all* those with comorbidity are identified as such. However, there will be bias in the absolute measures of effect. This is not the case if comorbidity is operationalised as a multichotomous or continuous variable. Lash et al suggest that the implication of this is that in order to maximise the chances of obtaining an

unbiased estimate of effect when comorbidity is the dependent variable it may be sensible to 1) treat comorbidity as a dichotomous variable, 2) set a high threshold for presence of comorbidity to ensure a high specificity, and 3) ensure there is no dependence between the exposure and outcome variables (Lash, Mor et al. 2004). If comorbidity is operationalised as an ordinal or continuous variable, the effects of misclassification are less predictable. However, in general non-differential misclassification of a continuous outcome will not change (on average) the slope of a regression line relating to that outcome, but it will increase the variance around it, and thus increase the width of confidence intervals (Hutcheon, Chiolero et al. 2010).

If the decision is made to treat comorbidity as a dichotomous variable, it probably does not matter to any large degree which index is used. In this case, it may be reasonable for practical reasons to use one of the more simple indices (e.g. SI2 or 3). The critical decision will be which cut-off to use to define 'no comorbidity' compared with 'any comorbidity'. To ensure perfect (or near perfect) specificity, it may be wise to have a cut-off somewhat above zero (albeit this will reduce the sensitivity), with the exact cut-off depending on the distribution of the scores. If comorbidity is to be treated as a continuous or ordinal variable, then, as for comorbidity as an exposure, the index with the least measurement error in the context of the study should be used.

## **Comorbidity as a confounding variable**

Comorbidity is often considered a confounder in health-related studies. If comorbidity is mismeasured, then there will be imperfect adjustment for comorbidity, and residual confounding by comorbidity is likely to exist. If the misclassification is both non-differential and independent, the adjusted estimate of effect will be biased towards the crude estimate if the confounder is a binary variable (Rothman, Greenland et al. 2008). The magnitude of this effect will depend on 1) the strength of the association between comorbidity and the exposure (independent) variable, 2) the strength of association between comorbidity and the outcome (dependent) variable and 3) the prevalence of comorbidity among those who are neither exposed nor have the outcome in question (Lash, Mor et al. 2004). If these parameters are known then the impact of misclassification of comorbidity as a confounder can be estimated. Lash et al (2004) showed that in many plausible scenarios, this effect is not large (Lash, Mor et al. 2004). For example even when the associations between comorbidity and both exposure and

outcomes are very strong (OR=8 for both), and comorbidity is assumed to be common (50%) among those without the exposure or outcome, the relative risk due to confounding does not exceed 1.6. When comorbidity is assumed to be uncommon (1%) the relative risk due to confounding becomes negligible under all plausible scenarios. As Lash et al note, the importance of this is that mismeasurement of comorbidity is more important in populations where comorbidity is common, for example, among elderly people.

If the confounding factor is a polytomous variable, the effects of misclassification are more complex. The effects vary depending on the pattern of misclassification across strata of the confounding variable and the distribution of the confounding variable among exposure groups (Rothman, Greenland et al. 2008). If error in measurement of a confounder is correlated with the true value of the variable then it is possible for the bias due to mismeasurement of a polytomous confounder to be in the opposite direction to the confounding so that the observed adjusted estimate does not lie between the crude and actual estimate of association (Brenner 1993; Wacholder 1995). While this is true, in most likely scenarios the observed adjusted estimate calculated using a mismeasured, polytomous confounding variables does lie between the crude and fully adjusted estimate (Brenner 1993; Wacholder 1995; Rothman, Greenland et al. 2008). Also of note is that if misclassification varies by strata of a confounding variable, then heterogeneity across these strata may be observed resulting in apparent effect modification, when in fact none exists (or vice versa) (Brenner 1993; Rothman, Greenland et al. 2008).

When different approaches to measuring comorbidity have been compared in terms of their ability to adjust for confounding, there tends to be little difference despite the fact that the measurement error inherent in the dissimilar approaches is likely to differ. For example, in the validation data presented here, when indices derived from administrative data were compared with those derived from manual review of clinical notes, their ability to adjust a model was very similar, despite there being moderate correlation between the indices themselves. To further investigate this, similar analyses were carried out on the data included in this study to assess the impact of ethnicity on survival from colon and rectal cancers. Cox regression models of all-cause mortality for patients with colon and rectal cancer (separately) were fitted. These were initially adjusted for age, sex, and stage of disease, then further adjusted for comorbidity using the site-specific C3 index, the PBCI and both combined (Table 39). Models including

the simplified indices were also fitted but not shown here; results were very similar to those for the C3 index alone. Māori patients with both colon and rectal cancers had somewhat worse survival than non-Māori patients after adjusting for age, sex and stage at diagnosis (HR=1.34; 1.09-1.66 and 1.21; 0.77-1.91 respectively) (Table 39). When these were additionally adjusted for comorbidity, the adjusted HR did not change appreciably in the case of colon cancer suggesting that comorbidity was not a driver of survival disparities between Māori and non-Māori in this cohort. In contrast, for rectal cancer the HR dropped from 1.21 to 1.06-1.08 after adjustment for comorbidity, suggesting that in this case comorbidity may be an important confounder (or mediator). In both cases, however, the choice of comorbidity measure made little difference in the magnitude of the adjusted hazard ratio.

**Table 39: hazard ratios of Māori compared with non-Māori cancer survival adjusted for age, sex and stage, and sequentially with different measures of comorbidity**

	Colon cancer	Rectal cancer
Age, Sex and Stage	1.34 (1.09-1.66)	1.21 (0.77-1.91)
+C3 Index	1.32 (1.06-1.63)	1.08 (0.68-1.71)
or +PBCI Index	1.29 (1.04-1.60)	1.08 (0.68-1.72)
or Gold standard (C3 + PBCI)	1.32 (1.07-1.63)	1.06 (0.66-1.68)

## Comorbidity as a mediating variable

If a research question is concerned with the extent to which an association is due to comorbidity, the comorbidity would be considered a mediating variable. An example, used above, might be the question of how much the observed association of poorer survival among Māori compared with non-Māori with colon cancer is due to differences in levels of comorbidity between those two populations (Hill, Sarfati et al. 2010). If comorbidity is mismeasured, then the proportion of the (in this case) excess hazard ratio due to comorbidity is likely to be underestimated in exactly the same way as for confounding. In other words, the statistical issues are identical to those described above, only the interpretation may be different.

# Pulling it all together

## Comorbidity is common and has adverse impacts on patients

Both the review of literature in the first part of the thesis and the results of the analyses presented here demonstrate that comorbidity is common among people with cancer, albeit it remains unclear whether comorbidity is more common than in a similarly aged population without cancer. Comorbidity has an adverse effect on a range of outcomes, so is clearly important from the perspective of a given patient and their clinician(s). At this individual level, comorbidity is relatively straight-forward to assess and consider in relation to a treatment plan and prognosis for that specific patient. However, the fact that comorbidity impacts outcomes suggests that it is also an important factor that needs to be considered if assessing the care and outcomes of *populations* of patients with cancer. Accurately measuring comorbidity in populations is more problematic, so how should comorbidity be measured in this context?

## Which comorbidity index should be used?

As discussed above, there are only two data sources currently available in New Zealand at a national level that can be practically and usefully employed to measure comorbidity in populations; the dataset that holds administrative hospitalisation data (National Minimum Dataset; NMDS), and the community pharmaceutical dataset. These two sources of data were used to develop cancer-specific indices of comorbidity. The most refined version of the hospitalisation-based indices (the C3 indices) included cancer site-specific weights. These were combined with the pharmaceutical-based comorbidity index (PBCI) to produce the so-called 'gold standard', in that it was considered from a theoretical perspective to be close to the optimal measure of comorbidity given these data and this approach to measuring comorbidity. The site-specific C3 indices were also simplified into an index in which weights for conditions were taken from all the cancer sites combined (the so-called all-sites C3 index, or SI1), and two indices which included a subset of the conditions included in the full C3 index, one of which included weights that had been further simplified. These indices were compared with the Charlson index, and in the case of the site-specific C3 indices, the

NCI indices which were derived from the Charlson index but also included site specific weights (Klabunde, Legler et al. 2007).

The results of the analyses presented here show that the fact of including a measure of comorbidity is more important than the specific measure chosen. In the context of a specific cancer site, a simple combination of patient and disease factors (particularly age and stage at diagnosis) can produce a model that has good predictive and discriminatory ability in terms of patient outcome particularly for cancer-specific and all-cause mortality. Including comorbidity generally improves the performance of these models but there is not much 'room' for one measure to substantially outperform another. Baldwin et al (2006) similarly concluded that there was little difference in the performance of four administrative-based indices of comorbidity in the context of patients with stage III colon cancer, but the authors were unable to generalise their findings beyond this relatively narrow patient group.

Whilst it is true that the differences in performance between the indices assessed here were generally not large, the gold-standard and C3-derived indices tended to perform better than the Charlson index for all sites combined, colorectal and upper gastrointestinal cancers, while the PBCI tended to outperform the Charlson index for non-cancer death among patients with breast and gynaecological cancers. The C3-based and PBC indices have been developed specifically for cancer, with careful inclusion of the conditions that are most likely to impact on the quantity or quality of cancer patients' lives. They were constructed with the input of cancer clinicians to ensure they make sense from a clinical perspective, and are designed for use with administrative data with the inherent advantages of low cost, ease of use and availability of population-level data. The C3 indices include a greater number of conditions, and therefore might be considered more complex to implement, but only in their initial coding; once the index is calculated, they are as simple to manipulate, and as statistically efficient as the other indices presented here. The versions of these indices that were calculated on the basis of site-specific weights performed very similarly to the version based on all-sites weights (SI1), so in the discussion below these are grouped together. The Charlson index, the two most simplified versions of the C3 indices (SI2 and SI3) and the PBCI are all based on 19 conditions (or condition categories) so are considered here the more 'simple' versions of comorbidity measures. SI2 and SI3 performed similarly for all sites.

There was no one index that out-performed all others for all sites (Table 40). For some sites particularly for all-cause death, all indices performed similarly, however where there were differences, the 'gold standard' approach tended to provide at least as good, and often better performance than any other measure. However, it is also true that the 'gold standard' approach often performed similarly to the best single measure of comorbidity for a particularly site (either the C3/SI1 or the PBCI).

For all cancer sites combined, the gold standard approach clearly outperformed all other measures for non-cancer mortality according to the c-statistics and AIC criteria. All the C3-based indices and the PBCI outperformed the Charlson index, although the Charlson index was similar to the other simplified indices for all-cause mortality.

For colorectal cancer, the gold standard and C3/SI1 indices outperformed Charlson according to all criteria for both all-cause and non-cancer mortality. The C3-based simplified indices (SI2 and SI3) also outperformed Charlson clearly for non-cancer mortality, but not for all-cause mortality. There was a similar pattern for upper GI cancers, with the C3-based indices tending to outperform Charlson for non-cancer death, but all performing similarly for all-cause death.

For breast and gynaecological cancers, no index clearly outperformed the others for all-cause mortality, although the hospitalisation-based ones tended to perform better than the PBCI. However, for non-cancer mortality, for both these sites, the PBCI (and gold standard) performed better than the other indices according to the c-statistic and AIC criteria.

For urological cancers, all measures of comorbidity performed similarly both for all-cause and non-cancer mortality, albeit the hospitalisation-based indices were slightly better for all-cause mortality.

In summary, for all cancer sites combined, colorectal and upper GI cancers, the optimal choice for measuring comorbidity from the indices presented here would be either the gold standard or the C3/ SI1 indices, with the best simplified indices being either SI2 or SI3. For breast and gynaecological cancers, for non-cancer death, the optimal approach would be either the gold standard or PBCI with PBCI also being a good simple approach, but a hospitalisation-based approach may be better for all-cause

death. For urological cancers, no measure clearly outperformed the others, although the gold standard and C3/SI1 approaches were slightly better for all-cause mortality.

**Table 40: Summary of recommendations for choice of measure of comorbidity by cancer site.**

Site	Type	All-cause mortality	Non-cancer mortality
<b>All sites</b>	Ideal	Gold standard, C3/SI1	Gold standard (C3/SI1)
	Simple	SI2, SI3 or Charlson	SI2, SI3, (PBCI)
<b>Colorectal</b>	Ideal	Gold standard, C3/SI1	Gold standard, C3/SI1
	Simple	SI2, SI3 or Charlson	SI2, SI3
<b>Breast</b>	Ideal	Gold standard, C3/SI1, Charlson	Gold standard, PBCI
	Simple	Charlson	PBCI (SI2, SI3, Charlson)
<b>Gynaecological</b>	Ideal	SI1, Charlson, SI3	Gold standard, PBCI
	Simple	SI2, SI3, Charlson	PBCI (SI2, SI3, Charlson)
<b>Upper GI</b>	Ideal	Any	Gold standard, C3/SI1, SI2, SI3
	Simple	Any	SI2, SI3
<b>Urological</b>	Ideal	Gold standard, C3/ SI1	Any
	Simple	SI2, SI3 or Charlson	Any

Based on highest c statistic; lowest AIC and/or highest IDI.

PBCI, SI2, SI3 and Charlson considered simple because smaller number of conditions included.

## Generalisability of findings

The findings of this study are clearly able to be generalised to populations diagnosed with the cancers included in the study within the New Zealand context. To what extent can the findings be generalised more broadly?

The data validity exercises which compared the data from routine sources to data collected directly from clinical notes were both carried out on specific cancer populations; colon cancer for the hospitalisation data, and upper gastrointestinal or rectal cancers for the pharmaceutical data. As discussed in the last chapter, it seems reasonable to assume that the errors that occur in administrative data are reasonably constant across cancer sites, and therefore these findings can be generalised to those diagnosed with cancer more generally. It may also be reasonable to assume that such errors are similar among patients of a similar age more generally given that the measure of comorbidity is taken from data prior to the diagnosis of cancer. Arguably the measurement of comorbidity among younger patients may be less robust using

hospitalisation data because these patients may be less likely to have been hospitalised than older patients. Indeed, the pharmaceutical-based index performed better than hospitalisation-based ones for cancers among younger women, a finding that would be consistent with this hypothesis.

New Zealand follows internationally consistent protocols when coding administrative data (World Health Organization 2008). It therefore seems reasonable to assume that indices based on these data could also be used in other countries that follow these protocols. In fact, the Cancer Council NSW (Australia) are planning to use the all-site version of the C3 index in work investigating the impact of comorbidity on inequities in outcomes between Indigenous and non-Indigenous cancer patients (personal communication, Prof Dianne O'Connell, Cancer Council NSW, 28 Aug 2013). This will provide an external validation of these indices outside of New Zealand. It would also be useful to assess the extent to which the PBCI is valid in countries outside New Zealand, but again, assuming similar data and prescribing practises, there is no reason not to assume that this index would be valid in these circumstances.

The comorbidity indices were developed for nine specific cancer sites, so can they be used for other cancer sites? The C3 indices in particular were developed using site-specific weights to optimise the measurement of comorbidity within these sites. However, one of the key findings of this thesis was that using site-specific indices did not appreciably improve the measurement of comorbidity over indices that were developed for all the sites investigated here combined. Of course, if all cancers (in general) were used to develop the all-sites weights, it is likely that the (all-sites) weights would be somewhat different. This is unlikely to be of substantial concern for two main reasons. First, the impact of specific conditions was reasonably consistent (in relative terms) across cancer sites, so their relative impact in any combined index is also likely to be similar. Second, the exact magnitude of the weights used in the index was considerably less important than the fact of the inclusion of conditions. Conditions were selected on the basis of their importance to cancer in general, not to these sites specifically, so it is likely that all (or most) important conditions will have been included. For these reasons, it seems reasonable to generalise the use of the indices to cancers beyond those specifically investigated here.

These indices were developed using weights calculated according to the impact of specific conditions on mortality. Cancer mortality (or survival) is not the only outcome of

interest in cancer-related studies. Other important outcomes might include receipt of treatment and quality of life. It is likely that if different outcomes were used, weights assigned to specific conditions would be different. For example, the impact of osteoarthritis on mortality may not be large, but it may have a substantial impact on quality of life. Therefore if quality of life was used as the primary outcome measure, the weight assigned to osteoarthritis would be larger than if mortality was the primary outcome. Reassuringly though, conditions were included in the indices if they were considered to have either (or both) an impact on quantity or quality of life. For these reasons, once again, most important conditions are likely to have been included for most common primary outcomes of interest. Therefore, it may well be reasonable to use these indices regardless of the outcome. However, this hypothesis was not able to be empirically investigated here because there were no sufficiently reliable data available on other outcomes (including receipt of treatment or quality of life) to investigate them in the context of this thesis.

Finally, these indices were developed for use in cancer populations. Conditions were identified on the basis of their impact on cancer outcomes, so could these indices be useful outside the context of cancer? In fact, an inclusive approach was used for the conditions in the indices. It may be reasonable to assume that conditions that are likely to have an impact on outcomes would be included, regardless of whether or not the primary condition was cancer. Therefore, possibly with some minor revisions, these indices may well be useful outside of the cancer context. In fact, in contexts where the primary disease does not have such a strong impact on mortality itself (as cancer does), the difference in performance between these indices may be easier to identify. This would, of course, require more research to confirm.

## **Concluding statement and recommendations**

The overarching aim of this thesis was to develop and validate a simplified index of comorbidity using routinely collected data specifically for use in cancer populations. The rationale for this aim was that comorbidity was demonstrably important in terms of cancer outcomes, but there was no gold standard approach to measuring comorbidity

in this context. However, there was a clear foundation of work to build from; earlier efforts to measure comorbidity had employed a variety of approaches but none met the aims of this thesis. Some approaches required data from clinical notes (e.g. ACE-27), some were overly simplified (e.g. ASA), others statistically inefficient (e.g. MACSS with its 102 variables to be included in models), some were designed for only specific cancer sites (e.g. WUHNCI, approaches developed by Fleming and Tammemagi) and others included constructs other than comorbidity (e.g. ICED, TIBI). Of the approaches identified, those that were based on weighted indices were considered the most promising as starting points for this project. The prototype for this approach is the Charlson Index which is the comorbidity index that has been used most extensively both within cancer studies and beyond. The Charlson index is simple and can be used with administrative data, but it was developed on the basis of the conditions identified in a small cohort of general medical patients from a single New York hospital three decades ago. Whilst there have been innovations applied to the Charlson Index, these tended to be related either to the sources of data used to calculate it (Deyo, Cherkin et al. 1992; Quan, Sundararajan et al. 2005; Klabunde, Harlan et al. 2006; Susser, McCusker et al. 2008), or to the approach used to weight the index (Klabunde, Potosky et al. 2000; Klabunde, Legler et al. 2007), rather than related to the conditions included in the index.

In terms of measuring the prevalence and impact of specific conditions in cancer populations, the work presented here extends the work of others in that there was a rigorous process to ensure that all important comorbid conditions were included and that the codes accurately represented the conditions that were important to clinicians. The entire population of people registered with cancer in New Zealand were included in the study, and nine cancer sites were investigated simultaneously. Two separate sets of indices were developed, one from hospitalisation and the other from pharmaceutical data. The performance of these indices was assessed both separately and together. Different approaches to weighting were also assessed; in particular, site-specific weights were compared to non-site specific weights. More simplified versions of indices were assessed against more inclusive indices. There were, of course, weaknesses in the methods used. The most fundamental weaknesses are those associated with using administrative data generally; conditions could only be identified if they were coded within hospitalisation or pharmaceutical data, there were likely to be inherent errors in the data in terms both of missing data and issues relating to coding, there was limited information on the timing or severity of conditions, and there are likely

to have been some biases inherent in the coding practice used. There were also some necessary simplifications in the construction of the indices and all approaches to validation required different assumptions and did not therefore necessarily tell a consistent story.

## **The conclusions and recommendations from this thesis are:**

### ***Comorbidity is considered and included in studies (or other work) that aim to assess or compare outcomes of cancer populations.***

Comorbidity is both common and has negative impacts on outcomes from cancer. It is therefore important to consider comorbidity in studies (or other work) that assess or compare the outcomes of people with cancer. The findings of this thesis support the idea that the fact of including a measure of comorbidity is more important than the specific measure used.

### ***Both administrative hospitalisation and pharmaceutical data can be used for measuring comorbidity in New Zealand.***

On balance the evidence from this thesis is that if only one of these sources of data is used, hospitalisation data would be a marginally better choice, for older cancer patients at least. However, pharmaceutical data have also been found to be useful in this context, and may be better than hospitalisation data in contexts where patients are younger and less likely to have been hospitalised. Both sets of data have the strengths of being population-based and relatively easily accessible, but also the weaknesses inherent in administrative data.

### ***Site-specific weights do not add appreciably to the validity of weighted indices in the context of cancer.***

Using versions of the indices that employ weights from standardised models is simpler, and means that the interpretation of a given score is the same across cancer sites. The performance of indices based on site-specific weights and those based on non-specific cancer weights was almost identical. It is therefore recommended that versions of the indices that use standard weights are used.

Where an administrative data-based measure of comorbidity in the context of cancer is required, the *optimal choice* depends to some degree on the study question. Some general recommendations can be made on the basis of the results of this thesis.

- ***If comorbidity is being treated as a confounding or mediating variable the choice of measure of comorbidity may be minimally relevant.*** However, if excellent adjustment is required, the optimal choice of index may be to use PBCI and hospitalisation measures in combination if possible. If not, using the C3/SI1 index is on balance the best choice, particularly if multiple sites are being investigated. If a simpler index is required, either SI2 or SI3 would be optimal. However, for gynaecological and breast cancers specifically, the PBCI should be considered as the optimal single index.
- ***If comorbidity is being treated as the outcome (dependent) variable,*** the choice of measure should emphasise specificity over sensitivity, and a less biased estimate may be obtained by dichotomising the comorbidity construct, with a relatively high cut-off for defining comorbidity. The specific choice of index is likely to be less important.
- ***If comorbidity is being treated as the exposure (independent) variable, the C3/SI1 index is likely to be the optimal choice*** because, of the indices here, it has the highest face validity and overall the best performance of any single index.
- ***If a simple measure of comorbidity is required, the SI2, SI3 and PBCI approaches tended to outperform Charlson index*** in some circumstances, particularly for all sites combined. For this reason, these are recommended over the Charlson index, although for many of the site-specific comparisons there was little or no difference between the simpler indices.

There are three clear avenues for future work to extend that presented here.

The first is ***an exploration into other possible data sources for the measurement of comorbidity***, specifically those from primary care. These data are currently collected in New Zealand separately by individual Primary Care Organisations, but are not collated in a nationally consistent and available manner. Work to assess the viability of facilitating such a collation would be useful, and if successful, would likely be beneficial to the measurement of comorbidity (and multimorbidity), and to work on chronic disease in general.

The second involves ***assessing the validity of the indices developed here in populations with cancers not evaluated here and in countries outside New Zealand.*** It is highly likely that these indices will be useful for cancers not examined here for reasons presented earlier. Their validity in settings outside of New Zealand has yet to be established, but work is underway in Australia to assess their usefulness in that context.

***The third involves extending the use of these indices to contexts outside of cancer.***

It may well be fruitful to examine the use of these indices in populations without cancer, and to investigate what, if any, amendments to them would be required. These indices could be used for measures of multimorbidity, or comorbidity with a non-cancer primary condition. An application for funding to allow this work to progress is in development.

*What we call the beginning is often the end. And to make an end is to make a beginning. The end is where we start from. ~T. S. Eliot*

# Appendices

Appendix 1: Conditions included in other comorbidity indices

Appendix 2: List of comorbid conditions identified from NMDS data and their ICD-10 codes

Appendix 3: Conditions included in the PBCI and drug classes included

Appendix 4: Evaluating the impact of multiple simultaneous conditions

Appendix 5: Association of all-cause and non-cancer mortality with categories of C3 and PBC indices.

Appendix 6: Weights for simplified indices

Appendix 7: Boxplots for predicted non-cancer death (development cohorts)

Appendix 8: Publications and papers submitted for publication arising from this thesis (to date)

# Appendix 1: Conditions included in other comorbidity indices

As a first step to identifying conditions that were likely to be important in a cancer-specific comorbidity index, other indices were reviewed to ascertain which conditions were included in previous work. Advice was also sought from three cancer clinicians, an oncologist and two cancer surgeons. They were asked to identify the conditions they considered most important in the care and outcomes of patients with cancer. The table below summarises this work. Conditions did not necessarily match exactly in different indices. For example liver disease might be included as a separate category, or further divided in mild and moderate/severe liver disease. The red cells below indicate that conditions within the same specific category were included in a given index, while those in yellow cells indicate that category of conditions was included in the index that would incorporate the specific condition.

	Charlson 1987	Sarfati 2009	Elixhauser 1998	NIA/NCI (Yancik 1996)	ACE-27 (Piccirillo 2000)	MACSS (Holman 2005)	Tammemagi :lung 2003)	Tammemagi : breast (2005)	Fleming Breast (1999)	Fleming Prostate (2003)	Satariano (1994)	SCI (Colinet 2005)	Clinicians (Personal comms)*
Myocardial infarct	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
CHF	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
PVD	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
CerebroVD	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Dementia	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Respiratory/ COPD	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Connective tissue disease*	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
PU disease	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Mild liver	Red	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
DM	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Hemiplegia/ paraplegia	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Mod/Severe renal	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
DM with end organ damage	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Any tumour	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Leukaemia	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Lymphoma	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Mod/Severe liver	Red	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
metastatic tumour	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
AIDS	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Hypertension: Uncomplicated	Red	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Hypertension: Complicated	Red	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Cardiac valve disease	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Cardiac arrhythmias	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Other neurological disorders*	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Previous PE	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Coagulopathy/ blood disorders	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow
Obesity	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow

	Charlson 1987	Sarfati 2009	Elixhauser 1998	NIA/NCI (Yancik 1996)	ACE-27 (Piccirillo 2000)	MACSS (Holman 2005)	Tammemagi :lung 2003)	Tammemagi : breast (2005)	Fleming Breast (1999)	Fleming Prostate (2003)	Satariano (1994)	SCI (Colinet 2005)	Clinicians (Personal comms)*
Fluid and electrolyte disorders													
Blood loss anaemia													
deficiency anaemias													
Alcohol abuse													
Drug abuse													
Major psychiatric: psychosis													
Major psychiatric: depression													
Angina													
Inflammatory bowel disease													
Acute or chronic pancreatitis													
Arthritis_osteo													
Asthma													
Eye problems													
Fracture													
Gall bladder problems													
GI problems_diverticulitis, hiatal hernia													
Cardiac arrest													
Cardiovascular disease'													
Osteoporosis													
Thyroid/ glandular issues													
Urinary tract_chronic cystitis, incont													
Other													
TB													
Septicaemia													
Other bacterial infections													

	Charlson 1987	Sarfati 2009	Elixhauser 1998	NIA/NCI (Yancik 1996)	ACE-27 (Piccirillo 2000)	MACSS (Holman 2005)	Tammemagi :lung 2003)	Tammemagi : breast (2005)	Fleming Breast (1999)	Fleming Prostate (2003)	Satariano (1994)	SCI (Colinet 2005)	Clinicians (Personal comms)*
Candidiasis													
Systemic mycosis													
Benign neoplasms of CR													
Uterine leiomyoma													
Malnutrition or cachexia													
Avitaminosis													
Gout													
Other metabolic disorders													
Immune system disorders													
Neurosis or personality disorders													
Mental retardation													
Haemorrhoids													
Pneumonia													
Pleurisy													
Other respiratory disorders'													
Oesophageal diseases													
Gastritis and duodenitits													
Cholelithiasis and cholecystitis													
Abdominal hernia													
Peritoneal adhesions													
GI haemorrhage													
Other kidney, bladder or ureter conditions'													
Benign prostatic hypertr.													
Breast disorders													
PID													

	Charlson 1987	Sarfati 2009	Elixhauser 1998	NIA/NCI (Yancik 1996)	ACE-27 (Piccirillo 2000)	MACSS (Holman 2005)	Tammemagi :lung 2003)	Tammemagi : breast (2005)	Fleming Breast (1999)	Fleming Prostate (2003)	Satariano (1994)	SCI (Colinet 2005)	Clinicians (Personal comms)*
cervicitis or vaginitis													
genital prolapse													
noninflamm ovarian conditions													
Uterine disorders													
gynaecological pain													
menstrual disorders													
Menopausal disorders													
Female infertility													
Chronic skin ulcers													
Dorsopathies													
Other arthropathies													
Congenital anomalies													
Migraine and headache													
Symptoms involving altered consciousness, syncope, collapse...													
Nausea or vomiting													
Abdominal pain													
Syptoms re nutrition, metabolism, development													
Late effects of injuries													
Pulmonary fibrosis													
Viral infection													
Meningitis													
Carditis, myopathy													
Aneurysms													
Arterial embolism/ thrombosis													
Other circulatory disease													
Pneumoconiosis													

	Charlson 1987	Sarfati 2009	Elixhauser 1998	NIA/NCI (Yancik 1996)	ACE-27 (Piccirillo 2000)	MACSS (Holman 2005)	Tammemagi :lung 2003)	Tammemagi : breast (2005)	Fleming Breast (1999)	Fleming Prostate (2003)	Satariano (1994)	SCI (Colinet 2005)	Clinicians (Personal comms)*
Abdo obstruction/ perf/ hmge													
Anorectal disease													
Hip replacement, limb amputation													
Dyslipidaemia													
Musculoskeletal													
Spine													
Smoking													

Those shaded ■ differentiate subcategories, those shaded ■ give general categories only

\*Different categories exist within this group \*\* Feedback from an oncologist; Andrew Simpson, and two cancer surgeons  
(Elizabeth Dennett and Jonathan Koea)

## Appendix 2: List of comorbid conditions identified from NMDS data and their ICD-10 codes

Diagnostic category	ICD-10 codes	List of 3 digit categories
Myocardial infarction	I21, I22, I23, I24.1, I25.2	I21 Acute myocardial infarction I22 Subsequent myocardial infarction I23 Certain current complications following acute myocardial infarction I24.1 Dressler's syndrome I25.2 Old myocardial infarction
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50	I09.9 Other rheumatic heart diseases I11.0 Hypertensive heart disease with (congestive) heart failure I13.0 Hypertensive heart and renal disease with (congestive) heart failure I13.2 Hypertensive heart and renal disease I25.5 Chronic ischaemic heart disease I42.0 Dilated cardiomyopathy I42.5 Other restrictive cardiomyopathy I42.6 Alcoholic cardiomyopathy I42.7 Cardiomyopathy due to drugs and other external agents I42.8 Other cardiomyopathies I42.9 Cardiomyopathy, unspecified I43 Cardiomyopathy in diseases classified elsewhere I50 Heart failure
Peripheral vascular disease	I70, I71, I72, I73.1, I73.8, I73.9, I77.1, K55.1, K55.2, K55.8, K55.9	I70 Atherosclerosis I71 Aortic aneurysm and dissection I72 Aneurysm I73.1 Thromboangiitis obliterans I73.8 Other specified peripheral vascular diseases I73.9 Peripheral vascular disease, unspecified I77.1 Stricture of artery K55.1 Vascular disorders of intestine\ K55.2 Angiodysplasia K55.8 Other vascular disorders of intestine K55.9 Vascular disorder of intestine, unspecified
Venous insufficiency	I83.0, I83.2, I87.2	I83.0 Varicose veins of lower extremities with ulcer

		<p>I83.2 Varicose veins of lower extremities with both ulcer and inflammation</p> <p>I87.2 Venous insufficiency (chronic)(peripheral)</p>
Cerebrovascular disease	I60, I61, I62, I63, I64, I65, I66, I67, I69, G45, G46	<p>G45 Transient cerebral ischaemic attacks and related syndromes</p> <p>G46 Vascular syndromes of brain in cerebrovascular diseases</p> <p>I60 Subarachnoid haemorrhage</p> <p>I61 Intracerebral haemorrhage</p> <p>I62 Other nontraumatic intracranial haemorrhage</p> <p>I63 Cerebral infarction</p> <p>I64 Stroke, not specified as haemorrhage or infarction</p> <p>I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction</p> <p>I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction</p> <p>I67 Other cerebrovascular diseases</p> <p>I69 Sequelae of cerebrovascular disease</p>
Dementia	F00, F01, F02.0, F02.1, F02.2, F02.3, F03, F05.1, G30, G31.0, G31.1	<p>F00 Dementia in Alzheimer's disease</p> <p>F01 Vascular dementia</p> <p>F02.0 Dementia in Pick's disease (G31.0+)</p> <p>F02.1 Dementia in Creutzfeldt-Jakob disease (A81.0+)</p> <p>F02.2 Dementia in Huntington's disease (G10+)</p> <p>F02.3 Dementia in Parkinson's disease (G20+)</p> <p>F03 Unspecified dementia</p> <p>F05.1 Delirium superimposed on dementia</p> <p>G30 Alzheimer's Disease</p> <p>G31.0 Circumscribed brain atrophy</p> <p>G31.1 Senile degeneration of the brain, not elsewhere classified</p>
Mental and behavioural disorders due to brain damage	F04, F06, F07.0, F07.1, F07.8, F07.9, F09, G93.1	<p>F04 Organic amnesic syndrome, not induced by alcohol and other psychoactive substances</p> <p>F06 Other mental disorders due to brain damage and dysfunction and to physical disease</p> <p>F07.0 Organic personality disorder</p> <p>F07.1 Postencephalitic syndrome</p> <p>F07.8 Other organic personality and behavioral disorders due to brain disease, damage and dysfunction</p> <p>F07.9 Unspecified organic personality and behavioral disorder due to brain disease, damage and dysfunction</p> <p>F09 Unspecified organic or symptomatic mental disorder</p> <p>G93.1 Anoxic brain damage, not elsewhere classified</p>

Chronic pulmonary disease	E84, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68.4, J70.1, J70.3, J84, J96.1, J98.0, J98.2, J98.3, J98.4	E84 Cystic fibrosis J40 Bronchitis, not specified as acute or chronic J41 Simple and mucopurulent chronic bronchitis J42 Unspecified chronic bronchitis J43 Emphysema J44 Other chronic obstructive pulmonary disease J45 Asthma J46 Status asthmaticus J47 Bronchiectasis J60 Coalworker's pneumoconiosis J61 Pneumoconiosis due to asbestos and other mineral fibers J62 Pneumoconiosis due to dust containing silica J63 Pneumoconiosis due to other inorganic dusts J64 Unspecified pneumoconiosis J65 Pneumoconiosis associated with tuberculosis J66 Airway disease due to specific organic dust J67 Hypersensitivity pneumonitis due to organic dust J68.4 Chronic respiratory conditions due to chemicals, gases, fumes and vapors J70.1 Chronic and other pulmonary manifestations due to radiation J70.3 Chronic drug-induced interstitial lung disorders J84 Other interstitial pulmonary diseases J96.1 Chronic respiratory failure J98.0 Diseases of bronchus, not elsewhere classified J98.2 Interstitial emphysema J98.3 Compensatory emphysema J98.4 Other disorders of lung
Connective tissue disease	L93, M05, M06, M08, M12.0, M12.3, M30, M31, M32, M33, M34, M35.0, M35.1, M35.2, M35.3, M35.4, M35.5, M35.6, M35.8, M35.9	L93 Lupus erythematosus M05 Seropositive rheumatoid arthritis M06 Other rheumatoid arthritis M08 Juvenile arthritis M12.0 Chronic postrheumatic arthropathy M12.3 Palindromic rheumatism M30 Polyarteritis nodosa and related conditions M31 Other necrotizing vasculopathies M32 Systemic lupus erythematosus M33 Dermatopolymyositis M34 Systemic sclerosis M35.0 Sicca syndrome [Sjögren] M35.1 Other overlap syndromes M35.2 Behcet's disease M35.3 Polymyalgia rheumatica M35.4 Diffuse (eosinophilic) fasciitis M35.5 Multifocal fibrosclerosis

		<p>M35.6 Relapsing panniculitis [Weber-Christian]  M35.8 Other specified systemic involvement of connective tissue  M35.9 systemic involvement of connective tissue, unspecified</p>
GI ulcer & upper GI disease	<p>K22.0, K22.1, K22.4, K22.5, K22.8, K22.9, K25, K26, K27, K28, K31.1, K31.2, K31.4, K31.6</p>	<p>K22.0 Achalasia of cardia  K22.1 Ulcer of oesophagus  K22.4 Dyskinesia of oesophagus  K22.5 Diverticulum of oesophagus, acquired  K22.8 Other specified diseases of oesophagus  K22.9 Disease of oesophagus, unspecified  K25 Gastric ulcer  K26 Duodenal ulcer  K27 Peptic ulcer, site unspecified  K28 Gastrojejunal ulcer  K31.1 Adult hypertrophic pyloric stenosis  K31.2 Hourglass stricture and stenosis of stomach  K31.4 Gastric diverticulum  K31.6 Fistula of stomach and duodenum</p>
Diabetes: uncomplicated	<p>E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9</p>	<p>E10.0 Insulin-dependent diabetes mellitus, with coma  E10.1 Type 1 diabetes mellitus with acidosis  E10.9 Type 1 diabetes mellitus without complication  E11.0 Type 2 DM with hyperosmolality  E11.1 Type 2 diabetes mellitus with acidosis  E11.9 Non-insulin-dependent diabetes mellitus without complications  E12.0 Malnutrition-related diabetes mellitus with coma  E12.1 Malnutrition-related diabetes mellitus, With ketoacidosis  E12.9 Malnutrition-related diabetes mellitus, Without complications  E13.0 Other DM with hyperosmolality  E13.1 Other specified diabetes mellitus with acidosis  E13.9 Other specified diabetes mellitus without complication  E14.0 Unspecified diabetes mellitus with hyperosmolality  E14.1 Unspecified diabetes mellitus with hyperosmolality  E14.9 Unspecified diabetes mellitus without complication</p>
Diabetes: with complications	<p>E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, E12.2,</p>	<p>E10.2 Type 1 Diabetes mellitus with renal complication  E10.3 Type 1 Diabetes mellitus with ophthalmic complication</p>

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E12.3, E12.4, E12.5, E12.6, E12.7, E12.8, E13.2, E13.3, E13.4, E13.5, E13.6, E13.7, E13.8, E14.2, E14.3, E14.4, E14.5, E14.6, E14.7, E14.8	<p>E10.4 Type 1 Diabetes mellitus with neurological complication</p> <p>E10.5 Type 1 Diabetes mellitus with circulatory complication</p> <p>E10.6 Type 1 Diabetes mellitus with other specified complication</p> <p>E10.7 Type 1 Diabetes mellitus with multiple complication</p> <p>E10.8 Type 1 Diabetes mellitus with unspecified complication</p> <p>E11.2 Type 2 Diabetes mellitus with renal complication</p> <p>E11.3 Type 2 diabetes mellitus with ophthalmic complication</p> <p>E11.4 Type 2 Diabetes mellitus with neurological complication</p> <p>E11.5 Type 2 Diabetes mellitus with circulatory complication</p> <p>E11.6 Type 2 Diabetes mellitus with other specified complication</p> <p>E11.7 Type 2 Diabetes mellitus with multiple complication</p> <p>E11.8 Type 2 Diabetes mellitus with unspecified complication</p> <p>E12.2 Malnutrition-related diabetes, With renal complications mellitus</p> <p>E12.3 Malnutrition-related diabetes, With ophthalmic complications mellitus</p> <p>E12.4 Malnutrition-related diabetes, With neurological complications mellitus</p> <p>E12.5 Malnutrition-related diabetes mellitus, With peripheral circulatory complications</p> <p>E12.6 Malnutrition-related diabetes mellitus, with other specified complication</p> <p>E12.7 Malnutrition-related diabetes mellitus, With multiple complications</p> <p>E12.8 Malnutrition-related diabetes mellitus, with unspecified complication</p> <p>E13.2 Other specified diabetes mellitus with renal complication</p> <p>E13.3 Other specified diabetes mellitus with ophthalmic complication</p> <p>E13.4 Other specified diabetes mellitus with neurological complication</p> <p>E13.5 Other specified diabetes mellitus with circulatory complication</p> <p>E13.6 Other specified diabetes mellitus with other specified complication</p> <p>E13.7 Other specified diabetes mellitus with multiple complication</p> <p>E13.8 Other specified diabetes mellitus, with unspecified complication</p> <p>E14.2 Unspecified diabetes mellitus with renal complication</p> <p>E14.3 Unspecified diabetes mellitus with ophthalmic complication</p>
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		<p>E14.4 Unspecified diabetes mellitus with neurological complication</p> <p>E14.5 Unspecified diabetes mellitus with circulatory complication</p> <p>E14.6 Unspecified diabetes mellitus, with other specified complication</p> <p>E14.7 Unspecified diabetes mellitus with multiple complication</p> <p>E14.8 Unspecified diabetes mellitus with unspecified complication</p>
Paralysis	<p>G04.1, G11.4, G80.0, G80.1, G80.2, G81, G82, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9</p>	<p>G04.1 Tropical spastic paraplegia</p> <p>G11.4 Hereditary spastic paraplegia</p> <p>G80.0 Spastic cerebral palsy</p> <p>G80.1 Spastic diplegia</p> <p>G80.2 Infantile hemiplegia</p> <p>G81 Hemiplegia</p> <p>G82 Paraplegia and tetraplegia</p> <p>G83.0 Diplegia of upper limbs</p> <p>G83.1 Monoplegia of lower limb</p> <p>G83.2 Monoplegia of upper limb</p> <p>G83.3 Monoplegia, unspecified</p> <p>G83.4 Cauda equina syndrome</p> <p>G83.9 Paralytic syndrome, unspecified</p>
Chronic renal disease	<p>N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N11, N18, N19, N25.0, N25.8, N25.9, I12.0, I13.1, Z49, Z94.0, Z99.2</p>	<p>N03.2 Chronic nephritic syndrome, diffuse membranous glomerulonephritis</p> <p>N03.3 Chronic nephritic syndrome, diffuse mesangial proliferative glomerulonephritis</p> <p>N03.4 Chronic nephritic syndrome, diffuse endocapillary proliferative glomerulonephritis</p> <p>N03.5 Chronic nephritic syndrome, diffuse mesangiocapillary glomerulonephritis</p> <p>N03.6 Chronic nephritic syndrome, dense deposit disease</p> <p>N03.7 Chronic nephritic syndrome, diffuse crescentic glomerulonephritis</p> <p>N03.8 Chronic nephritic syndrome, other</p> <p>N03.9 Chronic nephritic syndrome, unspecified</p> <p>N04.2 Nephrotic syndrome, diffuse membranous glomerulonephritis</p> <p>N04.3 Nephrotic syndrome, diffuse mesangial proliferative glomerulonephritis</p> <p>N04.4 Nephrotic syndrome, diffuse endocapillary proliferative glomerulonephritis</p> <p>N04.5 Nephrotic syndrome, diffuse mesangiocapillary glomerulonephritis</p> <p>N04.6 Nephrotic syndrome, dense deposit disease</p> <p>N04.7 Nephrotic syndrome, diffuse crescentic glomerulonephritis</p> <p>N04.8 Nephrotic syndrome, other</p> <p>N04.9 Nephrotic syndrome, unspecified</p> <p>N05.2 Unspecified nephritic syndrome, diffuse membranous glomerulonephritis</p>

	N05.3 Unspecified nephritic syndrome, diffuse mesangial proliferative glomerulonephritis
	N05.4 Unspecified nephritic syndrome, diffuse endocapillary proliferative glomerulonephritis
	N05.5 Unspecified nephritic syndrome, diffuse mesangiocapillary glomerulonephritis
	N05.6 Unspecified nephritic syndrome, dense deposit disease
	N05.7 Unspecified nephritic syndrome, diffuse crescentic glomerulonephritis
	N05.8 Unspecified nephritic syndrome, other
	N05.9 Unspecified nephritic syndrome, unspecified
	N11 Nephritis
	N18 Chronic renal failure
	N19 Unspecified renal failure
	N25.0 Renal osteodystrophy
	N25.8 Other disorders resulting from impaired renal tubular function
	N25.9 Disorder resulting from impaired renal tubular function, unspecified
	I12.0 Hypertensive renal disease with renal failure
	I13.1 Hypertensive heart and renal disease with renal failure
	Z49 Care involving dialysis
	Z94.0 Kidney transplant status
	Z99.2 Dependence on renal dialysis
	C00 Malignant neoplasm of lip
	C01 Malignant neoplasm of base of tongue
	C02 Malignant neoplasm of other and unspecified parts of tongue
	C03 Malignant neoplasm of gum
	C04 Malignant neoplasm of floor of mouth
	C05 Malignant neoplasms of the palate
	C06 Malignant neoplasm of other and unspecified parts of mouth
	C07 Malignant neoplasm of parotid gland
	C08 Malignant neoplasm of other and unspecified major salivary glands
	C09 Malignant neoplasm of the tonsil
	C10 Malignant neoplasm of the oropharynx
	C11 Malignant neoplasm of nasopharynx
	C12 Malignant neoplasm of the pyriform sinus
	C13 Malignant neoplasm of hypopharynx
	C14 Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
	C15 Malignant neoplasm of oesophagus
	C16 Malignant neoplasm of stomach
	C17 Malignant neoplasm of small intestine
	C18 Malignant neoplasm of colon
	C19 Malignant neoplasm of rectosigmoid junction
	C20 Malignant neoplasm of rectum
	C21 Malignant neoplasm of anus and anal
Other malignancy	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C23, C24, C25, C26, C30, C31, C32, C33, C37, C38, C39, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C72, C73, C74, C75, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95

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canal  
C23 Malignant neoplasm of gallbladder  
C24 Malignant neoplasm of other and unspecified parts of biliary tract  
C25 Malignant neoplasm of pancreas  
C26 Malignant neoplasm of other and ill-defined digestive organs  
C30 Malignant neoplasm of nasal cavity and middle ear  
C31 Malignant neoplasm of accessory sinuses  
C32 Malignant neoplasm of larynx  
C33 Malignant neoplasm of trachea  
C37 Malignant neoplasm of thymus  
C38 Malignant neoplasm of heart, mediastinum and pleura  
C39 Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs  
C43 Malignant melanoma of skin  
C45 Mesothelioma  
C46 Kaposi's sarcoma  
C47 Malignant neoplasm of peripheral nerves and autonomic nervous system  
C48 Malignant neoplasm of retroperitoneum and peritoneum  
C49 Malignant neoplasm of other connective and soft tissue  
C50 Malignant neoplasm of breast– exclude if primary site of interest  
C51 Malignant neoplasm of vulva  
C52 Malignant neoplasm of vagina  
C53 Malignant neoplasm of cervix uteri  
C54 Malignant neoplasm of corpus uteri  
C55 Malignant neoplasm of uterus, part unspecified  
C56 Malignant neoplasm of ovary  
C57 Malignant neoplasm of other and unspecified female genital organs  
C58 Malignant neoplasm of placenta– include, except if primary site of interest  
C60 Malignant neoplasm of penis  
C61 Malignant neoplasm of prostate  
C62 Malignant neoplasm of testis  
C63 Malignant neoplasm of other and unspecified male genital organs  
C64 Malignant neoplasm of kidney, except renal pelvis  
C65 Malignant neoplasm of renal pelvis  
C66 Malignant neoplasm of ureter  
C67 Malignant neoplasm of bladder  
C68 Malignant neoplasm of other and unspecified urinary organs  
C69 Malignant neoplasm of eye and adnexa  
C70 Malignant neoplasm of meninges  
C72 Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous

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		<p>System</p> <p>C73 Malignant neoplasm of thyroid gland</p> <p>C74 Malignant neoplasm of adrenal gland</p> <p>C75 Malignant neoplasm of other endocrine glands and related structures</p> <p>C81 Hodgkin's disease</p> <p>C82 Follicular [nodular] non-Hodgkin's lymphoma</p> <p>C83 Diffuse non-Hodgkin's lymphoma</p> <p>C84 Peripheral and cutaneous T-cell lymphomas</p> <p>C85 Other and unspecified types of non-Hodgkin's lymphoma</p> <p>C88 Malignant immune-proliferative diseases</p> <p>C90 Multiple myeloma and malignant plasma cell neoplasms</p> <p>C91 Lymphoid leukaemia</p> <p>C92 Myeloid leukaemia</p> <p>C93 Monocytic leukaemia</p> <p>C94 Other leukemia of specified cell type</p> <p>C95 Leukaemia of unspecified cell type</p>
Liver disease: moderate or severe	<p>K70, K71.1, K71.3, K71.4, K71.5, K71.7, K72.1, K72.9, K73, K74, K76.0, K76.2, K76.3, K76.4, K76.5, K76.6, K76.7, K76.8, K76.9, I85, I86.4, I98.2, Z94.4</p>	<p>K70 Alcoholic liver disease</p> <p>K71.1 Toxic liver disease with hepatic necrosis</p> <p>K71.3 Toxic liver disease with chronic persistent hepatitis</p> <p>K71.4 Toxic liver disease with chronic lobular hepatitis</p> <p>K71.5 Toxic liver disease with chronic active hepatitis</p> <p>K71.7 Toxic liver disease with fibrosis and cirrhosis of liver</p> <p>K72.1 Chronic hepatic failure</p> <p>K72.9 Hepatic failure, unspecified</p> <p>K73 Chronic hepatitis, not elsewhere classified</p> <p>K74 Fibrosis and cirrhosis of liver</p> <p>K76.0 Fatty (change of) liver, not elsewhere classified</p> <p>K76.2 Central haemorrhagic necrosis of liver</p> <p>K76.3 Infarction of liver</p> <p>K76.4 Peliosis hepatis</p> <p>K76.5 Hepatic veno-occlusive disease</p> <p>K76.6 Portal hypertension</p> <p>K76.7 Hepatorenal syndrome</p> <p>K76.8 Other specified diseases of liver</p> <p>K76.9 Liver disease, unspecified</p> <p>I85 Oesophageal varices</p> <p>I86.4 Gastric varices</p> <p>I98.2 Oesophageal varices in diseases classified elsewhere</p> <p>Z94.4 Liver transplantation</p>
AIDS	<p>B20, B21, B22, B23, B24, F02.4, Z21</p>	<p>B20 Human immunodeficiency virus [HIV] disease with infectious and parasitic diseases</p>

		B21 Human immunodeficiency virus [HIV] disease with malignant neoplasms B22 Human immunodeficiency virus [HIV] disease with other specified diseases B23 Human immunodeficiency virus [HIV] disease resulting in other conditions B24 Unspecified human immunodeficiency virus [HIV] disease F02.4 Dementia in human immunodeficiency virus [HIV] disease Z21 Asymptomatic human immunodeficiency virus [HIV] infection status
Angina	I20	I20 Angina pectoris
Hypertension: primary	I10 I11.9 I12.9 I13.9	I10 Essential (primary) hypertension I11.9 Hypertensive heart disease without heart failure I12.9 Hypertensive renal disease without renal failure I13.9 Hypertensive heart and renal disease, unspecified
Cardiac arrhythmia	I44.1, I44.2, I44.3, I45.6, I45.9, I47, I48, I49, T82.1, Z45.0, Z95.0	I44.1 Atrioventricular block, second degree I44.2 Atrioventricular block, complete I44.3 Other and unspecified atrioventricular block I45.6 Pre-excitation syndrome I45.9 Conduction disorder, unspecified I47 Paroxysmal tachycardia I48 Atrial fibrillation and flutter I49 Other cardiac arrhythmias T82.1 Mechanical complication of cardiac electronic device Z45.0 Adjustment and management of cardiac device Z95.0 Presence of cardiac device
Pulmonary circulation disorder	I26, I27, I28.0, I28.1, I28.8, I28.9	I26 Pulmonary embolism I27 Pulmonary heart diseases I28.0 Arteriovenous fistula of pulmonary vessels I28.1 Aneurysm of pulmonary artery I28.8 Other specified diseases of pulmonary vessels I28.9 Disease of pulmonary vessels, unspecified
Cardiac valve disease	I05, I06, I07, I08, I09.1, I09.8, I34, I35, I36, I37, I38, T82.0, Q23.0, Q23.1, Q23.2, Q23.3, Q23.8, Q23.9, Z95.2,	I05 Rheumatic mitral valve diseases I06 Rheumatic aortic valve diseases I07 Rheumatic tricuspid valve diseases I08 Multiple valve diseases I09.1 Rheumatic diseases of endocardium, valve unspecified

	Z95.3, Z95.4	<p>I09.8 Other specified rheumatic heart diseases</p> <p>I34 Nonrheumatic mitral valve disorders</p> <p>I35 Nonrheumatic aortic valve disorders</p> <p>I36 Nonrheumatic tricuspid valve disorders</p> <p>I37 Pulmonary valve disorders</p> <p>I38 Endocarditis, valve unspecified</p> <p>T82.0 Mechanical complication of coronary artery bypass and valve grafts</p> <p>Q23.0 Congenital stenosis of aortic valve</p> <p>Q23.1 Congenital insufficiency of aortic valve</p> <p>Q23.2 Congenital mitral stenosis</p> <p>Q23.3 Congenital mitral insufficiency</p> <p>Q23.8 Other congenital malformations of aortic and mitral valves</p> <p>Q23.9 Congenital malformation of aortic and mitral valves, unspecified</p> <p>Z95.2 Presence of prosthetic heart valve</p> <p>Z95.3 Presence of xenogenic heart valve</p> <p>Z95.4 Presence of other heart-valve replacement</p>
Bowel disease: Inflammatory	K50, K51, K52.2, K52.8, K52.9	<p>K50 Crohn's disease [regional enteritis]</p> <p>K51 Ulcerative colitis</p> <p>K52.2 Allergic and dietetic gastroenteritis and colitis</p> <p>K52.8 Other specified noninfective gastroenteritis and colitis</p> <p>K52.9 Noninfective gastroenteritis and colitis, unspecified</p>
Other neurological disorders excluding epilepsy	G10, G11.0, G11.1, G11.2, G11.3, G11.8, G11.9, G12, G13, G20, G21, G23, G25.5, G31.2, G31.8, G31.9, G35, G36, G37, G90, G93.4, R47.0	<p>G10 Huntington's disease</p> <p>G11.0 Congenital nonprogressive ataxia</p> <p>G11.1 Early-onset cerebellar ataxia</p> <p>G11.2 Late-onset cerebellar ataxia</p> <p>G11.3 Cerebellar ataxia with defective DNA repair</p> <p>G11.8 Other hereditary ataxias</p> <p>G11.9 Hereditary ataxia, unspecified</p> <p>G12 Spinal muscular atrophy and related syndromes</p> <p>G13 Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere</p> <p>G20 Parkinson's disease</p> <p>G21 Secondary parkinsonism</p> <p>G23 Other degenerative diseases of the basal ganglia</p> <p>G25.5 Other chorea</p> <p>G31.2 Degeneration of nervous system due to alcohol</p> <p>G31.8 Other specified degenerative diseases of nervous system</p> <p>G31.9 Degenerative disease of nervous system, unspecified</p>

		<p>G35 Multiple sclerosis  G36 Other acute disseminated demyelination  G37 Other demyelinating diseases of central nervous system  G90 Disorders of autonomic nervous system  G93.4 Encephalopathy, unspecified  R47.0 Dysphasia and aphasia</p>
Epilepsy	<p>G40.0, G40.1,  G40.2, G40.3,  G40.4, G40.6,  G40.7, G40.8,  G40.9, G41</p>	<p>G40.0 Localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset  G40.1 Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures  G40.2 Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures  G40.3 Generalized idiopathic epilepsy and epileptic syndromes  G40.4 Other generalized epilepsy and epileptic syndromes  G40.6 Grand mal seizures, unspecified (with or without petit mal)  G40.7 Petit mal, unspecified, without grand mal seizures  G40.8 Other epilepsy  G40.9 Epilepsy, unspecified  G41 Status epilepticus</p>
Muscular & peripheral nerve disorder	<p>G60, G61, G62.0,  G62.1, G62.2,  G62.8, G62.9, G64,  G70, G71, G72.0,  G72.1, G72.2,  G72.3, G72.4,  G72.8, G72.9, G73.1</p>	<p>G60 Hereditary and idiopathic neuropathy  G61 Inflammatory polyneuropathy  G62.0 Drug-induced polyneuropathy  G62.1 Alcoholic polyneuropathy  G62.2 Polyneuropathy due to other toxic agents  G62.8 Other specified polyneuropathies  G62.9 Polyneuropathy, unspecified  G64 Other disorders of peripheral nervous system  G70 Myasthenia gravis and other myoneural disorders  G71 Primary disorders of muscles  G72.0 Drug-induced myopathy  G72.1 Alcoholic myopathy  G72.2 Myopathy due to other toxic agents  G72.3 Periodic paralysis  G72.4 Inflammatory myopathy, not elsewhere classified  G72.8 Other specified myopathies  G72.9 Myopathy, unspecified  G73.1 Eaton-Lambert syndrome</p>
Major psychiatric	F20, F22, F25, F28,	

disorder	F29, F30.2, F31, F32.1, F32.2, F32.3, F32.8, F32.9, F33, F39	F20 Schizophrenia F22 Persistent delusional disorders F25 Schizoaffective disorders (with Psychosis) F28 Other nonorganic psychotic disorders F29 Unspecified nonorganic psychosis F30.2 Mania with psychotic symptoms F31 Bipolar affective disorder F32.1 Major depressive disorder, single episode, moderate F32.2 Severe depressive episode without psychotic symptoms F32.3 Severe depressive episode with psychotic symptoms F32.8 Other depressive episodes F32.9 Major depressive disorder, single episode, unspecified F33 Recurrent depressive disorder F39 Unspecified mood [affective] disorder
Anxiety and behavioural disorders	F40, F41, F42, F44, F45, F48, F50, F55, F59, F60, F61, F63, F64, F65, F66, F68, F69	F40 Phobic anxiety disorders F41 Other anxiety disorders F42 Obsessive-compulsive disorder F44 Dissociative [conversion] disorders F45 Somatoform disorders F48 Other neurotic disorders F50 Eating disorders F55 Abuse of non-dependence-producing substances F59 Unspecified behavioural syndromes associated with physiological disturbances and physical factors F60 Specific personality disorders F61 Mixed and other personality disorders F63 Habit and impulse disorders F64 Gender identity disorders F65 Disorders of sexual preference F66 Psychological and behavioural disorders associated with sexual development and orientation F68 Other disorders of adult personality and behaviour F69 Unspecified disorder of adult personality and behaviour
Coagulopathy and other blood disorder	D55, D56, D57, D58, D59.0, D59.1, D59.2, D59.3, D59.4, D59.8, D59.9, D60, D61, D64, D66, D67, D68.0, D68.1, D68.2, D68.8, D68.9, D69.1, D69.2, D69.3, D69.4, D69.6, D69.8, D69.9, D70, D71, D72, D74, D75.0,	D55 Anemia due to enzyme disorders D56 Thalassemia D57 Sickle-cell disorders D58 Other hereditary haemolytic anemias D59.0 Drug-induced autoimmune haemolytic anemia D59.1 Other autoimmune haemolytic anemias D59.2 Drug-induced nonautoimmune haemolytic anemia D59.3 Haemolytic-uremic syndrome

	D75.2, D75.8, D75.9	D59.4 Other nonautoimmune haemolytic anemias D59.8 Other acquired haemolytic anemias D59.9 Acquired haemolytic anemia, unspecified D60 Acquired pure red cell aplasia [erythroblastopenia] D61 Other aplastic anemias D64 Other anemias D66 Hereditary factor VIII deficiency D67 Hereditary factor IX deficiency D68.0 Von Willebrand's disease D68.1 Hereditary factor XI deficiency D68.2 Hereditary deficiency of other clotting factors D68.8 Other specified coagulation defects D68.9 Coagulation defect, unspecified D69.1 Qualitative platelet defects D69.2 Other nonthrombocytopenic purpura D69.3 Idiopathic thrombocytopenic purpura D69.4 Other primary thrombocytopenia D69.6 Thrombocytopenia, unspecified D69.8 Other specified haemorrhagic conditions D69.9 Haemorrhagic condition, unspecified D70 Agranulocytosis D71 Functional disorders of polymorphonuclear neutrophils D72 Other disorders of white blood cells D74 Methaemoglobinaemia D75.0 Familial erythrocytosis D75.2 Essential thrombocytosis D75.8 Other specified diseases of blood and blood-forming organs D75.9 Disease of blood and blood-forming organs, unspecified
Anemia deficiency	D50, D51, D52, D53	D50 Iron deficiency anemia D51 Vitamin B12 deficiency anemia D52 Folate deficiency anemia D53 Other nutritional anemias
Obesity	E66	E66 Obesity
Alcohol abuse	F10.1, F10.2, F10.3, F10.4, F10.5, F10.6, F10.7, F10.8, F10.9, Z50.2, Z71.4	F10.1 Harmful use F10.2 Dependence syndrome F10.3 Withdrawal state F10.4 Withdrawal state with delirium F10.5 Psychotic disorder F10.6 Amnesic syndrome F10.7 Residual and late - onset psychotic disorder F10.8 Other mental and behavioural disorders F10.9 Unspecified mental and behavioural disorder

		Z50.2 Alcohol rehabilitation Z71.4 Counselling and surveillance for alcohol use disorder
Drug abuse	F11, F12, F13, F14, F15, F16, F18, F19, Z50.3, Z71.5, Z72.2	F11 Mental and behavioural disorders due to use of opioids F12 Mental and behavioural disorders due to use of cannabinoids F13 Mental and behavioural disorders due to use of sedatives or hypnotics F14 Mental and behavioural disorders due to use of cocaine F15 Mental and behavioural disorders due to use of other stimulants, including caffeine F16 Mental and behavioural disorders due to use of hallucinogens F18 Mental and behavioural disorders due to use of volatile solvents F19 Mental and behavioural disorders due to multiple drug use and use of other psychoactive Substances Z50.3 Drug rehabilitation Z71.5 Counselling and surveillance for drug use disorder Z72.2 Drug use
Pancreatitis	K86.0, K86.1, K86.8	K86.0 Alcohol-induced chronic pancreatitis K86.1 Other chronic pancreatitis K86.8 Other specified diseases of pancreas
Endocrine disorder	E01, E02, E03, E05, E06.2, E06.3, E06.5, E07, E16.3, E16.4, E16.8, E16.9, E20, E21.0, E21.2, E21.3, E21.4, E21.5, E22, E23.0, E23.2, E23.3, E23.6, E23.7, E24.0, E24.1, E24.3, E24.4, E24.8, E24.9, E25, E26, E27, E31, E32, E34.5, E34.8, E34.9	E01 Iodine-deficiency-related thyroid disorders and allied conditions E02 Subclinical iodine-deficiency hypothyroidism E03 Other hypothyroidism E05 Thyrotoxicosis [hyperthyroidism] E06.2 Chronic thyroiditis with transient thyrotoxicosis E06.3 Autoimmune thyroiditis E06.5 Other chronic thyroiditis E07 Other disorders of thyroid E16.3 Increased secretion of glucagon E16.4 Abnormal secretion of gastrin E16.8 Other specified disorders of pancreatic internal secretion E16.9 Disorder of pancreatic internal secretion, unspecified E20 Hypoparathyroidism E21.0 Primary hyperparathyroidism E21.2 Other hyperparathyroidism E21.3 Hyperparathyroidism, unspecified

		<p>E21.4 Other specified disorders of parathyroid gland</p> <p>E21.5 Disorder of parathyroid gland, unspecified</p> <p>E22 Hyperfunction of pituitary gland</p> <p>E23.0 Hypopituitarism</p> <p>E23.2 Diabetes insipidus</p> <p>E23.3 Hypothalamic dysfunction, not elsewhere classified</p> <p>E23.6 Other disorders of pituitary gland</p> <p>E23.7 Disorder of pituitary gland, unspecified</p> <p>E24.0 Pituitary-dependent Cushing's disease</p> <p>E24.1 Nelson's syndrome</p> <p>E24.3 Ectopic ACTH syndrome</p> <p>E24.4 Alcohol-induced pseudo-Cushing's syndrome</p> <p>E24.8 Other Cushing's syndrome</p> <p>E24.9 Cushing's syndrome, unspecified</p> <p>E25 Adrenogenital disorders</p> <p>E26 Hyperaldosteronism</p> <p>E27 Other disorders of adrenal gland</p> <p>E31 Polyglandular dysfunction</p> <p>E32 Diseases of thymus</p> <p>E34.5 Androgen resistance syndrome</p> <p>E34.8 Other specified endocrine disorders</p> <p>E34.9 Endocrine disorder, unspecified</p>
Urinary tract problem: chronic (not incl gender specific conditions)	N30.1, N30.2, N31, N32, N35, N36	<p>N30.1 Interstitial cystitis (chronic)</p> <p>N30.2 Other chronic cystitis</p> <p>N31 Neuromuscular dysfunction of bladder, not elsewhere classified</p> <p>N32 Other disorders of bladder</p> <p>N35 Urethral stricture</p> <p>N36 Other disorders of urethra</p>
Tuberculosis	A15, A16, A17, A18, A19, B90	<p>A15 Respiratory tuberculosis, bacteriologically and histologically confirmed</p> <p>A16 Respiratory tuberculosis, not confirmed bacteriologically or histologically</p> <p>A17 Tuberculosis of nervous system</p> <p>A18 Tuberculosis of other organs</p> <p>A19 Miliary tuberculosis</p> <p>B90 Sequelae of tuberculosis</p>
Osteoporosis & bone disorder	M80, M81.0, M81.1, M81.5, M81.8, M81.9, M83.1, M83.2, M83.3, M83.4, M83.5, M83.8, M83.9, M85, M86.3, M86.4, M86.5, M86.6, M88	<p>M80 Osteoporosis with pathological fracture</p> <p>M81.0 Postmenopausal osteoporosis</p> <p>M81.1 Postophorectomy osteoporosis</p> <p>M81.5 Idiopathic osteoporosis</p> <p>M81.8 Other osteoporosis</p> <p>M81.9 Unspecified osteoporosis</p> <p>M83.1 Senile osteomalacia</p> <p>M83.2 Adult osteomalacia due to malabsorption</p> <p>M83.3 Adult osteomalacia due to malnutrition</p>

		<p>M83.4 Aluminium bone disease</p> <p>M83.5 Other drug-induced osteomalacia in adults</p> <p>M83.8 Other adult osteomalacia</p> <p>M83.9 Adult osteomalacia, unspecified</p> <p>M85 Other disorders of bone density and structure</p> <p>M86.3 Chronic multifocal osteomyelitis</p> <p>M86.4 Chronic osteomyelitis with draining sinus</p> <p>M86.5 Other chronic haematogenous osteomyelitis</p> <p>M86.6 Other chronic osteomyelitis</p> <p>M88 Paget's disease of bone</p>
Immune system disorder	D80, D81, D82, D83, D84, D86, D89	<p>D80 Immunodeficiency with predominantly antibody defects</p> <p>D81 Combined immune deficiencies</p> <p>D82 Immunodeficiency associated with other major defects</p> <p>D83 Common variable immunodeficiency</p> <p>D84 Other immune-deficiencies</p> <p>D86 Sarcoidosis</p> <p>D89 Other disorders involving the immune mechanism, not elsewhere classified</p>
Metabolic disorder	E70, E71, E72, E74, E75, E76, E77, E78, E79.1, E79.8, E79.9, E80, E83, E85, E88	<p>E70 Disorders of aromatic amino-acid metabolism</p> <p>E71 Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism</p> <p>E72 Other disorders of amino-acid metabolism</p> <p>E74 Other disorders of carbohydrate metabolism</p> <p>E75 Disorders of sphingolipid metabolism and other lipid storage disorders</p> <p>E76 Disorders of glycosaminoglycan metabolism</p> <p>E77 Disorders of glycoprotein metabolism</p> <p>E78 Disorders of lipoprotein metabolism and other lipidemias</p> <p>E79.1 Lesch-Nyhan syndrome</p> <p>E79.8 Other disorders of purine and pyrimidine metabolism</p> <p>E79.9 Disorder of purine and pyrimidine metabolism, unspecified</p> <p>E80 Disorders of porphyrin and bilirubin metabolism</p> <p>E83 Disorders of mineral metabolism</p> <p>E85 Amyloidosis</p> <p>E88 Other metabolic disorders</p>

Mental retardation	F70, F71, F72, F73, F78, F79, F84.2, F84.3, F84.4, E00.0, E00.1, E00.2, E00.9, Q90	F70 Mild mental retardation F71 Moderate mental retardation F72 Severe mental retardation F73 Profound mental retardation F78 Other mental retardation F79 Unspecified mental retardation F84.2 Rett's syndrome F84.3 Other childhood disintegrative disorder F84.4 Overactive disorder associated with mental retardation and stereotyped movements E00.0 Congenital iodine-deficiency syndrome, neurological type E00.1 Congenital iodine-deficiency syndrome, myxoedematous type E00.2 Congenital iodine-deficiency syndrome, mixed type E00.9 Congenital iodine-deficiency syndrome, unspecified Q90 Down's syndrome
Hepatitis: Chronic viral	B18, B94.2, Z22.5	B18 Chronic viral hepatitis B94.2 Sequelae of viral hepatitis Z22.5 Carrier of viral hepatitis
Sleep disorder	F51, G47.0, G47.1, G47.2, G47.3	F51 Nonorganic sleep disorders G47.0 Disorders of initiating and maintaining sleep G47.1 Disorders of excessive somnolence G47.2 Disorders of the sleep-wake schedule G47.3 Sleep apnoea
Inner ear disorder	H80, H81, H83, H90, H91.0, H91.1, H91.3, H91.8, H91.9, H93.0, H93.1, H93.2, H93.3	H80 Otosclerosis H81 Disorders of vestibular function H83 Other diseases of inner ear H90 Conductive and sensorineural hearing loss H91.0 Ototoxic hearing loss H91.1 Presbycusis H91.3 Deaf mutism, not elsewhere classified H91.8 Other specified hearing loss H91.9 Hearing loss, unspecified H93.0 Degenerative and vascular disorders of ear H93.1 Tinnitus H93.2 Other abnormal auditory perceptions H93.3 Disorders of acoustic nerve
Infection: Chronic NOS	A30, A31, A52, B91, B92, B94.1, B94.8, B94.9	A30 Leprosy [Hansen's disease] A31 Infection due to other mycobacteria A52 Late syphilis B91 Sequelae of poliomyelitis B92 Sequelae of leprosy B94.1 Sequelae of viral encephalitis

		B94.8 Sequelae of other specified infectious and parasitic diseases
		B94.9 Sequelae of unspecified infectious or parasitic disease
		E40 Kwashiorkor
		E41 Nutritional marasmus
		E42 Marasmic kwashiorkor
		E43 Unspecified severe protein-energy malnutrition
		E44 Protein-energy malnutrition of moderate and mild degree
		E45 Retarded development following protein-energy malnutrition
		E46 Unspecified protein-energy malnutrition
		E50 Vitamin A deficiency
		E51 Thiamine deficiency
		E52 Niacin deficiency
		E53 Deficiency of other B group vitamins
		E54 Ascorbic acid deficiency
		E55 Vitamin D deficiency
		E56 Other vitamin deficiencies
		E58 Dietary calcium deficiency
		E59 Dietary selenium deficiency
		E60 Dietary zinc deficiency
		E61 Deficiency of other nutrient elements
		E63 Other nutritional deficiencies
		E64 Sequelae of malnutrition and other nutritional deficiencies
Malnutrition and nutritional disorder	E40, E41, E42, E43, E44, E45, E46, E50, E51, E52, E53, E54, E55, E56, E58, E59, E60, E61, E63, E64	
		H16 Keratitis
		H18.1 Bullous keratopathy
		H18.4 Corneal degeneration
		H18.5 Hereditary corneal dystrophies
		H18.6 Keratoconus
		H20.1 Chronic iridocyclitis
		H21.2 Degeneration of iris and ciliary body
		H30.1 Disseminated chorioretinal inflammation
		H31.1 Choroidal degeneration
		H31.2 Hereditary choroidal dystrophy
		H31.3 Choroidal haemorrhage and rupture
		H31.4 Choroidal detachment
		H33.0 Retinal detachment with retinal break
		H33.2 Serous retinal detachment
		H33.3 Retinal breaks without detachment
		H33.4 Traction detachment of retina
		H33.5 Other retinal detachments
		H34 Retinal vascular occlusions
		H35 Other retinal disorders
		H43 Disorders of vitreous body
		H46 Optic neuritis
		H47 Other disorders of optic [2nd] nerve and visual pathways
Eye problems likely to affect vision long-term	H16, H18.1, H18.4, H18.5, H18.6, H20.1, H21.2, H30.1, H31.1, H31.2, H31.3, H31.4, H33.0, H33.2, H33.3, H33.4, H33.5, H34, H35, H43, H46, H47, H49, H50, H51, H53.0, H53.1, H53.2, H53.3, H53.4, H53.6, H53.8, H53.9, H54, Q12, Q13, Q14, Q15	

		<p>H49 Paralytic strabismus  H50 Other strabismus  H51 Other disorders of binocular movement  H53.0 Amblyopia ex anopsia  H53.1 Subjective visual disturbances  H53.2 Diplopia  H53.3 Other disorders of binocular vision  H53.4 Visual field defects  H53.6 Night blindness  H53.8 Other visual disturbances  H53.9 Visual disturbance, unspecified  H54 Blindness and low vision  Q12 Congenital lens malformations  Q13 Congenital malformations of anterior segment of eye  Q14 Congenital malformations of posterior segment of eye  Q15 Other congenital malformations of eye</p>
Cardiac disease: other	I24.8, I24.9, I25.0, I25.1, I25.3, I25.4, I25.6, I25.8, I25.9, I31.0, I31.1, I42.1, I42.2, I42.4	<p>I24.8 Other forms of acute ischaemic heart disease  I24.9 Acute ischaemic heart disease, unspecified  I25.0 Atherosclerotic CVD  I25.1 Atherosclerosis of heart vessel  I25.3 Aneurysm of heart  I25.4 Coronary artery aneurysm  I25.6 Silent myocardial ischaemia  I25.8 Other forms of chronic ischaemic heart disease  I25.9 Chronic ischaemic heart disease, unspecified  I31.0 Chronic adhesive pericarditis  I31.1 Chronic constrictive pericarditis  I42.1 Obstructive hypertrophic cardiomyopathy  I42.2 Other hypertrophic cardiomyopathy  I42.4 Endocardial fibroelastosis</p>
Intestinal disorder	K57, K59.2, K59.3, K90	<p>K57 Diverticular disease of intestine  K59.2 Neurogenic bowel, not elsewhere classified  K59.3 Megacolon, not elsewhere classified  K90 Intestinal malabsorption</p>
Joint or spinal disorder	M07, M13, M15.0, M15.1, M15.2, M15.4, M15.8, M15.9, M40.0, M40.2, M40.3, M40.4, M40.5, M41, M42, M43, M45, M46.0, M46.1, M46.2, M47, M48.0, M48.1, M48.2,	<p>M07 Psoriatic and enteropathic arthropathies  M13 Other arthritis  M15.0 Primary generalized (osteo)arthrosis  M15.1 Heberden's nodes (with arthropathy)  M15.2 Bouchard's nodes (with arthropathy)  M15.4 Erosive (osteo)arthrosis  M15.8 Other polyarthrosis  M15.9 Polyarthrosis, unspecified  M40.0 Kyphosis</p>

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M48.5, M48.8, M48.9, G95.0, G95.1	M40.2 Other unspecified kyphosis M40.3 Flatback syndrome M40.4 Other lordosis M40.5 Unspecified lordosis M41 Scoliosis M42 Spinal osteochondrosis M43 Other deforming dorsopathies M45 Ankylosing spondylitis M46.0 Spinal enthesopathy M46.1 Sacroiliitis, not elsewhere classified M46.2 Osteomyelitis of vertebra M47 Spondylosis M48.0 Spinal stenosis M48.1 Ankylosing hyperostosis M48.2 Kissing spine M48.5 Collapsed vertebra M48.8 Other specified spondylopathies M48.9 Unspecified spondylopathy G95.0 Syringomyelia and syringobulbia G95.1 Vascular myelopathies
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## Appendix 3: Conditions included in PBCI and drug classes included

Condition	Drug class included
Anaemias	Hypoplastic and haemolytic; Iron therapy; Megaloblastic agents.
Anticoagulation	Anticoagulants
Antiplatelet	Antiplatelet agents
Arrhythmias	Antiarrhythmics; Digoxin
Anxiety and tension	Anxiolytics (benzodiazepine; barbiturate); sedatives and hypnotics
Congestive heart failure	Loop diuretics.
Depression	Antidepressants
Diabetes	Insulin; Oral hypoglycemics
Epilepsy	Anticonvulsants
Gastric acid disorder	H2 blockers; Proton pump inhibitors
Hyperlipidaemia	Antilipemic agents
Hypothyroidism	Thyroid replacements
IHD/Angina	Nitrates
IHD/Hypertension	Beta blockers; Calcium channel blockers; ACE inhibitors; Angiotensin II inhibitors; Thiazides; Potassium-sparing agents; Combination antihypertensives; Other hypertensives (clonidine; Hydralazine);
Osteoporosis/Paget's	Alendronate; Etidronate
Parkinson's disease	Antiparkinsonian agents
Psychotic illness	Antipsychotics
Reactive airway disease	Inhaled bronchodilators; Leukotriene inhibitors; respiratory devices
Steroids-responsive conditions	Glucocorticoids (steroids)

## Appendix 4: Evaluating the impact of multiple simultaneous conditions.

In order to calculate weights for the indices presented in this thesis, parameter estimates (log hazards) from Cox regression models of non-cancer mortality were used. For the C3 indices, these models were site-specific and included adjustment for age and stage. In a 'perfect' comorbidity index, the weights might be taken from models after adjustment for other conditions to ensure that the estimates were specific to the individual comorbidity being assessed i.e. independent of the impact of other conditions; and there would be account taken of the possible interaction between conditions. However, because of the small number of non-cancer deaths in some site categories, it was not possible to include these two elements in the Cox regression models. This appendix addresses the questions:

- Does using weights which have been adjusted for the impact of all other conditions simultaneously change the validity of the index?
- Does adding important interactions between variables change the validity of the index?

For this purpose, I used the colorectal cancer cohort only, being the largest cohort with 255 non-cancer deaths. For this work, only conditions that had at least 5 deaths within this cohort were included. This means three conditions were excluded that were included in the actual colorectal cancer site-specific index (for which all-site weights had been substituted). These conditions were alcohol abuse, nutritional disorders and sleep disorders. This meant there were 34 conditions included, and 561 possible pairs of conditions ( $34 \times (34-1)/2$ ).

There were 148 pairs of conditions that occurred with a prevalence of at least 0.5%, 64 with a prevalence of at least 1%, 22 with a prevalence of at least 2% and 9 with a prevalence of at least 3%. All pairs with a minimum of 2% prevalence included at least

one cardiovascular condition (hypertension, cardiac arrhythmias, or other cardiac conditions). The most common were hypertension with other cardiac conditions (4.6%), with metabolic conditions (4.5%), with arrhythmias (4.5%), with coagulopathies (3.6%), previous myocardial infarctions (3.6%) or diabetes with complications (3.3%).

To address the two questions above, the results from three models were compared:

1. The first included age and stage, and one specified condition.
2. The second included age, stage and all 34 conditions.
3. The third included age, stage, all individual conditions as well as all two-way interactions between conditions which themselves had a statistically significant association with non-cancer mortality, and the where the prevalence of the interaction was  $>0.5\%$ .

Compared with models that only adjusted for age and stage, models that further adjusted for all other conditions resulted in condition-specific hazard ratios that were closer to the null (Table 41). In the models that included all conditions, only nine conditions (listed in Table 41) remained independently statistically significantly associated with non-cancer mortality (compared with 21 after adjustments for age and stage). Further adjustment for interactions made little difference, and the AICs were very similar suggesting no improvement in model fit.

Table 42 shows the interaction effects from model 3. Where an interaction term is greater than one, this suggests that the combination of the two conditions is greater than would be expected based on their individual impacts, and vice versa for those less than one. There is no consistent interaction 'effect', in that they ranged from a low of 0.2 for a combination of cerebrovascular disease and paralysis to a high of 1.6 for a combination of respiratory and renal disease. In all cases, the confidence intervals are wide and include the null, so it is possible that there are, in fact, no interactions between any of these conditions.

**Table 41: Hazard ratios and 95% confidence intervals (CI) from Cox regression models of non-cancer death (selected conditions only)**

	Crude		Adj		Adj		Adj	
	HR	95% CI	HR <sup>1</sup>	95% CI	HR <sup>2</sup>	95% CI	HR <sup>3</sup>	95% CI
Cardiac valve disorders	4.1	(2.7-6.3)	2.7	(1.7-4.1)	1.9	(1.2-3.0)	1.9	(1.2-3.0)
Cerebrovascular disease	5.5	(4.0-7.6)	3.3	(2.4-4.6)	2.0	(1.3-3.2)	2.3	(1.4-4.0)
Chronic resp disease	4.1	(3.0-5.7)	2.7	(2.0-3.8)	2.2	(1.6-3.2)	2.0	(1.2-3.2)
Dementia	7.0	(4.2-11.9)	3.1	(1.8-5.3)	2.3	(1.2-4.1)	2.4	(1.3-4.3)
Liver disorders	3.1	(1.6-6.4)	3.3	(1.7-6.8)	3.0	(1.5-6.3)	3.1	(1.5-6.5)
Previous MI	3.9	(2.8-5.5)	2.6	(1.8-3.6)	1.7	(1.1-2.6)	1.6	(0.9-2.9)
Hemi/ para/ quadriplegia	6.2	(4.0-9.6)	3.6	(2.3-5.6)	1.6	(0.9-2.9)	7.1	(1.6-32.2)
Pulmonary circ disorders	4.5	(2.2-9.1)	3.1	(1.5-6.3)	2.1	(1.0-4.7)	2.4	(1.1-5.4)
Renal disorders	5.1	(3.6-7.3)	3.3	(2.3-4.7)	1.6	(1.1-2.5)	1.8	(1.0-3.2)
AIC*					3892.5		3899.4	

<sup>1</sup> adjusted for age and stage (main effects only); <sup>2</sup> adjusted also for all 34 conditions included in CRC index (main effects only); <sup>3</sup> adjusted for age, stage, all conditions and all two-way interactions where the individual conditions were significantly related to non-cancer mortality and where prevalence of the interaction is >0.5%.

\* Akaike Information Criterion

**Table 42 Interaction effects from model 3.**

	Interaction	
	term	95% CI
CVD + Resp disease	1.00	0.4-2.6
CVD + MI	1.33	0.5-3.3
Resp Disease + MI	1.01	0.5-2.3
CVD + paralysis	0.20	0.0-1.0
CVD + renal	0.46	0.2-1.2
Resp Disease + renal	1.60	0.7-3.8
MI + renal	0.90	0.4-2.2

CVD= cerebrovascular disease; MI=previous myocardial infarction

Next, to assess whether weights based on either the model that adjusted for all other conditions, or the model that additionally added interaction terms resulted in a more valid

site-specific index, data from the validation cohort were used. C-statistics and AICs from logistic regression models of one-year all-cause and non-cancer mortality from a baseline model (adjusting for age and stage), and from models that included each of the different indices (the original C3 colorectal cancer specific index, the two new indices specified above, Charlson index and the NCI index (a modified site-specific version of Charlson)) were calculated and compared.

The results showed that the AIC were very similar regardless of which C3-based index was used, and these were slightly lower (suggesting slightly better model fit) than either the Charlson or NCI indices. For example for non-cancer mortality the models that included the C3-based indices had AIC ranging from 2234-2238, while those that included Charlson and NCI were 2248 to 2249.

The c-statistics from logistic regression models of both one-year all-cause and non-cancer death were also very similar (Table 43).

**Table 43: C-statistics from logistic regression models of one-year all-cause and non-cancer death among patients with colorectal cancer.**

	Baseline	Baseline + C3 index	Baseline + C3 index2	Baseline + C3 index3	Baseline + Charlson	Baseline + NCI Index
<b>All-cause death</b>	0.82	0.83	0.83	0.83	0.83	0.83
<b>Non-cancer death</b>	0.74	0.80	0.79	0.79	0.78	0.79

**C3 index** is the main C3 site-specific index presented in the thesis. **C3 index2** includes weights which have been adjusted for impact of all other conditions and **C3 index3** includes weights that have been adjusted for impact of all other conditions as well as interaction terms for all conditions that are independently significantly related to non-cancer mortality, and for which the prevalence of the interaction is >3%

In conclusion, the performance of the C3 index was largely unaffected, regardless of whether or not condition-specific weights had been adjusted for other conditions, or for interactions between conditions. For this reason, the more simple approach to weighting conditions was used.

## Appendix 5: Association of all-cause and non-cancer mortality with categories of C3 and PBC indices

Table 44: Hazard ratios of death by C3 index categories adjusted for age, sex (where relevant) and stage.

	<i>C3 Index Categories*</i>	<i>All-Cause Adj HR**</i>	<i>Non-Cancer Adj HR**</i>	<i>Cancer-Specific Adj HR**</i>
<b>Breast</b>	0	1.0	1.0	1.0
	1	1.5 (1.2-1.9)	2.0 (1.2-3.5)	1.4 (1.1-1.9)
	2	1.8 (1.4-2.3)	3.3 (1.9-5.6)	1.5 (1.1-2.1)
	3	2.3 (1.9-2.8)	5.4 (3.6-8.0)	1.5 (1.2-2.0)
<b>Colorectal</b>	0	1.0	1.0	1.0
	1	1.3 (1.2-1.5)	1.4 (1.0-2.1)	1.3 (1.1-1.5)
	2	1.6 (1.4-1.8)	2.5 (1.8-3.6)	1.5 (1.3-1.7)
	3	2.0 (1.8-2.3)	4.8 (3.6-6.3)	1.7 (1.5-2.0)
<b>Gynaecological</b>	0	1.0	1.0	1.0
	1	1.2 (0.9-1.6)	1.8 (0.5-6.8)	1.1 (0.8-1.6)
	2	1.3 (1.0-1.8)	3.7 (1.4-9.9)	1.2 (0.9-1.7)
	3	1.7 (1.3-2.1)	4.2 (1.8-9.8)	1.5 (1.2-2.0)
<b>Upper GI</b>	0	1.0	1.0	1.0
	1	1.2 (0.9-1.4)	3.7 (1.4-10.2)	1.1 (0.9-1.4)
	2	1.2 (0.9-1.5)	2.3 (0.7-7.6)	1.2 (0.9-1.5)
	3	1.4 (1.2-1.7)	4.8 (1.9-12.2)	1.3 (1.1-1.6)
<b>Urological</b>	0	1.0	1.0	1.0
	1	1.1 (0.8-1.4)	1.7 (0.8-3.5)	1 (0.8-1.3)
	2	1.2 (0.9-1.6)	1.0 (0.4-2.6)	1.2 (0.9-1.6)
	3	1.9 (1.6-2.2)	5.8 (3.6-9.3)	1.5 (1.3-1.9)

\*C3 categories: 0- raw score ≤0; 1-raw score >0 and ≤1; 2- raw score >1 and ≤2; 3-raw score >2

\*\*adjusted for age, sex (where relevant) and stage

**Table 45: Hazard ratios of death by PBCI index categories adjusted for age, sex (where relevant) and stage.**

	PBC Index Category*	All-Cause Adj HR**	Non-Cancer Adj HR**	Cancer-Specific Adj HR**
<b>Breast</b>	0	1.0	1.0	1.0
	1	0.9 (0.8-1.1)	0.9 (0.5-1.6)	1.0 (0.8-1.2)
	2	1.3 (1.1-1.6)	2.1 (1.2-3.6)	1.2 (0.9-1.5)
	3	1.9 (1.5-2.4)	3.6 (2.1-6.1)	1.4 (1.0-1.9)
<b>Colorectal</b>	0	1.0	1.0	1.0
	1	1.0 (0.9-1.1)	0.7 (0.4-1.2)	1.0 (0.9-1.2)
	2	1.0 (0.8-1.1)	1.2 (0.8-1.9)	0.9 (0.8-1.1)
	3	1.3 (1.2-1.5)	3.5 (2.4-5.1)	1.1 (1.0-1.3)
<b>Gynaecological</b>	0	1.0	1.0	1.0
	1	1.0 (0.7-1.2)	0.3 (0-3.9.0)	1.0 (0.8-1.3)
	2	1.1 (0.9-1.5)	2.5 (0.5-12.5)	1.1 (0.8-1.5)
	3	1.5 (1.2-2.0)	6.3 (1.4-27.7)	1.3 (1.0-1.8)
<b>Upper GI</b>	0	1.0	1.0	1.0
	1	1 (0.8-1.2)	1.0 (0.3-3.1)	1.0 (0.8-1.2)
	2	1.2 (0.9-1.5)	1.0 (0.3-3.3)	1.2 (0.9-1.5)
	3	1.2 (1-1.5)	2.8 (1.1-6.8)	1.2 (0.9-1.4)
<b>Urological</b>	0	1.0	1.0	1.0
	1	1 (0.8-1.2)	1.0 (0.6-1.9)	1.0 (0.8-1.2)
	2	1.2 (0.9-1.5)	2.2 (1.1-4.1)	1.1 (0.8-1.4)
	3	1.9 (1.5-2.5)	5.9 (3.2-11.0)	1.5 (1.1-2.0)

\*PBCI categories: 0- raw score ≤0; 1-raw score >0 and ≤1; 2- raw score >1 and ≤2; 3-raw score >2

\*\*adjusted for age, sex (where relevant) and stage

# Appendix 6: Weights for simplified indices.

## Background

In all cases, hospitalisation data were used, and coded as for the full C3 site-specific indices. Conditions that may have been caused by a particular primary cancer were excluded from patients with that cancer as was done for all previous indices (for example, liver and renal disease were excluded from upper GI and urological cohorts respectively):

**Simplified index 1:** This included all conditions used in the C3 indices but the weights were standardised across sites; parameter estimates from the all-site models adjusted for age, site and stage were used.

**Simplified index 2** also used all-site weights as above, but excluded conditions that had adjusted (for age, site and stage)  $HR < 1.2$  for non-cancer death, or had a prevalence less than 2% in the all-cancer cohort. Nineteen conditions were included.

**Simplified index 3** included the same conditions as the second index, but the weights were further simplified. Each parameter estimate was divided by the smallest beta coefficient (or the parameter estimate of the condition with the weakest association with non-cancer death), and then rounded to the nearest integer.

**Table 46: Weights used in calculation of simplified indices 1, 2 and 3. First nineteen conditions (shaded) included in SI 2 and 3.**

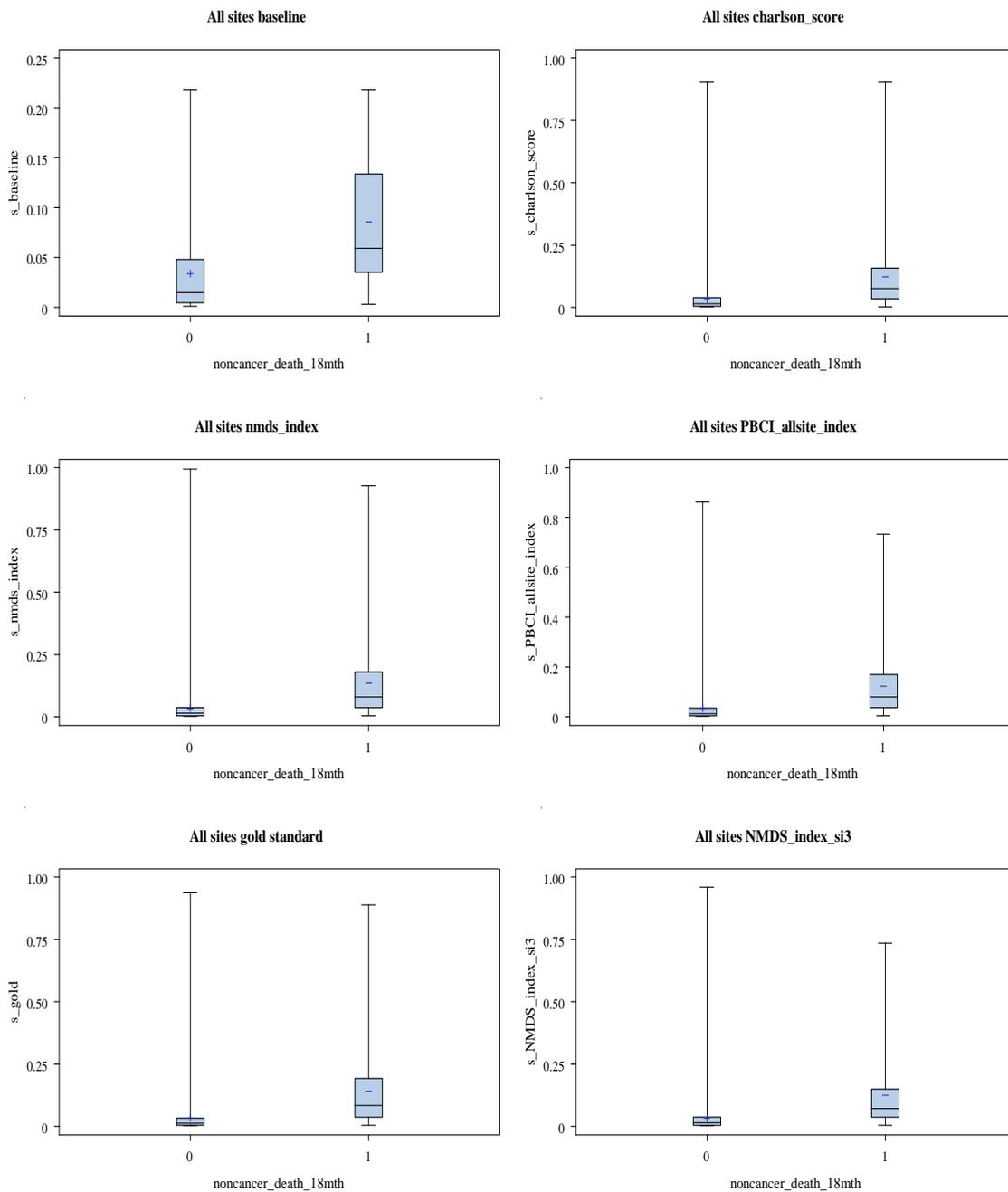
	Weights for SI1 and SI2	Simplified weight for SI3
Angina	0.513	1
Inflammatory bowel disease	0.524	1
Anaemia	0.589	1
Metabolic conditions	0.607	1
Other cardiac conditions	0.617	1
(Major) eye conditions affecting vision	0.627	1
Hypertension	0.723	1
Coagulopathies and other blood disorders	0.749	1
Cardiac Arrhythmia	0.768	1
Obesity	0.831	2
Diabetes with complications	0.877	2

Liver disease	0.923	2
Previous MI	0.934	2
Peripheral vascular disease	0.984	2
Cerebrovascular disease	1.087	2
COPD and asthma	1.091	2
Cardiac valve disorders	1.097	2
Congestive heart failure	1.264	2
Renal disease	1.378	3
Alcohol abuse	1.079	
Anxiety /behavioural disorders	0.566	
Connective tissue disorders	0.507	
Dementia	1.347	
Diabetes without complications	-0.027	
Endocrine disorders	0.767	
Upper GI disorders	0.110	
Inner ear disorders	0.541	
Intestinal disorders	0.108	
Joint and spinal disorders	0.689	
Major psychiatric disorders	0.786	
Nutritional disorders	1.156	
Neurological disorders excl epilepsy	1.063	
Osteoporosis and bone disorders	0.494	
Hemi/ para/ quadriplegia	1.029	
Peripheral nerve/ Muscular disorder	1.197	
Pulmonary circulation disorder	0.950	
Sleep disorders	1.405	
(Chronic) Urinary tract disorders	0.124	
Venous insufficiency	0.704	
Other Malignancy*	0.169	
Chronic hepatitis	0.387	
Epilepsy	1.042	

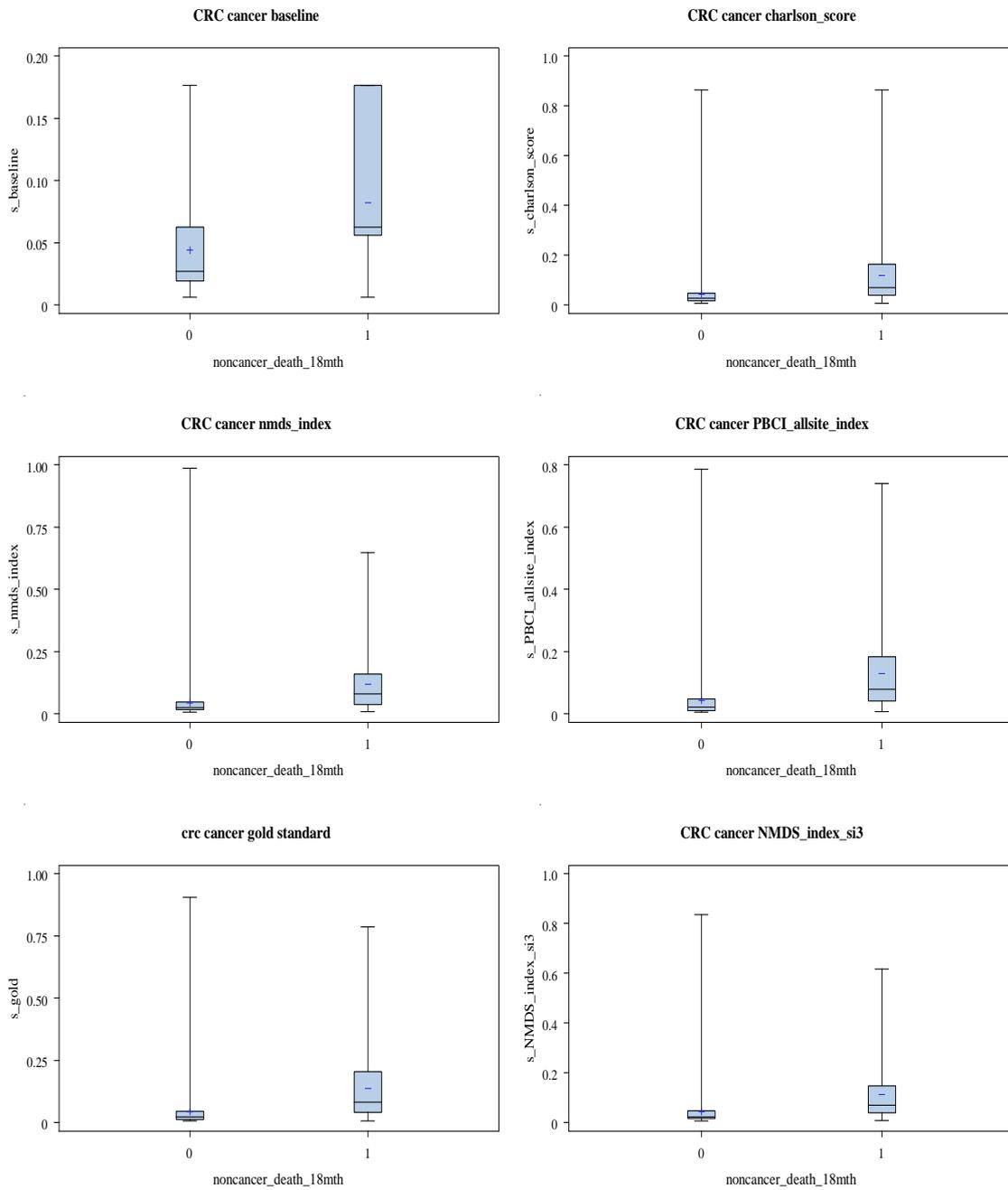
\* Excludes cancers related to primary, secondary cancers and lung, bone, liver or brain cancers

# Appendix 7: Boxplots Predicted non-cancer death Development cohort

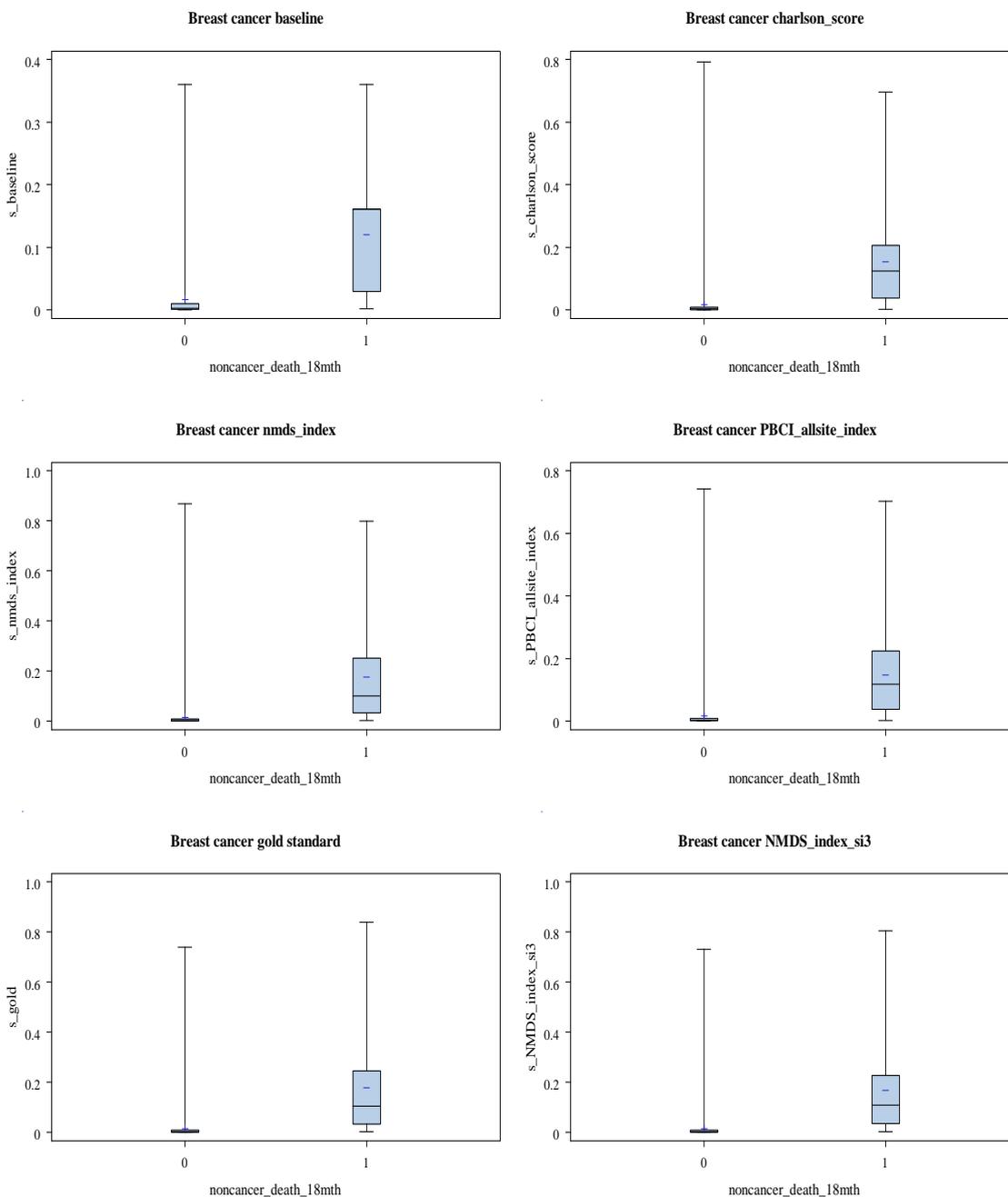
Baseline (age, site and stage) model, and baseline combined with various measures of comorbidity. : All sites combined



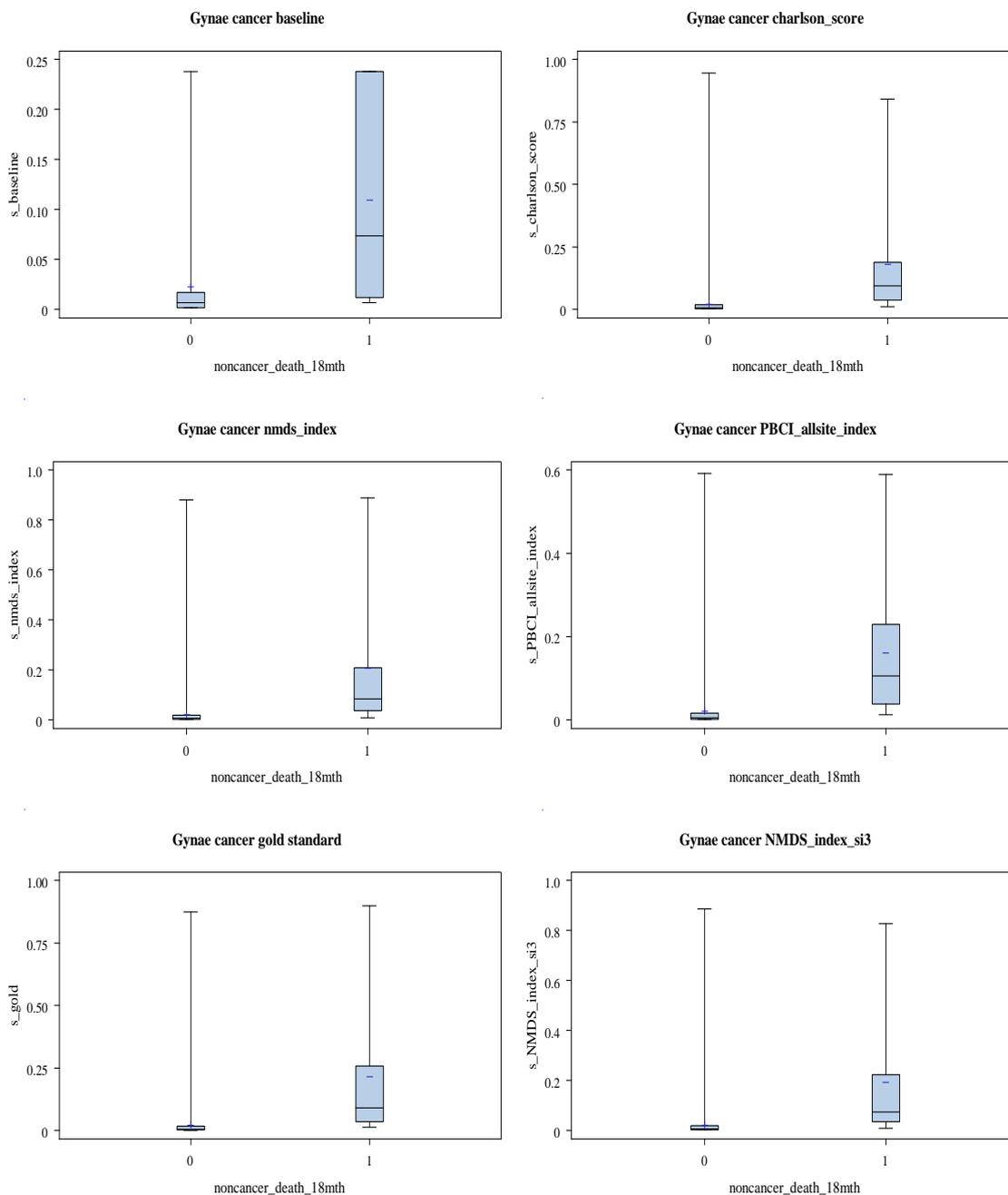
**Boxplots Predicted non-cancer death from baseline (age, sex and stage) model, and baseline combined with various measures of comorbidity. Development cohort: colorectal cancer**



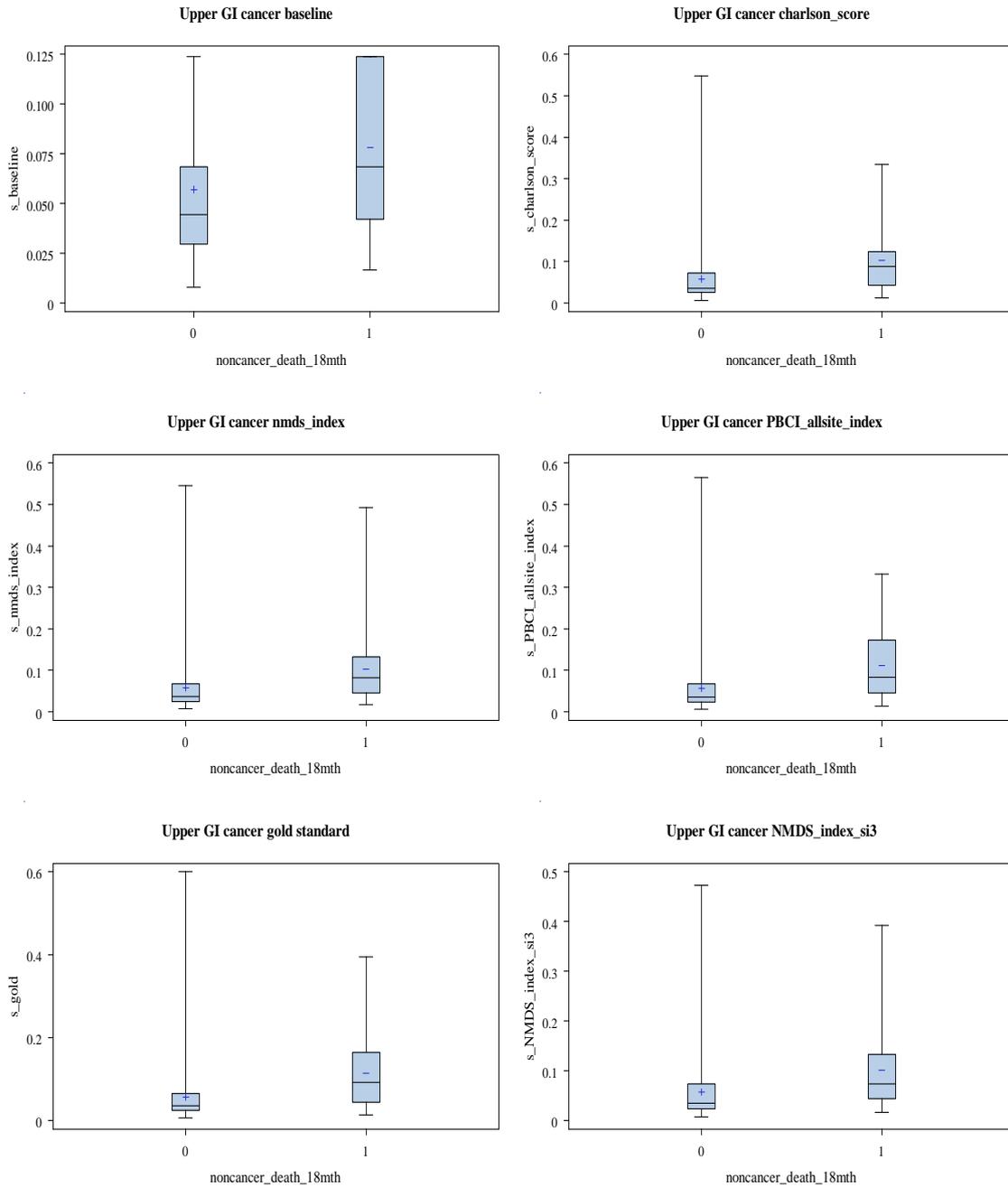
**Boxplots Predicted non-cancer death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Breast cancer.**



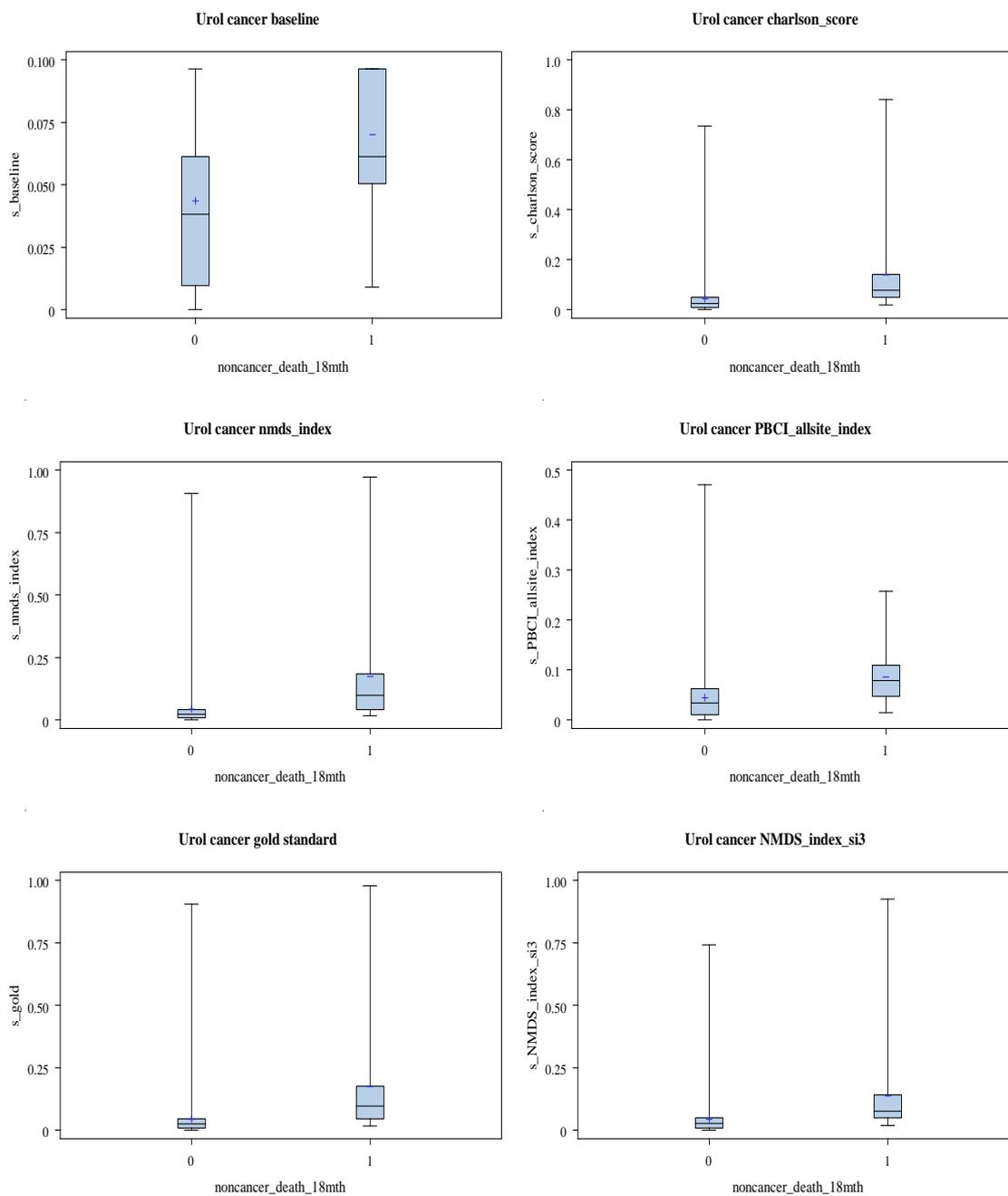
**Boxplots Predicted non-cancer death from baseline (age and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Gynaecological cancers**



**Boxplots Predicted non-cancer death from baseline (age, sex and stage) model, and baseline combined with various measures of comorbidity. Development cohort: upper GI cancer**



**Boxplots Predicted non-cancer death from baseline (age, sex and stage) model, and baseline combined with various measures of comorbidity. Development cohort: Urological cancer**



## **Appendix 8: Publications and papers submitted for publication arising from this thesis (to date)**

Sarfati D, Hill S, Purdie G, Dennett E, Blakely T. How well does routine hospitalisation data capture information on comorbidity in New Zealand? *New Zealand Medical Journal*. 2010; 212 (1310): 50-61.

Sarfati D. Review of methods to measure comorbidity in cancer populations: no gold standard exists. *Journal of Clinical Epidemiology* 2012; 65: 924-933.

Sarfati D, Gurney J, Lim B, Bagheri N, Simpson A, Koea J, Dennett E. Identifying important comorbidity among cancer populations using administrative data: prevalence and impact on survival. *Asia-Pacific Journal of Clinical Oncology* 2013;doi: 10.1111/ajco.12130.

Sarfati D; Gurney J; Stanley J; Salmond C; Crampton P; Dennett E; Koea J; Pearce N. Cancer site-specific comorbidity indices provided valid alternative to Charlson and NHI indices. *Journal of Clinical Oncology* 2014;**67**(5):586-95.

Sarfati D, Lim BT, Gurney J, McSherry C. Development of a Pharmacy-based Comorbidity Illness Index for Patients with Cancer. Paper under review.

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