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Optimising the measurement of comorbidity for a South Australian colorectal cancer population using administrative data

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Abstract:

Rationale and objectives: In epidemiological research, it is essential to account for the confounding effects of factors such as age, stage and comorbidity for accurate prediction of cancer outcomes. There are several internationally developed and commonly used comorbidity indices. However, none are regarded as the gold standard method. This study will assess and compare the predictive validity of established indices for use in a South Australian (SA) colorectal cancer (CRC) population against a local index. Furthermore, the prognostic influence of comorbidity on survival will be investigated.

Methods: A population-based study of patients diagnosed with CRC from 2003 to 2012 and linked to in-hospital data to retrieve comorbidity information was conducted. The predictive performance of established indices, Charlson comorbidity index (CCI), National Cancer Institute comorbidity index (NCI), Elixhauser comorbidity index (ECI), and C3 index was evaluated using the Fine and Gray competing risk regression and reported using measures of calibration and discrimination, area under the curve (AUC) and Brier score. Furthermore, to identify the optimal index, a local CRC comorbidity index (CRCCI) was also developed and its performance compared to the established indices.

Results: Comorbidity models adjusted for baseline covariates (age, sex and stage), showed that all indices were good predictors of two-year non-cancer mortality as measured by the AUC (CCI: 0.738, NCI: 0.742, ECI: 0.733, C3: 0.739). CRCCI had similar mortality prediction as established indices (CRCCI: 0.747). There was a significant increase in cumulative risk of noncancer and CRC-specific mortality with increase in comorbidity scores. The two most prevalent comorbidities were hypertension (uncomplicated) and diabetes.

Conclusions: The existing indices are still valid for adjusting for comorbidity and accurately predicting mortality in SA CRC population. Internationally developed indices are preferred when policymakers and researchers wish to compare local study results with those of studies (national and international) that have used these indices. Comorbidity is predictor of mortality and should be considered when assessing survival in a CRC population.

Keywords

Colorectal cancer, comorbidity, prediction models, survival.

Introduction

Cancer survival data are used to indicate the effectiveness of healthcare, with adjustments for extraneous factors such as comorbidity which may confound comparisons across different groups. Comorbidity negatively affects cancer care and outcomes [1-4], with some researchers suggesting that comorbidity may be as important as cancer stage for predicting survival [5,6]. People with comorbidity are less likely to receive recommended treatment and have poorer colorectal cancer (CRC) survival [7,8]. To predict survival differences across population subgroups, it is therefore essential that we can accurately measure and control for their comorbidity burden.

This study defined comorbidity as additional chronic health conditions coexisting with CRC. A comorbidity index is a means of aggregating comorbid conditions (referred to here as comorbidities) to predict and statistically adjust for their association with mortality. Several comorbidity indices have been developed for use at a population level, although the best index to use for cancer populations remains unclear [9-11]. Also, the predictive validity and utility of the commonly used indices have not been tested in a South Australian (SA) CRC

population. The Charlson Comorbidity Index (CCI) and the Elixhauser Comorbidity Index (ECI) are widely used indices in cancer populations [12,13].

The CCI was developed in the 1980s on a cohort of patients admitted over a month to a single New York hospital, by measuring the association of comorbidity with 1-year all-cause mortality. Klabunde *et al.* [14] later updated the CCI by redeveloping the assigned weights in breast and prostate cancer populations, with comorbid conditions identified from both administrative and pharmacy-based data [14]. This index was developed separately for each data source and cancer site and was referred to as the National Cancer Institute (NCI) index. The NCI was later updated and simplified by combining the administrative and pharmacy-based data to form a single index referred to as the combined NCI [15]. The combined NCI was developed for breast, prostate, colorectal and lung cancer site. Both versions of NCI have been shown to have similar performance with CCI [14,15].

In 2011, Quan and colleagues redeveloped weights for Charlson comorbidities using data from six countries and showed that there were differences in the weightings of each comorbid condition. Five of the comorbidities in CCI were no longer having a negative impact on mortality and therefore excluded from the updated CCI [16]. This finding is evidence that the weights and comorbid conditions in the original CCI may no longer be valid in some populations and therefore motivation for validation of indices before use outside populations of their development. Quan's index is not widely used, and it was therefore not part of the indices to be validated in this study.

The ECI was also developed using adult, nonmaternal patients admitted in 492 acute care hospitals in California and included 30 unweighted conditions which were associated with an increased hospital stay, hospital charges and mortality. However, conditions were not

simplified into a single index. ECI was later weighted according to their association with in-hospital mortality by van Walraven *et al.* [17].

The C3 index was developed in a New Zealand population diagnosed with cancer between 2006 and 2008, using data from the population-based cancer registry linked to hospital administrative data. Comorbidities were weighed based on their association with non-cancer mortality. The weights were summarised into a single measure to form a comorbidity index. C3 performed better than both the CCI and NCI [18].

Studies indicate that the ECI and C3 have superior predictive ability for mortality than the CCI [18-20]. The improved performance could be due to ECI and C3, including more and relevant conditions, for a cancer population compared to the CCI. For example, 30 comorbidities were used in the ECI and 42 in the C3 CRC-specific index compared to 17 in the CCI.

Given the existence of these established and widely used indices, it was essential to find which index would be optimal for mortality prediction in a SA CRC population. To confidently use these indices, they ought to be validated first in this population. Assuming that these indices are valid for use in the SA CRC population, then this provides a platform for comparison of our work with other international studies using the same indices. This study further extends the search for an optimal index by developing a local CRC comorbidity index (CRCCI). Despite the widespread use the established indices they have well known constructional flaws, for example, the CCI and ECI did not have an index disease. Therefore, it is plausible to expect a local index to perform better than international indices because the impact of comorbidity conditions on mortality may depend on the index disease. Also, it is expected that the comorbidity profile will also depend on the index disease; for example, chronic obstructive pulmonary disease (COPD) is prevalent in lung cancer.

In addition, the prevalence and profile of the comorbidities for an index disease can differ across different countries. This is particularly applicable to the C3 index which is relatively recent, however, it has not been validated with Australian data and its generalisability to Australia is uncertain due to potential differences in demographics, cultural practices and disease profiles.

Also, the C3 development only included diagnoses between 2006 and 2008, whereas the data used in this study included diagnoses between 2003 and 2012. It is therefore possible that the most prevalent conditions, their type and impact on mortality may have changed since then. Without validation of previous indices in our population, there is a lack of evidence of whether an index developed in one population may have the same predictive ability in another population which may have a different disease profile. There have been tremendous achievements in developing CRC management therapies (surgery, radiotherapy and chemotherapy) since the development of the established indices leading to better survival rates. It is, therefore, reasonable to investigate whether applying these established indices in data from the 21st century reflects the current standard of care for SA CRC patients. With improvements in medical technology, there is an expectation that the weights of established indices would be different from those computed for a custom index.

Therefore, we aim to identify the optimal comorbidity index for use in SA CRC population through firstly validation of the accuracy of CCI, ECI, NCI and C3 in predicting non-cancer mortality and secondly developing a local index whose predictive performance would be compared to that of established indices. The prevalence of comorbid conditions generally increases with age [21,22]. As CRC is more common in elderly populations who are likely to have a high prevalence of comorbidity [9] and a higher risk of dying from other causes, this study will take competing risks into account.

Methods

Data sources

Data for this study were obtained from the South Australian Cancer Registry (SACR), which receives legally mandated cancer notifications under the Health Care Act (2008) for all invasive cancer diagnoses and deaths for the South Australian population (except for non-melanoma skin cancers) [23]. These data are coded using the International Classification of Diseases-Oncology (ICD-O-3). SACR is routinely linked to official death records and the Australian National Death Index and codes causes of death using the ICD–10 classification system. SACR data were linked to the Integrated South Australian Activity Collections (ISAAC) database which collects ICD-10-AM coded inpatient hospital separations from SA hospitals. A combination of probabilistic and deterministic linkage methods was used by SA-NT DataLink and the SA Government Epidemiology staff, replacing personal identifiers with unique project linkage keys in the de-identified data file for researchers.

Study population and data variables

This study included all confirmed cases (n=7008) of primary CRC (ICD-10 C18-20) diagnosed from 2003 through 2012 with a recorded Australian Clinico-Pathological (ACPS) (approximately two-thirds of cases). ACPS is an extension of the Duke's staging system which includes provision for coding distant metastases. Cases aged under 40 years were excluded from the study, as comorbidity and CRC were uncommon in these younger ages. Comorbidity data were abstracted from ICD-10-AM diagnosis codes for hospital records collected between 2003 and 2013 and were linked to all identified cases in SACR.

Data were extracted from the SACR for other demographic and clinical characteristics including sex, tumour grade, degree of spread (local, regional, distant and unknown) and diagnostic period (2003–2007 or 2008–2012). Remoteness of residential area was classified according to the Accessibility/Remoteness Index of Australia 2006, derived from residential postcode at diagnosis and classified as major city, inner regional, outer regional or remote [24].

Socioeconomic status (SES) was indicated using a Socio-Economic Index for Areas called the Index of Relative Socioeconomic Disadvantage (IRSD) 2006. This was derived from residential location (in this study, at the level of the census Collection District). The IRSD represents the average SES of specified Collection Districts (CDs) and based on characteristics such as household income, education level and unemployment rate. SES was categorised in quintiles (Q1: most disadvantage; Q5 least disadvantage) [25]. Death details were extracted from the SACR and used to define outcomes of interest (i.e., non-cancer deaths, CRC deaths, and all-cause mortality). For all analyses, follow-up was restricted to two years after diagnosis of CRC or at their date of death, if that occurred earlier.

Statistical analysis

Validation of comorbidity indices

To validate the established indices (CCI, NCI, ECI and C3), ICD-10-AM coded in-hospital diagnoses which occurred five years before or at the date of primary CRC diagnoses were first mapped to ICD-10-CM coding. The mapped diagnoses were then used to identify comorbidities listed in the comparison indices, using previously validated coding algorithms for each of the four indices [26]. Binary variables were generated, indicating the presence and absence of each comorbid condition in the entire cohort. To calculate the total scores for the

193 respective indices, the weights from the original comorbidity indices were applied to the
194 identified conditions. For CCI, weights originally developed by Charlson et al. [12]; NCI based
195 on cancer-specific weights developed for CCI conditions by Stedman et al. [27] for a CRC
196 cohort; ECI based on weights developed by van Walraven et al. [28]; and C3 based on weights
197 developed by Sarfati et al. [18] for a CRC cohort, respectively. All cancer-related diagnosis
198 codes were excluded when calculating these comorbidity index scores. For each index, the
199 total individual score was calculated as the sum of weights for all conditions identified for
200 each person. In the analyses, comorbidity indices were treated as continuous variables. The
201 distribution of comorbidity scores for each index was compared between all indices.

202 To assess the ability of each index to predict 2-year non-cancer mortality and determine
203 which index would provide the best measure and adjustment of comorbidity, we fitted the
204 Fine and Gray competing risk regression models for CCI, NCI, ECI and C3 respectively.
205 Models of comorbidity indices adjusting for baseline covariates (age, sex and stage) and
206 models with just baseline covariates were compared using measures of discrimination and
207 calibration, area under the ROC curve known as the AUC and Brie score. The AUC is an
208 equivalent of the c-index and is used to assess the discrimination of the model with
209 AUC > 0.7 indicating good discrimination accuracy. Brie score measures both discrimination
210 and calibration with lower values indicating the best model. Proportional hazards assumption
211 was assessed using Schoenfeld's residuals plotted against failure time for each factor and
212 found to be met. All analyses were done using *riskRegression* and *cmprsk* packages in R
213 version 3.5.1. statistical software.

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Development of CRCCI

A further comparison of the established indices with a locally developed CRCCI was done to optimise the measurement of comorbidity. Although the split sample method has been commonly considered for developing and validating the comorbidity index, this method was not used due to low non-cancer deaths and large numbers of predictors involved in the index development. Instead, the entire dataset (n=7008) was used to develop a new CRCCI to avoid overfitting. A bootstrap resampling method was used to generate a validation cohort based on multiple samples (1000 iterations) of the development cohort.

A list of comorbidities identified through literature review and those used in prior indices (CCI, NCI, ECI and C3) was considered potentially relevant for the cancer population. The most common chronic conditions in Australia identified by Australian Institute of Health and Welfare were also considered [29]. Conditions were identified using mapped ICD-10-CM codes recorded for in-hospital diagnoses occurring five-years before or at the date of primary CRC diagnosis. Binary variables were generated, indicating the presence or absence of each comorbid condition. Conditions with a prevalence of less than 0.5 per cent and cancer-related diagnosis codes were excluded, leaving a total of 35 comorbidities considered in the index development.

Fine and Gray competing risks regression models were separately developed for each comorbid condition to avoid overfitting [30,31]. To determine the association with 2-year non-cancer mortality, they were adjusted for age, sex and stage. Deaths due to cancer occurring within the 2 years after CRC diagnosis were considered as competing risks.

The log sub-distribution hazard ratios (sHRs) (beta coefficients) from these models were used as weights for each condition, regardless of their statistical significance. Of 35 comorbidities, five had negative beta coefficients and were given a weight of zero. Comorbidity scores for

each person were calculated as the sum of weights of all present conditions present. This score was referred to as the CRCCI score and was used in subsequent analyses as a predictor (a continuous variable). CRCCI scores were categorised into the following groups for descriptive analysis; score = 0 (indicating no comorbidity), $0 < \text{score} < 1$, $1 \leq \text{score} < 2$, $2 \leq \text{score} < 3$ and score ≥ 3 (indicating severe comorbidity burden). Further, to explore the distribution of comorbidity in the cohort, comorbidities were only reported as counts for descriptive analysis.

To internally validate the CRCCI and compare its predictive accuracy with a baseline model (i.e., a model with only age, stage and sex as predictors) and with comparison indices (CCI, NCI, ECI, C3), 1000 samples of the development dataset were generated using a bootstrap method with replacement. Calibration plots for each model were developed from the Fine and Gray competing risk model with 2-year non-cancer mortality as the outcome. The AUC and Brier score were computed for each model using the *cmprsk* library and *plotCalibration* packages in R following a method used by Zhang *et al*. [32]. The *plotCalibration* packages also calculate differences in AUC and Brier scores with their 95% confidence interval (CI). The *plotCalibration* uses k-fold cross-validation method where k samples of equal sizes are generated from the original sample. One sample is then used for validation and k-1 used as the development sample. Single values of AUC or Brier score are then reported as the average of all measures for the k-1 samples.

AUCs and Brier scores for the baseline model and for models that also included each index separately were compared, to evaluate the performance of CRCCI against the baseline model and other comparison indices.

To determine whether there was an increase in the predictive ability between indices and baseline model, the percentage change between the model's AUCs was calculated using the formula below:

$$\% \text{ change between AUCs} = [(AUC_{baseline} - AUC_{CRCCI})/AUC_{baseline})] \times 100$$

First looking at the difference between baseline model's AUC and AUCs from extended models (models that including different indices, i.e. baseline + CRCCI, baseline + NCI, baseline + CCI, baseline + C3 and baseline + ECI) then between CRCCI and other indices.

Effect of comorbidity on non-cancer and cancer-specific survival

To explore the role of comorbidity in cancer survival, further analyses were undertaken to assess the differences between non-cancer and cancer-specific survival according to comorbidity index score using the CRCCI, using the same bootstrap samples used for validation. The Fine and Gray competing risk regression analysis was used to test whether there were significant differences between those with and without comorbidity. The sHRs indicated the cumulative risk of death due to CRC and non-cancer mortality, respectively. However, the sHR should be interpreted carefully as the measure does not have a direct or simple interpretation compared to cause-specific HR [33].

Descriptive analyses of the CRC cohort were undertaken to describe their demographics, clinical characteristics and numbers of comorbidities. This was undertaken by summarising normally distributed variables using means and standard deviations and skewed distributions by medians and interquartile ranges (IQRs). Categorical variables were cross-tabulated and summarised as counts and percentages. Analyses were performed using Stata version 14 (StataCorp, College Station, Texas) (StataCorp, 2015) and R version 3.5.1 [34]. The study was

reviewed and approved by the Human Research Ethics Committees of the South Australian Health Department and the University of South Australia.

Results

Descriptive analyses

Descriptive characteristics of CRC cases in the development dataset are shown in Table 1. A total of 7008 cases were included with a median age of 70 years (IQR = 61–77), of whom 56% were male. By the end of a two-year follow-up, 1806 cases had died, with 82.5% of deaths attributed to CRC, 4.4% to other cancers and 13.1% to non-cancer causes.

Insert Table 1 here

Validation of comorbidity indices

Table 2 shows the predictive ability and model fit of the internationally developed and established indices compared with the baseline model using the original sample. The addition of the CCI, NCI, ECI and C3 to the baseline model showed similar improvements in predictive accuracy for 2-year non-cancer mortality (see Table 2). AUCs of the international indices were all above 0.7, indicating that they are good predictors of non-cancer mortality. AUCs for all models ranged between 0.730 and 0.747 for this outcome with NCI having the highest AUC (0.748) and lowest Brier score (0.0293).

Insert Table 2 here

Development of CRCCI

Table 3 shows the prevalence of each comorbid condition included in the development of the CRCCI along with their sHRs for 2-year non-cancer mortality and associated beta coefficients (for use as weights).

Insert Table 3 here

The prevalence of comorbidity ranged from a low of 0.5% for osteoporosis to a high of 9.7% for hypertension (uncomplicated). The distribution of comorbidity scores differed slightly between indices. The CRCCI included more conditions and identified more people with at least one comorbidity.

The CRCCI scores in the development cohort ranged between 0 (for those without comorbidity) to 8.7 (for those with comorbidity) (median=0.73; IQR=0.37–1.32). For the CCI, NCI, ECI and C3, the ranges of CRCCI scores were 0–8, 0–8.2, 0–7.9, and 0–10.3 respectively, with median (and IQR) scores of 1 and higher (1–2), 1.37 (1.37–1.89), 0.76 (0.37–1.21) and 1.07 (0.63–1.93) respectively. The algorithms used for weighting the comorbid conditions differed between indices.

Internal validation of CRCCI and comparison with CCI, ECI, NCI and C3.

Table 4 indicates the predictive ability of all indices. The CRCCI performed marginally better than the comparison indices (although confidence intervals overlapped), as demonstrated by the lowest Brier score and highest AUC for predicting two-year non-cancer mortality (Brier score = 0.0292 and AUC = 0.749). The minimal increase in predictive ability (AUCs) when adding the respective comorbidity indices ranged from 1.1% for ECI to 3.3% for CRCCI. Differences in AUCs between baseline and extended CRCCI models indicate a 3.3% increase in the AUC and therefore in the prediction of non-cancer mortality. However, the percentage

gain between the CRCCI AUC and comparison indices AUCs was marginal, ranging between 0.8% against the NCI to 1.9% against the ECI.

Insert Table 4 here

Effect of comorbidity on non-cancer and cancer-specific survival

Table 5 indicates that sHR for non-cancer mortality in the group with CRCCI scores greater than or equal to 3 was 10.5 times that of the sHR of the group without comorbidity (crude sHR = 10.5; 95 % CI: 6.87–16), with a progressive increase indicated with increasing CRCCI scores. The crude sHR for CRC mortality, by comparison, did not show a progressive increase with increasing CRCCI score, with peak sHRs of 1.40; 95% CI: 1.17-1.67 and 1.60; 95% CI: 1.22-2.10 applying to the middle two score groups and little if any increase in sHR evident for scores less than 1 and greater than or equal to 3 (see Table 5).

Insert Table 5 here

Discussion

This study aimed to identify the optimal comorbidity index for use in a SA CRC population by firstly assessing the validity of CCI, NCI, ECI and C3 indices for predicting 2-year non-cancer mortality. Secondly, the search for an optimal comorbidity index is extended to the development of a local index whose predictive performance was compared against the four established indices. The prognostic effect of comorbidity on survival was also explored. Our results show that the internationally developed and commonly used indices CCI, NCI, ECI and C3 are still valid predictors of mortality in SA CRC population and can provide accurate adjustments of comorbidity locally. When predicting non-cancer survival, additional adjustment for comorbidity to that from age, sex and stage increased the predictive accuracy of the models regardless of the comorbidity index used.

Further efforts of optimising the measurement of comorbidity included development and comparison of a local index CRCCI to established indices. The prevalence rates of comorbidities differed slightly between indices and from those generally reported in the literature. For example, one of the conditions prevalent in the study by Charlson et al [12] and with the strongest negative effect on mortality was AIDS. However, in this study, AIDS was not included in CRCCI due to its prevalence being less than 0.5 %. The improved management of this condition has resulted in better survival, which is reflected in a reduction in the assigned weights. In the original CCI, AIDS had a weight of 6, based on its relative risk of mortality [12]. In the updated CCI [16], the weight decreased to 4.

The results also show differences in the prevalence of comorbidity between the present CRC cohort and other CRC cohorts reported in the comorbidity literature. Previous studies reported an average of three or more comorbidities in elderly CRC populations [20,35]. In the present study, 66% of CRC cases had no comorbidity, and those with comorbidity had a mean of two conditions.

In the present study, comorbidities included in CRCCI presenting the greatest risk of non-cancer mortality (weights) included renal failure, congestive heart failure, hypothyroidism, blood loss anaemia and cardiovascular disease (CVD). These weights differed from those derived for other comparison indices using similar weighting systems. In general, weights redeveloped in the present study were higher than those in CCI and consistent with those for the ECI, C3 and NCI indices. These higher weights may indicate differences in the severity of comorbidities and their effect on mortality in an ageing SA CRC population compared to the populations in which the established indices were developed. As such, it is suggested that the development of locally-based indices is desirable where the identification of such variation is relevant.

The comparison of CCI, NCI, ECI and C3 to a local index CRCCI, showed that CRCCI performed marginally better or as well as the comparison indices when predicting non-cancer mortality. The modest improvement in predictive ability between indices (all indices had quite similar performance) indicates that inclusion of a comorbidity index may be more important than the type of index used [10,18]. The finding that established indices had a comparable fit and predictive ability as CRCCI (with marginal differences in the magnitude of AUC performance values), makes established indices suitable alternatives for measuring comorbidity within the SA CRC population. The finding of a quite similar performance from the customised index is consistent with previous studies comparing the performance of customised indices against the CCI and ECI [20,36-38]. The similarity in the performance for all indices could be due to that in this CRC cohort, comorbidity had less impact on cancer mortality due to mortality being driven more by tumour characteristics or cancer due to poor prognosis of CRC. It will be interesting to see how the different indices perform in a cancer site with good prognoses such as breast cancer or prostate cancer.

Although the results indicated a similar performance of all indices, it is reasonable to expect that the performance of the CRCCI could be improved by including pharmaceutical data. A study by Klabunde et al. [15], in which a comorbidity index was developed based on comorbidities identified from administrative and pharmaceutical data, demonstrated that the combined index performed significantly better than indices developed from these sources separately [14,15]. As such, the inclusion of pharmaceutical data may have the potential to identify more people with comorbidity who may be missed when only in-hospital data is used and improve the predictive accuracy of the present CRCCI.

This analysis confirmed that comorbidity negatively affects the survival of CRC patients. The cumulative risk of non-cancer and CRC mortality increased with increasing comorbidity

index scores. However, there was a much higher (and significant) increase in mortality risk for non-cancer mortality than CRC mortality at lower levels of comorbidity i.e. those with a score greater than zero but less than one. For CRC, the risk of mortality in those having a comorbidity score less than one was not that different to the group with no comorbidity (sHR = 1 vs 1.03). For non-cancer mortality, the risk of mortality in the group with a comorbidity score less than one was much higher compared to those without comorbidity (sHR = 1 vs 1.44). Overall, the cumulative risk of mortality was more pronounced for non-cancer mortality compared to cancer-specific mortality.

One of the strengths of this study was combining comorbidities found in the three comparison indices into forming the customised index. The combination increased the potential for more relevant conditions to be identified and improving the content validity of the index. For example, the CCI does not include AMI, mental health conditions and hypertension, which are part of the ECI and C3, and therefore considered as potential candidates in the development of CRCCI. In this population, hypertension was the most prevalent condition. The two conditions, AMI and hypertension, had a negative impact on survival and therefore included in the final customised CRCCI. However, psychoses, anxiety and behavioural disorders, and depression had either prevalence of less than 0.5% or a protective effect (negative coefficients) and were excluded from the CRCCI.

This study used competing risk analysis rather than cause-specific Cox regression, which may provide a more accurate and more detailed estimate of the absolute risk of mortality in the presence of competing risks [17,39,40] . In the South Australian context, another strength was access to data for a CRC cohort where approximately 70% had a record of the stage. Before June 2017, Australian cancer registries were not mandated to include cancer stage. While every attempt is being made to include stage on cancer records in South Australia, limitations

in resources have not yet provided this cohort complete staging information. Restricting this study to staged cases may have affected the representativeness of results.

The use of linked administrative data, in which the quality of coding of hospital diagnoses and procedures has been previously validated in Australia, is another strength [41]. The identification of comorbidity based on the ICD-10 coding system is a further strength, in that it can be easily replicated or applied in other populations using the same ICD coding system. This study confirms the utility of administrative data to identify comorbidity that is predictive of mortality.

Conclusions

The internationally developed and commonly used indices are valid predictors of non-cancer mortality. This indicates that these established indices can still be used to measure comorbidity and predict mortality in SA CRC population adequately. This will allow policymakers and researchers to compare the role of comorbidity in local cohort data with that observed in international cohorts that have used previously developed and commonly used indices. This finding is important and gives us confidence in the results of previous studies that have used comparison indices to measure and adjust for comorbidity in cancer research.

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Conflict of interest.

The authors declare no conflict of interest.

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Ethics approval and consent to participate

The study was reviewed and approved by the Human Research Ethics Committees of the South Australian Department of Health and the University of South Australia. Due to the retrospective nature of the study and the present research data being non-identifiable, a waiver of patient consent was granted. All methods and analysis in this study were carried out in accordance with the Declaration of Helsinki and following the set guidelines and regulations established by both ethics' committees.

589 **Table 1: Descriptive characteristics of the development cohort**

Demographic and clinical factors	N (%)
Total	7008 (100)
Age in years (mean, ± SD)	68.8 (±10.9)
Sex	
Male	3951 (56.4)
Female	3057 (43.6)
Period	
2003-2007	4219 (60.2)
2008-2012	2789 (39.8)
Geographic remoteness	
Major cities	4939 (70.5)
Regional	1784 (25.5)
Remote	283 (4.04)
Missing	2 (0.03)
Areal level SES	
Q1 (Most disadvantaged)	1806 (25.8)
Q2	1808 (25.8)
Q3	710 (10.2)
Q4	1764 (25.2)
Q5 (Least disadvantaged)	909 (13.0)
Missing	11 (0.16)
Differentiation	
Well	281 (4.01)
Moderate	4784 (68.3)
Poorly/undifferentiated	1398 (20.0)
Unknown	545 (7.78)
ACPS stage	
A	1190 (17.0)
B	2069 (29.5)
C	2218 (31.6)
D	1531 (21.9
Number of comorbidities	
0	4543 (63.9)
1	1391 (19.6)
2	611 (8.6)
3+	570 (8.0)
Died at 2 years post diagnosis	1806 (25.8)
Non-cancer deaths	236 (3.37)
CRC deaths	1490 (21.3)
Other cancer deaths	80 (1.14)

590 † SES: socio-economic status, ACPS: Australian Clinico-Pathological Staging; CRC: colorectal cancer.

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Table 2: Predictive validity of baseline model and models of established comorbidity indices CCI, NCI, ECI and C3 adjusted for baseline covariates

Models	**non-cancer mortality**	
	AUC (95% CI)	**Brier score**
Baseline (BL)	0.730 (0.72 - 0.74)	0.0300
BL + NCI	**0.748 (0.74 - 0.76)**	**0.0293**
BL + C3	0.747 (0.74 - 0.76)	0.0294
BL + CCI	0.744 (0.73 - 0.76)	**0.0293**
BL + ECI	0.738 (0.73 - 0.75)	0.0297

† Baseline covariates: age, sex and stage; Baseline model: model with baseline covariates – Bold entries represent greatest improvement from baseline model. AUC: area under the curve; CCI: Charlson comorbidity index, NCI: National cancer institute comorbidity index, ECI: Elixhauser comorbidity index, and C3: cancer care and comorbidity

Table 3: Prevalence of comorbidity as a percentage of all cases, and assigned weights based on 2-year non-cancer mortality

Comorbidities	N (%)	sHR	Beta coefficients (CRCCI weights)
Total cohort	**7008 (100)**		
Hypertension (uncomplicated)	681 (9.72)	1.44	0.37
Intestinal disorders	376 (5.37)	1.29	0.26
Diabetes (uncomplicated)	366 (5.22)	1.35	0.30
Cardiac arrhythmias	330 (4.71)	1.61	0.48
Diabetes (complicated)	260 (3.71)	1.78	0.58
Other cardiac conditions	246 (3.51)	2.07	0.73
Metabolic disorders	237 (3.38)	1.85	0.62
Chronic obstructive pulmonary disease	220 (3.14)	2.43	0.89
Alcohol abuse	170 (2.43)	1.99	0.69
Congestive heart failure	128 (1.83)	3.25	1.18
Angina	118 (1.68)	1.73	0.55
Acute myocardial infarction	105 (1.50)	1.10	0.09
Peptic ulcer	93 (1.33)	1.92	0.65
Cerebrovascular diseases	90 (1.28)	2.59	0.95
Bowel disease	89 (1.27)	1.20	0.19
Renal failure	76 (1.08)	5.90	1.77
Obesity	69 (0.98)	2.11	0.75
Blood loss anaemia	67 (0.96)	2.83	1.04
Valvular disorders	61 (0.87)	2.13	0.76
Sleep disorders	56 (0.80)	1.74	0.56
Weight loss	53 (0.76)	2.21	0.79
Paralysis	50 (0.71)	2.52	0.92
Dementia	49 (0.70)	1.55	0.44
Urinary tract disorders	49 (0.70)	1.35	0.30
Peripheral vascular disease	47 (0.67)	2.31	0.84
Eye problems	47 (0.67)	1.57	0.45
Coagulopathy	45 (0.64)	1.77	0.57
Other neurological disorders	42 (0.60)	2.11	0.75
Hypothyroidism	39 (0.56)	3.16	1.15
Osteoporosis	36 (0.51)	1.74	0.55

Abbreviations: CRCCI, colorectal cancer comorbidity index; sHR, sub-distribution hazard ratio.

Table 4: Internal validation of CRCCI and comparison with CCI, NCI, ECI and C3 using a bootstrap sample

Models	**non-cancer mortality**	
	AUC (95% CI)	**Brier score**
Baseline (BL)	0.725 (0.67 - 0.77)	0.0301
BL + CRCCI	**0.749 (0.70 - 0.80)**	**0.0292**
BL + NCI	0.742 (0.69 - 0.79)	0.0294
BL + C3	0.741 (0.69 - 0.79)	0.0295
BL + CCI	0.739 (0.69 - 0.78)	0.0294
BL + ECI	0.734 (0.68 - 0.78)	0.0298
Difference in AUC between BL and other models		
BL/CRCCI	0.024 (0.00 - 0.04)	
BL/CCI	0.013 (-0.008 - 0.03)	
BL/NCI	0.017 (-0.004 - 0.04)	
BL/ECI	0.008 (-0.01 - 0.02)	
BL/C3	0.016 (-0.004 - 0.03)	
Difference in AUC between CRCCI and other models		
BL/CRCCI	0.024 (0.00 - 0.04)	
CRCCI/NCI	-0.006 (-0.02 - 0.01)	
CRCCI/C3	-0.008 (-0.02 - 0.00)	
CRCCI/CCI	-0.010 (-0.02 - 0.00)	
CRCCI/ECI	-0.014 (-0.03 - 0.00)	

Note. Bold entries represent greatest improvement from baseline model. Abbreviations: AUC, area under the curve; CCI, Charlson comorbidity index; CRCCI, colorectal cancer comorbidity index; C3, cancer, care, and comorbidity; ECI, Elixhauser comorbidity index; NCI, National Cancer Institute Comorbidity Index.

Table 5: Crude subdistribution hazard ratios for non-cancer and CRC mortality by CRCCI

		non-cancer mortality	CRC mortality
CRCCI score groups	**N (%)**	**Crude sHR (95% CI)**	**Crude sHR (95% CI)**
score = 0	4653 (66.4)	Reference	Reference
0 < score < 1	1552 (22.2)	**1.44 (1.04 – 1.98)**	1.03 (0.91 – 1.17)
1 ≤ score < 2	509 (7.3)	**1.91 (1.23 – 2.96)**	**1.40 (1.17 – 1.67)**
2 ≤ score < 3	183 (2.6)	**3.61 (2.15 – 6.07)**	**1.60 (1.22 – 2.10)**
score ≥ 3	111 (1.8)	**10.5 (6.87 – 16.0)**	1.17 (0.77 – 1.77)

† Bold entries represent significant results. Abbreviations: CRCCI, colorectal cancer comorbidity index; sHR, sub-distribution hazard ratio.