Adjusting for comorbidity in observational cancer studies: A systematic review to assess alignment between index and study

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Abstract. Epidemiological and retrospective clinical studies on cancer outcomes frequently adjust for patients' comorbid conditions. Despite the existence of multiple comorbidity indices, the Charlson comorbidity index (CCI) is the most frequently applied. Indices are developed in specific settings and the extent of alignment between the development setting and subsequent study is unclear. The present study provides a contemporaneous snapshot of comorbidity indices used in retrospective observational cancer studies and the extent to which cancer type(s), data source(s) and outcome(s) matched the studies in which the indices were developed. A systematic literature search in PubMed identified retrospective, observational studies on outcomes in patients with cancer published between March 2015 and March 2020. Information including the cancer type, data source and outcome were extracted and compared to those used in the validation study of the comorbidity index used. Of 158 papers reviewed, 79 used the CCI, either alone or in combination with other indices. The cancer type matched to that used in the validation study of the comorbidity index in 16 of the 115 studies using an established index, whilst the data source matched in 27 studies and outcome in only two. Justification was rarely provided for index choice (15 of the 115 studies). It may be concluded that, while the CCI remains the dominant comorbidity index, it may not always align to key elements of the study design in terms of cancer type, data source and outcome. A range of indices exists and identification of the most appropriate measure has the potential to improve adjustment for comorbidity. The present study provided information about the indices used in included studies and encourages future studies to consider which comorbidity index offers the best alignment with the study population, data source and question addressed.

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Introduction

In the context of cancer, both comorbidity, the presence of an additional long-term condition (LTC) and multimorbidity, the presence of multiple LTCs, are a significant consideration. Studies have indicated that LTCs are associated with increased cancer pathogenesis (1), more advanced disease (2), lower rates of, and delays to commencing, active treatment (1,3-6), unfavorable survival (7-10), increased cost and use of healthcare (11,12) and lower health-related quality of life (13-15). Cancer treatments carry significant side-effects and complications, rates of which are also higher in patients with other LTCs (11-15). As such, understanding the impact of LTCs is crucial, both at an individual level and when undertaking large-scale health services studies.

Comorbidity has also been indicated to be associated with demographic features, with the presence of LTC rising with age (16,17), and in the context of an ageing population, accurate assessment of the associated increasing levels of comorbidity and their impact upon cancer care and outcomes, are becoming an ever more pressing concern.

In order to support the evaluation of comorbidity, multiple indices have been developed. These allow adjustment of outcomes for comorbidity, both within academic studies and in comparisons between provider organisations. These indices typically weigh the severity of a comorbidity in a population against a specific outcome. They have been indicated to be user-friendly, with high test-retest reliability, and demonstrate that comorbidity is a strong predictor of outcome (18). Among the most widely used of these is the original Charlson Comorbidity Index (CCI). Previous systematic reviews have indicated that the CCI is the most frequently utilised index (19,20), a pattern which is thought to be continuing despite the availability of multiple other comorbidity indices.

There remain doubts about the reliability and validity of certain indices. Of the 13 methods for measuring comorbidity examined by de Groot *et al* (21), only four, including the CCI,

were indicated to have sufficient data on the clinimetric properties to properly assess their validity and reliability. Insufficient data were available for the others and whilst multiple types of reliability were examined, the authors did not consider how closely matched studies using comorbidity indices were to the studies that validated these indices.

Mismatches have the potential to reduce the efficacy of a comorbidity index's use. Hall (22) suggested that when selecting a comorbidity index, researchers should look for indices that were validated in similar patients to those of the study. Not doing so may mean the index is not suitable for use in the study population, leading to questions around the generalisability, reliability and robustness of results. Even where an element of generalisation is necessary, certain indices have performed better when investigating specific cancer types. For instance, the Adult Comorbidity Evaluation 27 (ACE-27) performed better than the CCI in patients with acute myeloid leukaemia (23) and laryngeal cancer (24). Head and neck cancers were included in the validation of ACE-27, but not CCI. This therefore arguably supports Nitz's (25) expectation that a disease-specific comorbidity measure would explain more variance in the outcome than either a general or non-cancer-specific measure.

Indices derived from different data sources have also been explored in relation to outcomes. When comparing diagnosis-based (comorbidities identified based on diagnoses) and pharmacy-based (comorbidities identified based on medications from pharmacy data) indices, diagnosis-based measures provided superior prediction for mortality, while medication-based indices better predicted care utilisation and costs (26). This suggests there may also be an important need for authors to consider the alignment between study and index in terms of data source and/or outcome when selecting an appropriate measure of controlling for comorbidity.

At one level, the present systematic literature review aimed to provide a snapshot of the comorbidity indices used in retrospective observational studies of patients with cancer and document the justifications for these choices. Beyond that, it also aimed to evaluate the alignment between these studies and the studies in which the indices of comorbidity were initially developed. With cancer type, data source and outcome all potentially influencing the effectiveness of comorbidity indices, alignment was assessed with respect to these key parameters.

Materials and methods

Literature search. A structured search was conducted in PubMed covering a five-year period between 23 March 2015 and 22 March 2020 in accordance with the PRISMA guidelines (27). Studies were restricted to those published in the English language. The search terms used were as follows: [cancer(Title)] AND [comorb*(Title)] AND [population(Title/Abstract) OR observational(Title/Abstract) OR retrospective(Title/Abstract) OR regist*(Title/Abstract)].

Literature screening. Following the literature search, papers were de-duplicated and screening based on study title and abstract was carried out independently by two reviewers (AB and RB) to assess against key inclusion criteria. These were as follows: Retrospective observational studies; studies on patients with cancer; a relationship to an outcome. While the 'relationship to an outcome' criterion was defined broadly in terms of a specific outcome, the relationship aspect was more restrictive to those studies utilising comorbidity for predictive or effect modification purposes. It therefore did not include studies that were restricted to, e.g., simply describing comorbidities in cancer populations or being used as a confounder. The decision to restrict the 'cancer' and 'comorb*' search terms to the title was made with the aim of maximising results meeting the inclusion criteria while reducing the proportion of those that did not. The full text was subsequently reviewed if insufficient information was available to include the paper based on title/abstract. Where there was disagreement around inclusion between the two reviewers, a third individual (KS) also assessed the paper and inclusion was based on a majority decision.

Data extraction. Data extraction took place following this evaluation. Two reviewers (AB and RB) obtained data pertaining to the following five parameters: i) First, the time period covered by the study was denoted. ii) Furthermore, the type of comorbidity index or indices used in the paper was extracted. Both those using established indices of comorbidity in patients with cancer and novel study-specific measures were identified. Established indices were denoted, whilst free text fields were used to record more detailed information on how novel measures were calculated. This included, for instance, the methodology for calculating the comorbidity score and, if relevant, details of the validation population. For established measures, paper-specific modifications to the original methodology were also denoted. iii) In addition, the primary cancer diagnosis/diagnoses included in the studies were recorded. All solid-organ diagnoses were classified by primary diagnosis, with haematological cancers and lymphomas grouped separately. Histological subtypes and stages were not considered. If an unselected cancer population was included in the study, the individual diagnoses were not recorded separately. iv) The data source for each included study was defined. This involved not only identifying the primary data source, e.g., cancer registries or hospital records, but also whether different sources were formally linked. Each source, including linked data, was classified individually. v) Outcome(s) for each paper were identified. This included capturing both the primary outcome and any secondary outcomes explored in the study. With a majority of established cancer comorbidity indices validated against differing measures of mortality, each time-specific mortality and overall survival outcome was classified separately.

Comparisons. Comparisons were then made between the extracted studies and the paper in which the selected comorbidity index was initially validated. The comorbidity index validation paper was identified from the reference lists of reviewed studies during data extraction and confirmed via a separate literature search. For each index validation paper, the cancer type(s), data source(s) and outcome(s) were identified and summarised in Table I. Comparisons with respect to these three parameters between the study paper and comorbidity index validation paper were then made. For each parameter, 'complete' or 'no' match were primarily explored, although

Table I. Data source, study population [including cancer type(s)] and outcome of the validation studies for comorbidity indices used by extracted papers included in the systematic review.

Comorbidity index	Paper source	Data source (country)	Study population	Outcome	(Refs.)
Adult comorbidity evaluation 27	Piccirillo *et al*	Multi-centre registry data (USA)	19,268 patients at two hospitals with lung, female breast, gastrointestinal tract, gynecological, urinary tract, and head and neck cancers	Overall survival	(28)
Aggregated diagnosis groups	Austin *et al*	Population registry linked with claims data (Canada)	All adult residents of Ontario (10,498,413) divided into development and validation cohorts	1-year mortality	(29)
C3	Sarfati *et al*	Population registry data (New Zealand)	14,096 patients (development), 11,014 patients (validation) diagnosed with colorectal, uterine, ovarian, liver, stomach, female breast, kidney or bladder cancers	1-year non-cancer mortality	(30)
CCI	Charlson *et al*	Hospital notes/ records (USA)	559 medical patients (development), 685 breast cancer patients (validation)	1-year mortality	(31)
Age-adjusted CCI	Charlson *et al*	Hospital notes/ records (USA)	218 patients with hypertension or diabetes undergoing elective surgery	3-year and 5-year mortality	(32)
Deyo-CCI	Deyo *et al*	Claims data (USA)	27,111 patients who underwent lumbar spine surgery	Postoperative mortality	(33)
Head & Neck CCI	Bøje *et al*	Population registry data (Denmark)	9,388 patients with head and neck cancer receiving radiotherapy	5-year mortality	(34)
Romano CCI	Romano *et al*	Claims data (USA)	Multiple non-cancer diagnostic groups considered	Various	(35)
Elixhauser	Elixhauser *et al*	Discharge data (USA)	1,779,167 acute admissions across 438 hospitals	In-hospital mortality	(36)
Klabunde comorbidity index	Klabunde *et al*	Population registry linked with claims data (USA)	28,868 males diagnosed with prostate cancer and 14,943 females diagnosed with breast cancer	2-year non-cancer mortality	(37)
National cancer institute comorbidity index	Klabunde *et al*	Population registry linked with claims data (USA)	28,868 males diagnosed with prostate cancer and 14,943 females diagnosed with breast cancer	2-year non-cancer mortality	(37)
	Klabunde *et al*	Population registry linked with claims data (USA)	26,377 female breast, 53,503 prostate, 26,460 colorectal and 33,975 lung cancer patients	2-year non-cancer mortality	(38)

Table I. Continued.

Comorbidity index	Paper source	Data source (country)	Study population	Outcome	(Refs.)
Ovarian cancer comorbidity index	Noer *et al*	Population registry data (Denmark)	2,020 patients (development), 1,975 patients (validation) diagnosed with ovarian, peritoneal or fallopian tube cancer	Overall survival (up to 5 years)	(39)
Rx-Risk-V model	Sloan *et al*	Collective registry linked with pharmacy data (USA)	126,075 users of Veteran Health Administration services	Associations between pharmacy and ICD-9 diagnostic classes	(40)
Simplified comorbidity score	Colinet *et al*	Case reports (France)	735 patients (development), 136 patients (validation) diagnosed with non-small cell lung cancer	1 and 2-year mortality	(41)

Two measures of comorbidity, the 'Adapted self-administered comorbidity questionnaire' and the 'Australian Bureau of Statistics list of health conditions' were each used in one paper examined. However, no information was provided regarding their validation. CCI, Charlson Comorbidity Index; ICD, International Classification of Diseases.

matches were also classed as 'partial' or 'uncertain' where they did not fit into either of the prime categories. Descriptive analyses were then performed to evaluate these matches, both separately and combined.

Results

Literature search and selection. According to the search criteria, 236 studies were identified over the five-year period selected. Of these, the full text was available for 233 studies, while only the abstract was available for the remaining three. Following de-duplication and removal of non-English language papers, 230 articles remained. All 230 studies were then screened against the inclusion criteria and this process identified a total of 158 papers to be included in the review. A full list of these studies is provided in Data S1. Of the 158 studies included in the review, 115 used one or more of the established comorbidity indices or measures outlined in Table I. Of the remaining papers, 34 used a study-specific evaluation of comorbidity and nine papers did not specify how comorbidities were weighted and scored (Fig. 1).

Comorbidity index. A total of 16 established indices or measures of comorbidity were used across the papers reviewed, with 38 studies using or including a measure of comorbidity developed specifically for the published study. The number of papers using each index or measure is presented in Fig. 2, with Table I outlining basic information about the indices identified during data extraction where available (28-41). Of these, the CCI was the most frequently utilised, with 65 (41.1%) papers using it alone (Fig. 2). This increased to 79 (50.0%) papers when studies using CCI alongside others were included. When combined with the various adaptations of the CCI, this increased to 85 (53.8%) using one of these measures alone, or 104 (65.8%) where studies using multiple indices were included. Other indices were used at a markedly lower frequency. While the ACE-27 was used as the sole comorbidity index in four (2.5%) studies, the Elixhauser index was used alone in two studies (1.3%). When studies using multiple indices were also included, they were each featured in eight (5.1%) of the 158 papers reviewed.

In 75.7% (n=87) of studies, no modifications to the indices were made. Where changes were made, however, these typically involved removing comorbidities (generally cancers) [n=7 (6.1%)] (42-48), adding and removing comorbidities [n=6 (5.2%)] (49-54) or adding comorbidities [n=3 (2.6%)] (55-57). Modified indices were used in five (4.4%) studies where the nature of the modification was not provided in the manuscript (58-62).

Of the 115 eligible papers, only 15 (13.0%) provided a justification for the index used. Where justifications were provided, these typically involved statements to the effect that the index is widely used, or has been validated in populations of cancer patients. However, whilst certain studies, such as that by Stordeur *et al* (57), provided detailed justifications with supporting references, others provided minimal detail.

Cancer type. The cancer types used in the studies included in the present review are presented in Fig. 3. The most common single type was colorectal cancer [n=26 of the 158 included studies (16.5%)], followed by lung [n=25 (15.8%)], breast [n=21 (13.3%)] and prostate cancer [n=15 (9.5%)]. A total of 16 studies (10.1%) examined multiple named cancer types.

In total, a complete match between the study paper and comorbidity index validation paper for cancer type was observed in only 16 (13.9%) of the 115 studies that used an established index. In all but three studies (60,63,64), matches were with the CCI. For other studies that had a match, these were the C3 index, Deyo-Charlson Comorbidity Index (DCCI)

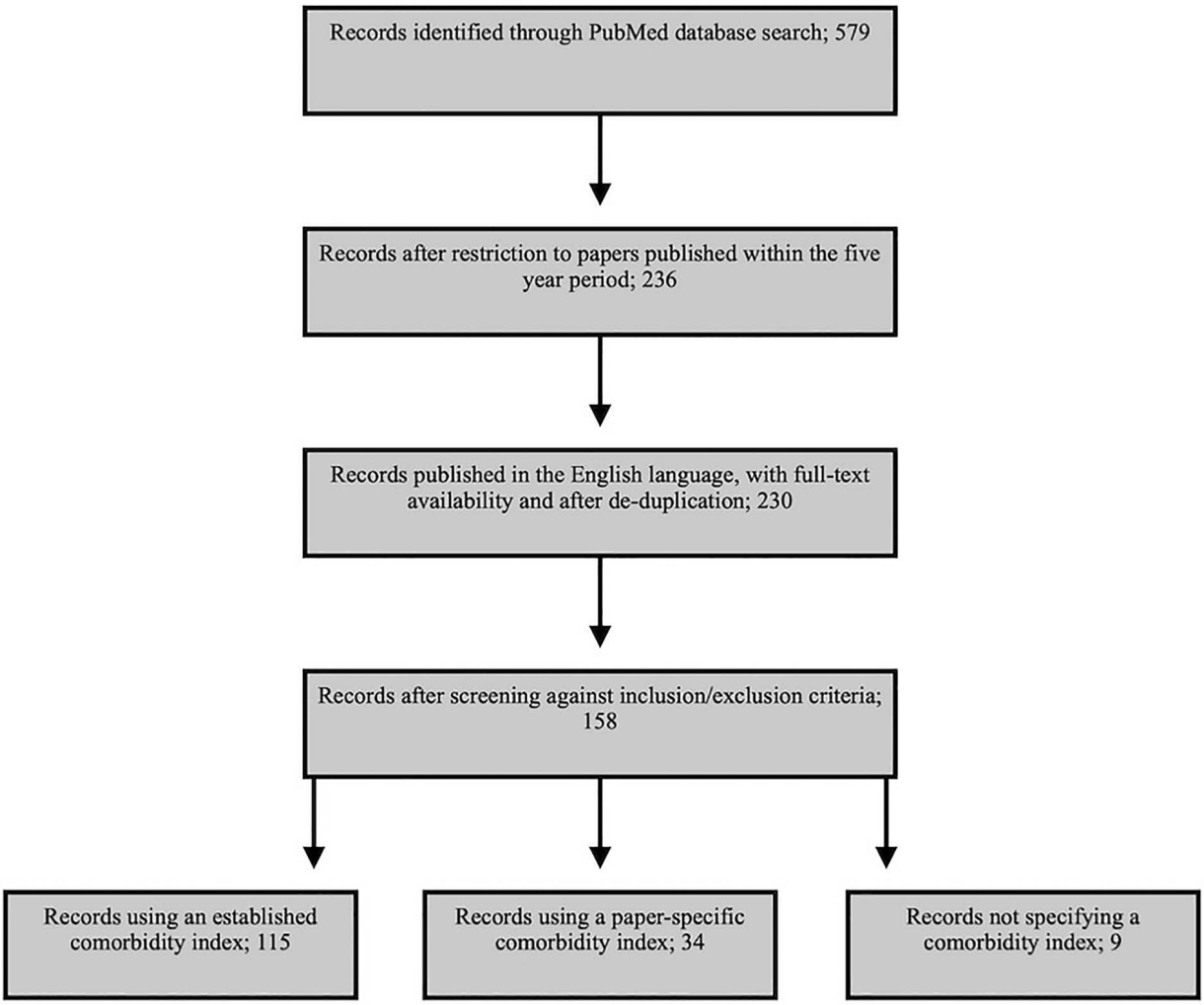

Figure 1. PRISMA diagram of the literature search.

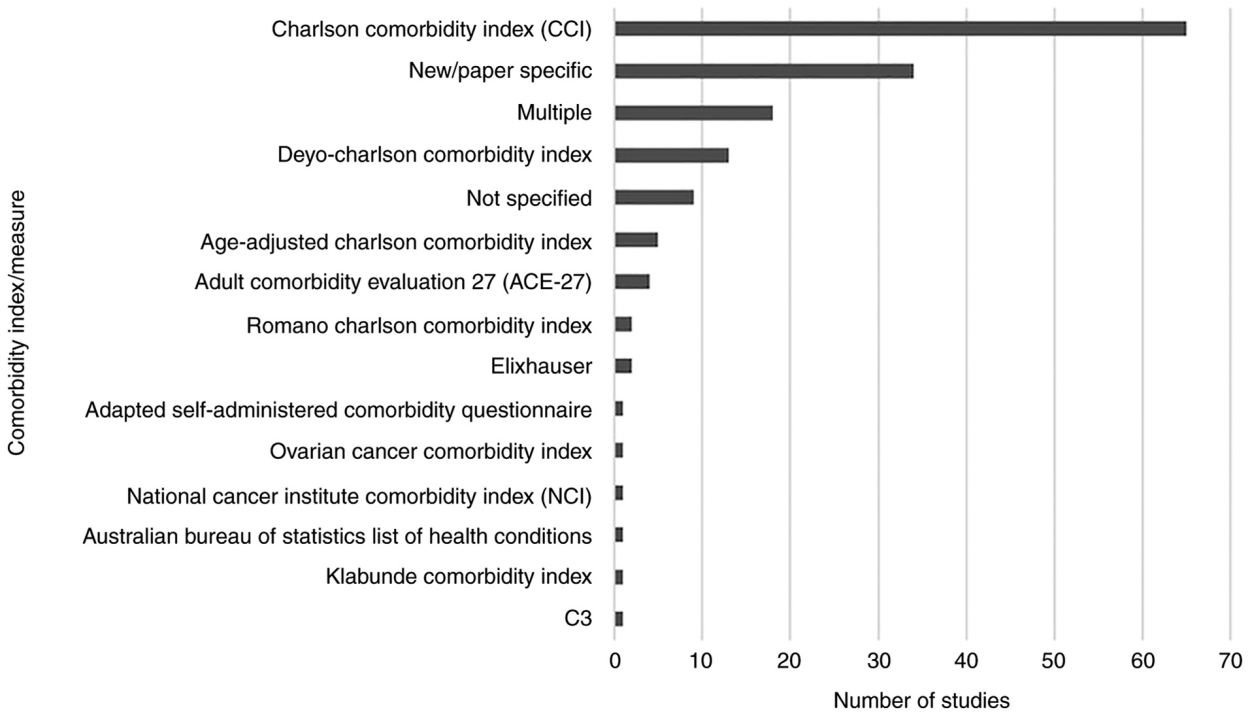

Figure 2. Number of studies using each comorbidity index or measure.

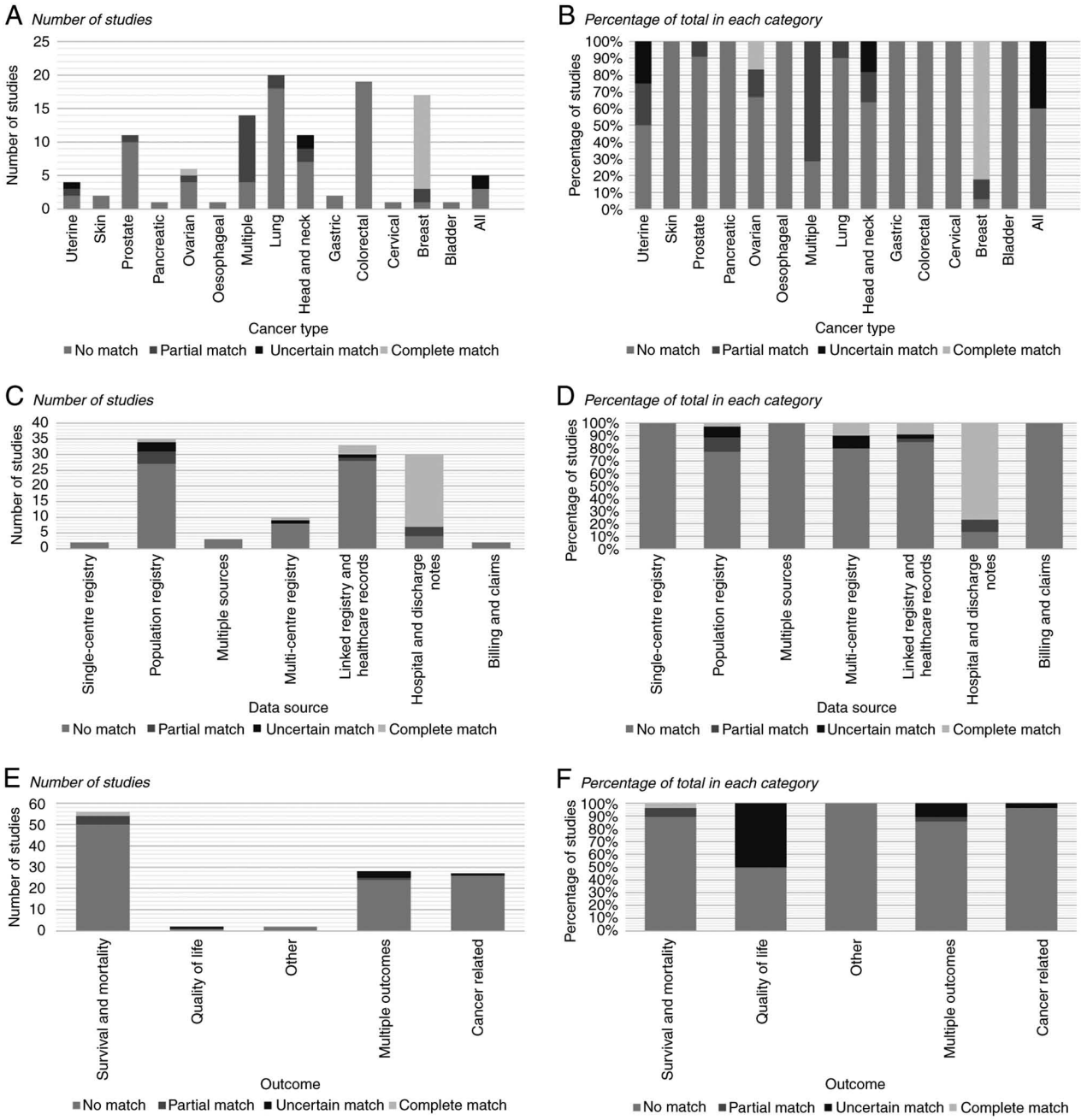

Figure 3. Match between study paper and comorbidity index validation paper in terms of the following items: Cancer type(s) presented as (A) number and (B) percentage; data source presented as (C) number and (D) percentage; and outcome presented as (E) number and (F) percentage.

and Ovarian Cancer Comorbidity Index (OCCI). A full breakdown of matches by cancer type is provided in Fig. 3.

Data source. Registries or other databases were the most common data source, being used in 60 of the 158 extracted studies (38.0%). Of these, 45 used population registries, three used single-centre registries and 12 used multi-centre registries. Hospital and discharge notes [n=46 (29.1%)] and linked registry and billing data [n=44 (27.9%)] were also commonly used data sources (Fig. 3).

A complete match between the study paper and comorbidity index validation paper for data source was observed in 26 of the 115 studies including an established measure (22.6%). Matches by data source are detailed in Fig. 3. As with cancer type, a majority of these matches were in studies using the CCI [n=18 (15.7%)]. There were additionally three matches in papers using the age-adjusted CCI, and one for each of ACE-27, C3, National Cancer Institutes and OCCI indices.

Outcome. Overall survival was the most commonly identified outcome, being used in 45 of the 158 studies (28.5%). Other mortality outcomes used included in-hospital/28-day, 1, 2, 3 and 5-year mortality. Multiple outcomes were examined in 35 studies (22.2%) (Fig. 3).

There were only two studies in which there was a complete match between the study paper and comorbidity index validation paper for the outcome (44,65). One of these was a study using ACE-27, while the other used the CCI.

Combined matches between study and comorbidity index used. Overall, no studies were identified where there was a complete match between the study paper and comorbidity index validation paper across different cancer types, data sources and outcomes. Of the 115 studies using an established comorbidity index, complete matches in two domains and a partial match in the third was observed in one study (65). Partial matches were identified for all three domains in three studies (3.5%) (66-68), all of which used multiple comorbidity indices. Complete or partial matches were found across two domains in 15 studies (13.0%) and in only one domain in 37 studies (32.2%). However, 57 (49.5%) had no complete or partial matches. For the remaining studies, the index or measure being used did not specify the relevant information (Table I), meaning the comparison could not be made.

Discussion

The results of the present study confirmed the findings of Sarfati (19) and Connolly *et al* (20), highlighting the dominance of the CCI and its derivatives in studies of cancer populations. Of the papers reviewed, none included a complete match between the study population and comorbidity index development population for all domains assessed. While it is difficult for a study to achieve a match with the comorbidity validation paper across all three domains, the most common finding was that of no matches.

Of the papers utilising the CCI, the majority used either an unadjusted or modified version (e.g., exclusion of a single condition). Where a validated adaptation was selected, the DCCI was more popular than the Romano Charlson Comorbidity index (RCCI). This was in line with Yurkovich *et al* (26). It is notable, however, that both the DCCI and RCCI were developed in non-cancer populations (Table I). As such, despite their relatively frequent use, it would be reasonable to question how well suited they are for use in studies of cancer populations and whether indices developed in cancer populations would be more appropriate.

Studies frequently used comorbidity indices which were developed for use in a cancer type other than that which was the focus of the study. The CCI was validated in a population with breast cancer, but has been used to adjust for comorbidity in cancers with distinctly different disease trajectories and treatment pathways. As such, the impact, and presence of, comorbidity is likely to differ significantly. For instance, anthracyclines are routinely used in adjuvant chemotherapy regimens for breast cancer, whilst in other cancer types, these are used predominantly in subsequent lines of therapy. As such, the presence of cardiac disease is expected to have quite a different impact on the decision making around adjuvant breast cancer treatment.

Advances in the treatment of numerous diseases have meant that the initial weighting defined in the CCI validation paper may not correspond to their significance now. Reflecting these advances, a re-evaluation of the CCI weights by Quan *et al* (69) saw the weights decreased for eight diseases, reflecting improvements in their management and outcomes. In a further four diseases, an increase in weighting was seen. These findings suggested that the original CCI may not always be the most appropriate index for predicting outcomes in contemporary cancer populations. Authors therefore need to consider both the generalisability of modified CCIs and the requirement for updated weightings to reflect contemporaneous outcomes.

For most studies included in the present review, indices were largely used without detailed justification. As such, it was not possible to fully evaluate the reasons for the widespread use of the CCI. It is possible that its continued use is largely down to its previous popularity. Of the nine studies which did state a reason for selecting the CCI, five stated its popularity without providing supporting references. The most detailed justification came from Grønhøj *et al* (70), who referenced a previous Danish National Patient Register-based study where the CCI had a high positive predictive value.

The CCI is calculated from routinely collected population data, meaning it is more readily accessible for registry-based health services studies, potentially leading to its selection for use over alternative site-specific indices. Several considerations exist contributing to this. First, the availability of sufficient information to derive relevant indices may influence selection. For instance, several papers included in the present review used the CCI in studies of patients with non-small cell lung cancer (NSCLC), despite the Simplified Comorbidity Score (SCS) having been validated in an NSCLC population (41). The SCS, however, includes smoking status and alcohol consumption, which are not routinely collected by cancer registries and discharge records among others, and would thus prevent its use in studies using such sources, unless these items are specifically sought. As such, whilst such an alternative measure may seem more appropriate, this does not always relate to practice. This should be borne in mind where new indices are developed; the advantage of the CCI is its simplicity. Indices aiming to replace it must recognise the limitations of the available data.

Whilst justifications for the use of the CCI exist, arguably its widespread use reflects a limited number of indices designed and/or validated for specific cancer types. This was particularly evident for two of the most common cancer types, colorectal and prostate cancer. While Marventano *et al* (71) proposed an adjusted CCI for patients with colorectal cancer, this has remained to be validated. An opportunity therefore exists to develop and validate comorbidity indices that are better tailored for specific cancer types and may better predict outcomes than existing, less diagnosis-specific measures. In the absence of such new indices though, a more comprehensive understanding of the relative performance of alternative cancer-specific indices would be valuable for identifying the most appropriate indices for certain cancer types.

'Data source' proved to be the domain in which a match was most frequently observed. Despite this, 77% of studies had a mismatch for data source. Of the data sources identified, one of the lesser used was billing data. While valuable and readily available, billing data potentially capture billable comorbidities while disregarding numerous diagnoses that are not. It is therefore likely that the number of comorbidities from this source reflect conditions that may be billed by the treating hospital, and thus, have limited generalisability. This has been observed in the USA, where the proportion of patients assigned to a Diagnosis-Related Group (DRG), the basis on which hospitals are reimbursed, has increased over time (72).

The authors suggest this may reflect financial incentives to improve the management of recorded diseases that contribute to these DRGs. As such, the use of billing data may not fully reflect patient comorbidity.

The impact of this variation in recording is likely to be increased between jurisdictions and where the rationale for recording differs. Using linked registry and hospital discharge data from Australia, Canada, Norway and the UK, Lüchtenborg *et al* (73) determined that it was possible to calculate the CCI, Elixhauser and inpatient bed day comorbidity scores from the data captured. However, they noted that differences in coding and hospital admission practices may make comparability of recorded comorbidity among the countries difficult. The potential limitations to the use of individual comorbidity indices resulting from the data source from which they were derived clearly warrant consideration where researchers are seeking an appropriate measure.

Beyond the infrastructure and rationale for data capture in a given healthcare setting, the demographics of the population in which the comorbidity index was developed and validated should be considered when selecting an index. The socioeconomic and demographic differences observed among populations may reduce generalisability, particularly when validation has occurred based on a single hospital or limited geographical area. For instance, compared with Caucasians, those of South Asian ethnicity are at a higher risk of type two diabetes and hypertension (74). Ethnicity has also been associated with outcome, with patients of Asian ethnicity having better survival from lung cancer compared with Caucasians (75), whilst Asian females aged 15-64 years have reduced breast cancer survival (75). With indices including the CCI, ACE-27 and Elixhauser validated in patients from a limited number of locations, it may be important for authors to consider population generalisability when selecting an index. This is also true for the patient age range, with older patients likely to have both greater comorbidity and a different impact of comorbidity when compared with younger patients.

The final area in which a match was sought was between the outcome of the reviewed study and validation of the relevant comorbidity index. As expected, there were a significant number of outcomes identified and it would be impractical to expect indices to be developed which cover the full range of those that were able to be measured. In the domain 'cancer type', however, the CCI appeared to be frequently used despite other indices potentially being more appropriate. With regard to outcomes, only one study using the CCI had one-year mortality as its primary outcome (58). With overall survival being the most frequent outcome, the OCCI may have been more appropriate than the CCI if a study examined gynaecological cancers, or ACE-27 for other cancer types, both of which have been validated for this end point.

Given the large number of possible measurable outcomes, it may be more appropriate for authors to consider comparisons that were made between indices with respect to different outcomes, rather than seeking a perfect match. For instance, ACE-27 has performed better than the CCI with respect to five-year mortality (24) and was also found to be the best among the compared indices at predicting overall survival (23). Unlike Nesic *et al* (24), Hwang *et al* (76) found the CCI to be the most effective index in estimating hospital costs for patients treated surgically for gastric cancer among the four compared. However, it was less useful in predicting the length of hospital stay. Meanwhile, Elixhauser has been indicated to be a better predictor of both short- and long-term mortality than the CCI (26). Such comparative studies offer authors the opportunity to evaluate the performance of different indices against their desired outcomes, allowing the most appropriate to be selected.

The present review has demonstrated that, while the CCI remains the dominant comorbidity index in studies of cancer populations, it may not always be the most closely aligned with key elements of the study design in terms of cancer type, data source and outcome. These factors have the potential to make the CCI a less effective index in predicting outcomes than others that have been designed and/or validated for particular cancer types or with respect to specific outcomes. Further work to examine this is key, and particularly, to determine in which domains matches should be prioritised, which was beyond the scope of the analyses in the present study.

Study authors may nonetheless benefit from questioning whether other indices are more closely aligned with their study design prior to selecting which index to use. Table I provided in the present study may assist with this process. They should also consider justifying their decision in more detail, as well as discussing the potential limitations of their choice. Registry data controllers may assist in and facilitate the use of a wider range of indices by providing the means for them to be calculated by authors. Going further though, registries may also be able to recommend to researchers the optimal index to use within the available data and in relation to the population and outcome of interest. Finally, gaps have been identified in terms of index development, particularly for specific diagnostic groups. Researchers may consider the development of new indices better tailored to not only specific diagnostic groups, but also data sources or outcomes.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RJB initially conceived the study with AMB and KS contributing to the refinement of the study design. AMB, KS and RJB were all involved in literature screening and data extraction. Data analysis was primarily performed by AMB. The manuscript was initially drafted by AMB. KS and RJB provided critical revisions of the manuscript prior to submission and during the revision process. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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