Chapter 2
How Do We Measure Comorbidity?

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Abstract This chapter reviews methods used to measure comorbidity in the context of cancer; summarising methods, identifying contexts in which they have been used and assessing the validity, reliability and feasibility of each approach. Measures of comorbidity are categorised according to whether they are based on individual conditions or simple counts, on dysfunction/function of organ systems, on conditions that have been weighted and combined into indices or based on alternative approaches. Twenty-one separate approaches are described. Content and face validity of the measures varied but tended to be higher for those developed for cancer populations. Some evidence supporting criterion validity of all approaches was found. Where reported, reliability tended to be moderate to high. Some approaches tended to score well on all aspects, but were resource intensive in terms of data collection. There is no gold standard approach to measuring comorbidity in the context of cancer. All summary approaches require simplifying assumptions and, by necessity, result in loss of information. Approaches vary in their strengths and weaknesses, with the choice of measure depending on the study question, population studied and data available.

List of abbreviations

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
ICED	Index of Coexistent Disease

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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
PBCI   Pharmacy-based Comorbidity Index

Key Points

- There is no single measure of comorbidity that is optimal for all purposes.
- All summary measures of comorbidity require simplifying assumptions, which results in loss of information.
- There are four broad approaches to measuring comorbidity identified in the literature; individual conditions or condition counts, organ-based systems, weighted indices or other miscellaneous approaches.
- The choice of comorbidity measure depends on the study question, the population studied and the data available.

2.1   Introduction

Given the importance of comorbidity, it is important to consider how we quantify it, particularly in the context of cancer-related 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 [1]. 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 [2–4].
- *Defining what a comorbid condition is can be difficult* [5–7]. 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, their importance is likely to vary depending on other factors, such as the timing and severity of conditions [8].

- *Understanding the combined effects of multiple conditions is 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 that the effects of combinations of comorbidities on survival among cancer patients were complex and difficult to predict [9].
- *The best approach to measuring comorbidity may also be affected by the outcome that is being investigated* [10, 11]. 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 [11].

This section reviews approaches to measuring comorbidity in the context of cancer studies. It summarises the various approaches used to measure comorbidity, indicates the context in which each has been used, and assesses the validity of each approach. This section is an updated and extended version of work published previously [1].

Data relating to each index or measure are presented in relation to:

1. *A general description of the measure or index.* This includes the original purpose of the index or measure, a description of the process through which comorbid conditions were identified, whether severity was accounted for, whether and how conditions were combined to form an index and the extent to which the index has been used in the context of cancer patients.
2. *Content and face validity.* Both these measures relate to the degree to which a measure actually evaluates the construct that it purports to measure [12]. 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.
3. *Criterion validity* relates to the extent to which an index or measure performs in the expected way [12]. Specifically it 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.

   (a) *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.

(b) *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.

4. *Reliability* is "*the extent to which repeated measurements of a stable phenomenon by different people at different times and places get similar results*" [13]. Reliability 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 a 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 [12]. Both the k statistic and the ICC are in a 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 [2].

5. *Feasibility* includes the simplicity, cost, time and effort required to use the measure.

Table 2.1 summarises the key characteristics of twenty-one separate approaches used to measure comorbidity among cancer populations in order of the date of the first 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 2.2 summarises the scoring approaches for each measure of comorbidity, including the number of items, the severity scale, the score range (if relevant), and the distribution of each index or measure.

Following these tables is a description of the different approaches used to measure comorbidity; individual conditions or simple condition counts, organ-based approaches, weighted indices and other approaches.

2.2   Individual Conditions or Counts of Conditions

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 [27, 39–45].

The total count of conditions depends on how conditions are defined, and which are included in the count. There are several examples where authors have identified individual conditions using an explicit process in the context of cancer.

Satariano et al. [21] identified seven conditions (myocardial infarction, other types of heart disease, diabetes, other forms of cancer, and respiratory, gallbladder and liver conditions) that were associated with all-cause mortality, breast cancer mortality or mortality from other causes after adjustment for age, stage and other comorbid conditions among a cohort of patients with breast cancer. 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

Table 2.1 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) [14]	Measure of physical impairment	?	Clinical notes data	No	Judgement
KFI	Kaplan and Feinstein (1974) [15]	Measure of comorbidity among diabetic patients	188 men with diabetes	Clinical notes data	No	Judgement
Charlson	Charlson (1987) [16]	To develop a 'prognostic taxonomy' for comorbid conditions	608 general medical patients	Clinical notes data	Administrative data, Patient questionnaire	Empirical
ACGs	Weiner (1991) [17]	To predict resource use in HMOs	16,000 HMO enrollees	Administrative data	No	Empirical
CDS/Rx-Risk	Von Korff (1992) Clark (1995) [18, 19]	To predict resource use in HMOs	122,911 enrollees in a Health Maintenance Organization	Pharmaceutical data	No	Judgement and empirical
ICED	Greenfield (1993) [20]	To measure impact of comorbidity and physical functioning	356 patients undergoing total hip replacement	Clinical notes data	No	Judgement
Satariano	Satariano (1994) [21]	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) [22, 23]	To measure total burden of disease	1738 general patients and 2894 prostate cancer patients	Patient symptom report	No	Judgement and empirical
NIA/NCI collaborative study	Yancik (1996) [24]	To investigate comorbidity burden among older cancer patients	7600 cancer patients	Clinical notes data	No	Empirical

(continued)

Table 2.1 (continued)

Index name	Author (year)	Purpose	Population developed	Initial data sources used	Alternative data sources	Item generation
Elixhauser	Elixhauser (1998) [25]	To measure comorbidity using administrative data	1,779,167 adult acute care hospital patients	Administrative data	No	Judgement and empirical
Comprehensive prognostic index	Fleming (1999) [26]	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) [27, 28]	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) [29]	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) [30]	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	Picirillo (2002) [31]	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) [32]	To assess comorbidity among cancer patients	11,906 cancer patients	Clinical notes data	Administrative data	Judgement
Tammemagi	Tammemagi (2003) and (2005) [33, 34]	To assess comorbidity among breast and lung cancer patients	1155 lung and 906 breast cancer patients	Administrative data	No	Empirical

(continued)

Table 2.1 (continued)

Index name	Author (year)	Purpose	Population developed	Initial data sources used	Alternative data sources	Item generation
SCI	Colinet (2005) [35]	To assess comorbidity among patients with lung cancer	735 patients with lung cancer	Clinical notes data	No	Judgement
Elixhauser	van Walraven (2009) [36]	To combine Elixhauser conditions into index	228,565 adult acute care hospital patients	Administrative data	No	Judgement and empirical
C3 index	Sarfati (2014) [37]	To assess comorbidity using administrative data in cancer populations	14,096 cancer patients	Administrative data	No	Judgement and empirical
PBCI	Sarfati (2014) [38]	To assess comorbidity using community pharmaceutical data in cancer populations	14,096 cancer patients	Administrative data	No	Judgement and empirical

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Table 2.2 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-year mortality (RR)	Sum of weighted conditions	0–33	Skewed to right
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 to 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

(continued)

Table 2.2 (continued)

Index name	System or condition based	Items	Severity	Scoring method	Score range	Distribution
Comprehensive Prognostic Index	Condition	11 categories with 34 subcategories	Based on impact on 1-year mortality (RR)	Multiplicative	0–14.8	Skewed to right
NCI comorbidity index	Condition	12 conditions (in 14 categories)	Based on impact on 2-year non-cancer mortality (β)	Summing β 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-year mortality (β)	Summing β 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
SCI	Condition	7 comorbidity categories	Based on impact on mortality (β)	Summing β coefficients	0–20	Not specified
Elixhauser	Condition	21 conditions	Based on impact on in-hospital mortality (β)	Summing β coefficients	−19 to 89	Skewed to right
C3	Condition	42 conditions	Based on impact on non-cancer mortality	Summing β coefficients	−0.13 to >15	Skewed to right
PBCI	Condition	19 conditions	Based on impact on non-cancer mortality	Summing β coefficients	0–11.6	Skewed to right

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[46], and for use in combination with measures of performance, functional status, depression and cognitive status in the Comprehensive Geriatric Assessment tool [47].

Yancik et al. [24] 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) and investigated the comorbidity burden of older people with cancer. Their aim was 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 the SEER program, relating to incident cancers linked to standardised data on comorbidity, abstracted from medical notes by trained registrars. 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 subsequent papers (including chronic obstructive pulmonary disease, diabetes requiring insulin, high severity heart disease, previous malignant cancer and renal failure) [48]. Conditions were treated separately in most descriptive and multivariable analyses, but were combined as a simple count in some [48].

Tammemagi et al. [34] 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. 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. The authors identified 19 conditions which predicted survival among lung cancer patients. 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 [33].

Elixhauser et al. [25] developed a measure of comorbidity using administrative data for general (not cancer specific) use. 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. excluded the primary reason for hospitalisation and only included secondary conditions that were not related to the Diagnosis-related group (DRG) of the primary condition. They excluded diagnoses that could have been due to complications of treatment or conditions that were likely to have a trivial impact on resource use or outcomes. There was a final list of 30 comorbidities, which was tested to assess the impact of each condition on cost, 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. However more recently, van Walraven et al. [36] modified the Elixhauser system to allow it to be expressed as a summary score.

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 [9, 45, 49–51].

2.3   Content and Face Validity

The validity of using individual conditions or condition counts varies with different studies, the approach used to identify relevant conditions, and the number of conditions included. The content and face validity will be higher in studies where conditions have been specifically identified due to their likely importance for cancer patients [21, 24, 34]. 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 the case.

2.4   Criterion Validity

2.4.1   Concurrent

Comorbidity counts tend to be correlated with other measures of comorbidity where such comparisons are made [33, 39, 52].

2.4.2   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 [9, 27, 39, 41, 42, 44, 53]. For example, Satariano et al. found that comorbidity as measured by their index was strongly associated with an increased risk of all-cause mortality, and non-breast cancer mortality [21]. Subsequently, higher Satariano index scores were found to be associated with poorer colon cancer survival, whether medical records, administrative data, or both were used [46]. For the NIA/NCI index, patients with comorbidity were less likely to receive aggressive treatment and had poorer survival compared with other patients [24, 48, 54]. 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 [55–57]. Tammemagi's approach to measuring comorbidity was better at predicting all-cause and competing mortality than the Charlson index or simple comorbidity counts [33, 34].

2.5   Reliability

Newschaffer et al. found that the Satariano index had an excellent inter-rater reliability with a kappa score of 0.955 (p < 0.001) [46]. No reliability data have been reported for the NIA/NCI approach. Reliability is generally not relevant for those approaches that are based on administrative data, because, within a given study, data are extracted in a standardised way from electronically stored records.

2.6   Feasibility

Approaches which require notes review are more time consuming and require training, however in many cases these could be converted to administrative data based systems [46].

2.7   Organ-Based Approaches

These 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 earliest example of this, and one of the earliest attempts to measure comorbidity in general, is the *cumulative illness rating scale* (*CIRS*). CIRS is a measure of physical impairment based on assessment of organ dysfuntion [14]. Each of 13 independent body systems (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 the 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 the 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 modified by Miller et al. to form CIRS-G, which was specifically created to be used in geriatric populations [58]. Subsequent minor modifications have been made for geriatric psychiatric populations and for use with acute conditions [59, 60]. CIRS has been used to identify the negative impact of comorbidity on cancer survival in general [61, 62], and for a number of specific cancers, including laryngeal cancer [63, 64], prostate cancer [65], and colorectal cancer [66].

Kaplan and Feinstein [15] were particularly interested in the role of comorbidity among adult diabetic patients. 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. 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 [46], head and neck [64] and prostate cancer [65].

Piccirillo et al. modified the Kaplan-Feinstein Index, initially into the Modified Medical Comorbidity Instrument and then into the *Adult Comorbidity Evaluation-27 (ACE-27) index* [32, 67, 68]. 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 protocols [69]. Twenty-seven conditions that occurred reasonably frequently and were considered to have a negative impact on prognosis were included [67]. The ACE-27 was initially assessed using newly diagnosed patients from one of six hospitals between 1999 and 2002, for whom ACE-27 data were available (n = 11,906) [32]. 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 [70]. Picirrillo et al. assessed ACE-27 among 17,712 patients admitted for prostate, respiratory tract, breast, digestive system, gynaecological, urinary or head and neck cancers at a single academic cancer specialist centre [67]. ACE-27 has also been used successfully in a number of other cancer-related studies [54, 70–76].

The *Index of Coexistent Disease* combines two dimensions; a measure of comorbid disease severity and a measure of functional impairment [20]. 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 [77, 78]. The earlier index included three dimensions:

1. A measure of severity of comorbid conditions
2. A measure of acute exacerbations of these conditions
3. A measure of functional impairment.

However, the index was later modified to exclude the acute aspect of comorbid conditions [20]. 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 Table 2.3 [79]. Data are required from clinical notes (ideally including nursing, medical, and laboratory findings). The ICED (or its immediate precursor) has been used for assessment of the role of comorbidity in treatment and survival for breast, [39, 78] prostate [77, 80, 81] and head and neck cancers [63, 64].

The *Total Illness Burden Index* (*TIBI*) was developed as a measure of case-mix for use in comparisons between hospitals, treatments or health care organisations [22]. It is based on a patient report of symptoms and was designed to be a measure of impact on poor health, on functional status and on 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. TIBI has subsequently been adapted specifically for use among men with prostate cancer

Table 2.3 Scoring system for the index of coexistent disease (OECD)

Highest comorbidity severity score (0–3)	Highest functional status score (0–2)	ICED level (0–3)
0	0	0
0	1	0
1	0	1
2	0	1
1	1	2
2	1	2
3	Any	3
Any	2	3

(TIBI-CaP) [23, 82]. In this instrument, 84 items are included in 11 sub-dimensions for which severity scores are calculated, based on patient symptom reports. The sub-dimensions are also weighted according to the greatest expected clinical impact on the patient [23, 82]. A subset of TIBI (the cardiopulmonary index) has been used to assess patient outcomes among breast cancer patients [39, 52].

2.8   Content and Face Validity

The content and face validity of the organ-based approaches varies depending on the purpose for which they were developed and the approach that was used to categorise individuals into severity categories. For example, the KFI 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. Both the KFI and the ICED require major simplifying assumptions in the scoring system, with a variety of comorbidity and functional status score combinations being treated as equivalent.

CIRS was also not developed specifically for cancer. It allows for a variety of approaches for measuring overall illness, 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 [83]. 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.

Both ICED and TIBI include elements of functional status. TIBI, in particular, 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. Some authors argue that as comorbidity and functional status are distinct constructs, they should not be combined [84, 85], it is not clear whether the method used to combine the two scores is optimal or even appropriate.

In this group of indices, ACE-27 has the highest content and face validity, because it was developed specifically to evaluate the role of comorbidity in the context of cancer. Consideration was given to ensure that all relevant conditions were included. There are clear criteria for the inclusion of conditions, and their severity. However, a number of highly simplifying assumptions are made regarding both the equivalence of severity ratings across conditions and the effect of multiple conditions.

2.9 Criterion Validity

2.9.1 Concurrent

A number of studies have shown that there is correlation between CIRS, KFI, ICED and other comorbidity indices (particularly CCI) [16, 46, 64, 65]. CIRS scores based on medical notes review were found to be closely correlated with those based on autopsy, which is considered the gold standard, and supports (concurrent) criterion validity [86]. TIBI has been found to be more closely correlated with the Charlson and Satariano indices calculated from patient interview, than with those from medical records review [52]. ACE-27 has been found to be significantly correlated with CCI and ASA score [87].

2.9.2 Predictive

Newschaffer et al. found that unlike the Charlson and Satariano 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 [46]. Similarly, Castro et al. found that KFI was not an independent predictor of all-cause mortality among 90 laryngeal patients [63]. In contrast, Hall et al. compared KFI with Charlson, ICED and CIRS, and found the KFI performed best in terms of predicting survival [64]. Boulos et al. 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 [65].

ICED has been found to be associated with higher all-cause mortality among patients with head and neck cancer. ICED has also been shown to be (slightly) more effective at predicting non-cancer death or all-cause mortality among prostate cancer patients, when compared to CIRS, KFI or CCI [65, 81] and more strongly associated with treatment received for early breast cancer in comparison to CCI [39].

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 [14, 62–66, 88]. 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 [63].

TIBI-CaP scores were found to be related to non-cancer mortality among prostate cancer patients after adjustment for sociodemographic factors [23, 89]. A number of studies have shown an association between higher ACE-27 grades and poorer all-cause and cancer-specific survival [32, 54, 67, 71–74, 76]. 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 [32]. 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. Subsequent work by the same authors also supports the predictive validity of ACE-27 [67, 71–74].

2.10 Reliability

In studies that have assessed the reliability of these indices with the exception of TIBI, all have found moderate or high levels of interrater reliability, with k or ICC scores almost all in the range of 0.55 and 0.85 [13, 46, 58, 65, 79, 80, 88, 90–92]. Inter-relater reliability has been reported to be particularly high for ACE-27, with kappa scores tending to be greater than 0.8 [69]. The reliability of TIBI has not been reported.

2.11 Feasibility

These indices have all been designed to require clinical note review and training for abstractors, except for TIBI which requires patient interview. 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 min) and the Index of Coexistent Disease (ICED; 9.5 min) [90]. Several problems in interpreting the instructions for rating individuals using ICED have been reported [79].

Like the KFI (from which it was adapted), the ACE-27 requires special collection of comorbidity data. Registrars require training, which takes a full day to complete, to ensure the quality of the comorbidity data. Once training is completed, the authors report 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 min [69]. However, other studies have reported the time taken is longer, averaging 16.8 min per person in a cohort of patients with head and neck cancers [87]. Recent work involving the use of claims data to measure ACE-27 is promising [70].

2.12 Weighted Indices

Weighted indices score individuals based on the number of conditions that the individual has, with each condition weighted according to its severity.

The *Charlson Index* was the first example of this and is easily the most cited comorbidity index in the literature. It was developed in 1987 by Charlson et al. [16]. 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. 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 an 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 one-year mortality for each condition, with a maximum weight of six. 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 [93–96]. Studies that have attempted to validate the Charlson index using administrative data have found that it performs reasonably well [27, 97–100]. More recently, questionnaires have been developed to allow the calculation of Charlson scores using patients' self-reports [101]. Other studies have used the Charlson approach, but re-weighted the index specifically for the outcome under study (for example [102–104]). 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 uses the beta coefficients (rather than the relative risk) of the association of each condition with one-year mortality to assign weights and does not exclude conditions with a RR less than 1.2 [27, 28].

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 [16, 105, 106], lung [107, 108], colorectal [42, 66, 109–112], urological cancers [113–115], cervical [116], head and neck [30, 64, 87] and haematological cancers [117].

Fleming et al. [118] 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. 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 of 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 indices for each of all-cause and breast cancer specific mortality by multiplying together the relative risk for each comorbidity category and by the interaction term of combinations of comorbidities if it was significant. In a later article, Fleming et al. [119] used a similar approach to develop a comorbidity index for prostate cancer patients'.

Both the *Washington University Head and Neck Comorbidity Index* (*WUHNCI*) [120] and the Simplified *Comorbidity Index* (SCI) [35] were developed for specific cancer sites (head and neck and lung cancer, respectively). Both assessed the impact of specified conditions on mortality and combined them by summing weights based on beta coefficients from multivariable models using mortality as the outcome of interest.

The *C3 index* was developed as a cancer specific comorbidity index for use with administratively collected data [37, 121]. It was developed using data from over 14,000 patients with a range of cancers. Comorbid conditions were identified using ICD-10 codes from administratively collected hospital discharge data, and included if they were were likely to have an impact on function or length of life. There were forty-two conditions in the final index and 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. The index has been used for patients with colorectal, breast, urological, upper gastrointestinal and gynaecological cancers [37, 38, 122, 123].

The final group of weighted indices use pharmaceutical data to identify comorbid conditions. The first, the *Chronic Disease Score* was designed to measure the chronic disease status of a population [19]. The CDS was developed using data from a database held by a large Health Maintenance Organisation in the United States. 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. 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. Subsequently, the CDS weights were refined [18] and later modified, and re-named the *RxRisk Model* [124]. The main purpose of this index was to predict health care costs in the managed care environment of the US [125, 126], although it has recently also been used in Australia [127]. 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 [64, 65]. The CDS has also been used to adjust for comorbidity in a study of cancer outcomes among patients with diabetes [128, 129], and in a cost of illness study relating to cervical cancer [130].

A more recent pharmaceutical-based index, the *Pharmacy-based Comorbidity Index* (*PBCI*) was developed specifically as a measure of comorbidity for cancer populations [38]. Each medication identified in a pharmaceutical database was categorised according to its primary indication for use. Acute and self-limiting conditions were excluded, as were conditions with a prevalence of <1 % in the cancer populations studied. In the final index, 19 conditions were weighted according to their impact on non-cancer mortality and scores were assigned to individuals with cancer based on a sum of the weights for all conditions identified for that patient.

2.13 Content and Face Validity

The Charlson Index was not specifically developed for use among cancer patients, but was validated by its 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), and it assumes that the impact of multiple conditions is additive on a relative risk scale [95, 131–133]. The NCI index also used conditions identified by Charlson, although the weights for included conditions are cancer-specific.

The strengths of Fleming's indices are 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. However these indices were designed for specific cancers, so it may not be easy to generalise this index to other populations with cancer. Similarly, for other site specific indices (WUHNCI and SCI), the process of identifying and combining conditions seems reasonable, but they have only been validated for those specific cancer sites.

The C3 index was designed specifically for cancer populations and included a large number of conditions that are likely to be relevant to cancer patients. Site specific and overall weights were provided and scores were calculated by adding the beta coefficients, which assumes that conditions have a multiplicative effect on each other.

Pharmaceutical-based indices (CDS, RxRisk and PBCI) are based only on conditions for which regular medications have been prescribed. This means that these indices may be subject to provider variation, due to prescribing habits, and utilisation bias, as 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 PBCI was specifically designed for cancer populations.

2.14   Criterion Validity

2.14.1   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, ASA score, C3 index and PBCI index, supporting the concurrent validity of both the Charlson index and these other measures of comorbidity [16, 29, 37, 38, 52, 64, 66, 67, 87]. The concurrent validity of the CDS was assessed by comparing CDS scores with physician-rated disease severity scores, and self-rated health status for individual patients, with moderate correlation with the former and poor correlation with the latter [19]. More recently, the Rx-Risk

index was found to correlate poorly with the Charlson comorbidity index, whilst the correlation between the PBCI and the Charlson index was moderate [38, 127].

2.14.2 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) compared to those with no noted comorbidity. Subsequently, the Charlson index has been found to predict cancer-specific and all-cause mortality in a large number of cancer-related settings [30, 42, 46, 54, 64–66, 108–110, 115, 116]. 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 [40, 76, 104, 134].

The NCI outperformed the Charlson index in predicting two year non-cancer mortality, [27, 28] however the authors used a non-standard approach to calculating the Charlson index, meaning 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).

The C3 index slightly outperformed both the Charlson and NCI indices, both overall and for some cancer sites, in terms of predicting non-cancer mortality [37]. All the site specific indices (Fleming, WUHNCI, SCI) were found to be predictive of mortality among the relevant cancer populations, with the SCI slightly outperforming Charlson in the lung cancer population studied [31, 75, 118, 119, 135].

The performance of pharmaceutical-based indices within cancer populations is 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 [64]. In contrast, Boulos et al. found that CDS was better than CIRS, ICED, KFI, or CCI, in distinguishing groups with different survival probabilities [65]. The PBCI was found to perform similarly to diagnostic-based comorbidity indices (Charlson and C3) in predicting non-cancer mortality among cancer populations [38].

2.15 Reliability

Many of the weighted indices are based on routinely collected administrative hospitalisation or pharmaceutical data. For these, reliability is not relevant, because data are extracted in a standardised way from electronically stored records. 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 to 0.93 [13, 46, 90, 91, 136]. The reliability of data collection for WUHNCI and SCI has not been formally reported.

2.16   Feasibility

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. Those that require data from notes review are more time consuming. 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 min, respectively) [90]. In contrast, Boulos et al. reported that data abstractors rated the Charlson Index as the least easy to use, when compared with ICED, KFI and CIRS in their study of 269 patients with prostate cancer [65].

2.17   Other Approaches to Measuring Comorbidity in Cancer Populations

Case mix approaches, such as the *ACG system*, described in the previous chapter, have been used as a proxy measure for comorbidity in some cancer studies [55, 137–139]. These systems categorise individuals into groups with similar health resource use expectations. The ACG system, for example, 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 Ambulatory Diagnostic Groups (ADGs) [17, 140]. Patients can be included in multiple ADGs, which are then further divided into Adjusted Clinical Groups (ACGs), based on factors such as age, sex, the presence of specific ADGs, and the 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 [17].

The *American Society of Anesthesiologists'* (*ASA*) classification was developed as a pre-operative summary measure of risk of perioperative complications [29]. 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 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). The ASA classification has been used as a method of measuring comorbidity in patients with head and neck, prostate, bladder and breast cancer [29, 141–145].

2.18 Content and Face Validity

The development of ACGs and similar case-mix approaches, is related to health resource consumption, rather than either cancer or comorbidity per se. Similarly, while ASA may be a useful measure of acute outcomes in the surgical setting, it was not developed for the purpose of measuring comorbidity in a cancer cohort [29].

2.19 Criterion Validity

2.19.1 Concurrent

The ASA class has been found to be moderately correlated with the Charlson index [146].

2.19.2 Predictive

The ACG system had similar predictive performance when compared to four other indices included in a study of treatment receipt and outcomes among patients with colon cancer [55].

The ASA class has been associated with all-cause mortality among patients with head and neck cancers in some [29, 147], but not all studies [142]. Similarly, higher ASA scores were associated with poorer all-cause and non-cancer mortality among men with early prostate cancer [141, 143].

2.20 Reliability

For case-mix approaches, reliability is not relevant, because data are extracted in a standardised way from electronically stored records. The reliability of the assignation of an ASA score has been questioned, but some evidence suggests that the reliability of this measure can be considerably improved with minimal training [29].

2.21 Feasibility

Specialised software is available to group patients into ACGs. 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.

2.22   So Which Index Is Best?

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).

There is no gold standard measure of comorbidity in the context of cancer [1]. In an ideal world, we would be able to perfectly measure the underlying construct of 'comorbidity' for every individual. However, because of the complexities of comorbidity, we are only ever going to be able to estimate a measure of this concept. All approaches that are designed to measure comorbidity are necessarily simplifications of this concept. In other words, there will always be some mis-measurement of comorbidity. The choice of measure depends on a number of factors and there is unlikely to be a single 'correct' choice in any context. Some of the key considerations in choosing a comorbidity measure are:

1. *The study question*: For example, if the question relates to a single cancer site, it may be reasonable to use an index developed specifically for that site. However, if comparability with other studies or other cancer sites is important, it may be more reasonable to use a more general index.
2. *The role of comorbidity in the study*: If comorbidity is being measured as a key exposure or outcome, it is likely to be important to optimise the measure to the extent possible. For example, if comorbidity is being considered as an exposure (for example, does comorbidity affect cancer survival), then mis-measurement of comorbidity will most commonly result in an underestimation of the association between comorbidity and the outcome of interest (although biases can occur in both directions). To minimise this bias, it would be reasonable to consider using the index with the highest possible validity for the particular study question. In contrast, if comorbidity is being considered as primarily a confounding (or mediating) variable, then the choice of measure may be less important. When different approaches to measure 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, 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 only moderate correlation between the indices themselves [99].
3. *Practical considerations*: If clinical data have been collected or if it is feasible to do so, indices which require this are available. However, if this is not the case, only indices based on routinely collected data can be considered. In this context, appropriate data and data management skills will be required to operationalise these indices.

Table 2.4 Qualitative criteria used to assess measures of comorbidity

Criteria	*	**	***	NR
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
Feasibility	Requires substantial resource to implement	Moderate ease of implementation	Easy to implement. Does not require substantial resource	

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Table 2.4 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 2.5 provides the assessment for measures of comorbidity in the context of cancer, though it should be noted that the outcomes of this assessment may well differ if specific research questions or contexts were considered. For example, if clinical data have already been 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.

Table 2.5 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[a]	Feasibility[b]
CIRS	***	**	***	***	**	*
KFI	**	**	***	***	**	*
Charlson	***	**	***	***	**	***
ACGs	*	*	NR	**	NA[c]	**
CDS/Rx-Risk	**	*	**	**	NA[c]	**
ICED	**	**	***	***	**	*
Satariano	**	**	***	**	***	***
TIBI/TIBI-CaP	**	*	***	**	NR	*
NIA/NCI collaborative study	***	**	NR	**	NR	*
Elixhauser (count)	***	**	NR	***	NA[c]	***
Comprehensive prognostic index	**	***	NR	***	NA[c]	**
NCI comorbidity index	***	**	**	***	NA[c]	***
ASA	**	*	**	**	**	**
Alcohol-Tobacco related comorbidities index	**	**	**	**	NA[c]	***
Washington University head and neck comorbidity index	**	***	NR	**	**	***
ACE-27	***	**	***	***	***	*
Tammemagi	**	***	**	**	NA[c]	**
SCI	**	**	**	**	NR	*
C3 index	***	***	***	***	NA[c]	***
PBCI	***	***	**	***	NA[c]	***

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[a]Reliability assessed when notes review or patient interview carried out

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

[c]NA Not applicable

The content and face validity depends on the extent to which indices are likely to capture all elements of comorbidity important to cancer patients. All indices will do so to some extent. In general, those that are designed specifically for assessing outcomes among cancer patient populations may arguably have higher face validity than those that do not. For example, ACGs and Rx-Risk were 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 have not been used a lot in the context of cancer patients (e.g. ACG and ASA), so there is relatively little evidence on their validity in this particular context. These approaches also rate lower on content and face validity.

Another key consideration in relation to content and face validity relates to the process of assessing the severity of individual conditions and to combining them into a single metric. Simple counts of conditions make the implicit assumption that all conditions are equally important in relation to outcomes, regardless of their severity. Weighted indices use various approaches to combine conditions. For example, the Charlson index assumes that the impact of multiple conditions is additive, and that the prognostic impact of a condition is constant over time and regardless of the primary condition being investigated. Subsequent indices have used alternative approaches, including the use of beta coefficients as weights rather than relative risks, and the calculation of cancer specific weights. Few have explicitly explored the impact of specific combinations of conditions [118, 119]. Organ and systems-based approaches tend to use highly simplified scoring systems. For example, KFI and ACE-27 both assume that a 'severe' rating in any body system is equivalent to two 'moderate' ratings in different systems.

There is some evidence to support the predictive validity of all approaches. However, some indices have been used more extensively in the context of cancer than others, improving the evidence base for those indices (for example, CIRS, Charlson, ICED, Elixhauser, NCI combined, ACE-27, C3 index and PBCI). For all indices, where data could be found, there was also at least moderate evidence for concurrent validity. Studies that have compared the performance of various measures of comorbidity have had inconsistent results, depending on various factors, such as the size of the study, the cancer site studied, the way the comorbidity indices were categorised and the outcome measure used [1].

Reliability is most relevant for indices that are dependent on the manual collection of clinical data or from patients themselves. Reliability tends to depend on simplicity, clarity and ease of use of the index, as well as the quality of the training of the abstractors. For some indices, no specific data on reliability were found (e.g. for TIBI, NIA/NCI Collaborative Study Index or SCI). For CIRS, CCI and ICED and ACE-27, interrater reliability tended to be moderate to high in all studies reported [64, 65, 69, 77, 78, 91, 148–157]. Reliability is less of an issue for the other measures, because they are based on administrative data abstracted in a standard manner. However, there are inherent weaknesses with administrative data. Data may be missing or inaccurate, it can be difficult to differentiate complications of disease from pre-existing conditions, and there may be biases inherent in coding

practices, for example in some jurisdictions there may be an over-emphasis on recording those conditions that attract higher funding [25, 99, 158].

The feasibility criterion for the indices relates the extent to which time and resource is likely to be required to use it. Those that require special collection of data, for example, may not be appropriate for population level cancer studies because of the resource required to collect the data. For this reason, some indices that scored well on all other criteria scored low on the feasibility criterion, for example, CIRS, ICED and ACE-27. The recent work underway to develop a claims-based version of ACE-27 will, if further validated, improve the feasibility of this measure [70].

In summary, many approaches to measuring comorbidity in cancer-related studies exist. They vary in terms of the purpose for which they were developed, the type of data required for their estimation and the methodological approaches they use. There is no approach that is clearly superior to the others, with the choice of measure being dependent on factors relating to the study questions, validity concerns and practical considerations.

2.23 Future Directions for Practice or Research

Whilst there are no gold standard measures of comorbidity, the assessment of the impact of comorbid conditions on cancers is important. Comorbidity is an important variable to consider as a moderator of cancer outcomes. Future work could focus on the impact of comorbidities in cancer care and outcomes from the perspective of those affected by cancer (such as the impact of comorbidity on survival, disability and individual costs of care) and from the perspective of the health system (such as overall cost of care and health care utilisation).

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Cancer and Chronic Conditions
Addressing the Problem of Multimorbidity in Cancer
Patients and Survivors
Koczwara, B. (Ed.)
2016, XII, 475 p. 28 illus., 20 illus. in color., Hardcover