PERGAMON

European Journal of Cancer 36 (2000) 453–471

European Journal of Cancer

www.elsevier.com/locate/ejconline

Review

Measuring comorbidity in older cancer patients

M. Extermann *

Senior Adult Oncology Program, H. Lee Moffitt Cancer Center at the University of South Florida, 12902 Magnolia Drive, Tampa, FL 33612, USA

Received 6 July 1999; received in revised form 12 November 1999; accepted 23 November 1999

Abstract

The aim of this article was to provide oncology researchers with adequate tools and practical advice to integrate comorbidity into clinical studies. Open research questions are also discussed. Commonly used comorbidity indexes were identified and a detailed literature search was done by MEDLINE and cross-referencing. Expert opinion was sought on each index. A common scheme exploring the description of the index, clinical experience, metrological performance, easiness of use, cross-compatibility and preservation of data was followed. The actual indexes are included in the Appendix. Four commonly used indexes were identified: the Charlson Comorbidity Index (Charlson), the Cumulative Illness Rating Scale (CIRS), the Index of Coexistent Disease (ICED), and the Kaplan–Feinstein index. The Charlson is the most commonly used whereas the performance of the first two indexes is best characterised. Most studies are retrospective and focus on mortality as an outcome and a base of grading. All indexes are easy to use and require a maximum of 10 min to be filled. Inter-rater and test–retest reliability is generally good. Little is known about other outcomes and the way various diseases cumulate in influencing prognosis. Thus, several reliable indexes are available to measure comorbidity in cancer patients. They show that globally comorbidity is a strong predictor of outcome. Since little is still known about the importance of individual comorbidities for various outcomes and the way comorbidity cumulates in influencing cancer treatment, a wide integration of comorbidity in prospective studies is essential.

Keywords: Comorbidity; Aged; Aged >80; CIRS; Charlson; ICED; Kaplan–Feinstein; Cancer

1. Introduction

Cancer is a disease that has an increasing incidence with age. Presently, 60% of cancers and two-thirds of cancer deaths occur beyond the age of 65 years in developed countries [1]. Due to the ageing of the population, this proportion is expected to increase markedly in the next decades. As a result, oncologists will be increasingly treating cancer in patients who have concomitant diseases. In a 'typical' geriatric series, people 65 years of age and older suffer on average from three different diseases [2]. Similarly, older cancer patients present a high level of comorbidity, both in the general population and in oncology consultations (Fig. 1). Multiple studies have demonstrated that comorbidities are relevant to the prognosis of cancer patients, e.g. survival (reviewed in [3]). Therefore, comorbidity can become a major confounder in oncological practice and studies in the elderly. Indeed, geriatric oncology can be defined as "when the health status of a patient population begins to interfere with oncological decision-making guidelines". A solution largely applied by oncological investigators in the past was either to exclude older cancer patients, or to consider comorbidities as an exclusion criterion. Therefore, randomised studies offer a mortality principally related to the cancer treated. However, given the high prevalence of comorbidity in older cancer patients, these patients are very under-represented, even in studies without an upper age limit [4,5]. In addition, as the comorbidity level of these selected older patients is seldom reported, clinicians are given few clues as to how to adapt the results from cooperative studies to patients with comorbid diseases.

Another approach would be to integrate comorbidities as a variable in the studies, in the same way as functional status presently is. Functional status does not appear to correlate closely with either tumour stage or comorbidity [6]. Therefore, comorbidity should be assessed independently.

However, contrary to functional status, comorbidity presents the unique challenge of being a multidimensional variable. Diseases influencing mortality

* Corresponding author. Tel.: +1-813-979-3822; fax: +1-813-972-8468.

E-mail address: extermann@moffitt.usf.edu (M. Extermann).

0959-8049/00/$ - see front matter
PII: S0959-8049(99)00319-6

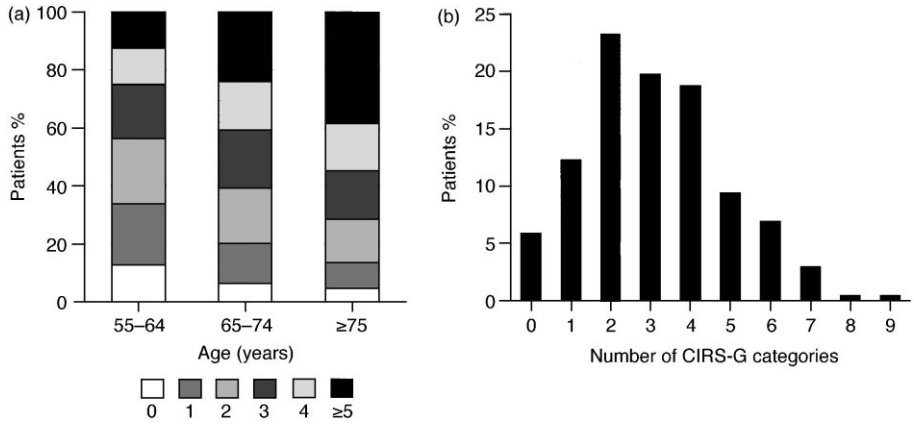

Fig. 1. Prevalence of comorbid diseases in older cancer patients. (a) Epidemiologically: in the SEER registry: qualitative definition [11]. (b) Outpatient oncological consultation: in Moffitt's Senior Adult Oncology Program [6] (reproduced from [3] with permission).

may not be the same as diseases influencing function or tolerance to treatment. Several scoring systems with varying approaches to that problem have been proposed which will be reviewed in this article, with their characteristics and their validity. Comorbidity indexes can be used in different settings: epidemiological studies (e.g. tumour registries), clinical trials of chronic diseases (e.g. cooperative oncological studies) and clinical trials in acute care settings (such as Intensive Care Units). Each of these settings has a considerable influence on the way comorbidity is approached. The focus of this article is to provide measurement tools for use by oncologists in the clinical study setting. Four validated indexes applicable to this setting will be reviewed in careful detail, their metrological performances, the indexes themselves and rating references, and their practical implementation. Key research issues that need to be investigated are also addressed as well as a few pitfalls to avoid. The reader interested in a larger overview of the indexes available for different settings, as well as a comprehensive review of the prognostic impact of comorbidity is referred to a parallel article [3].

2. Why focus on four indexes?

Comorbidity is a rather young field of research, and as discussed in more detail in the research section below, much remains to be learned about how comorbidities cumulate to influence prognosis. Therefore, it may seem restrictive to some to review only four scales and suggest their use for clinical studies in oncology. Essentially two situations must be distinguished. The first is comorbidity as the focal point of a study. That kind of study necessitates large collectives of several hundred to several thousand patients, typically epidemiological databases. Here a large freedom is warranted to approach the problem and learn more about how individual diseases interact. Careful attention, however, needs to be paid in this case to the definitions employed for each disease and the way data are collected, in order to allow the data to be tested reproducibly by other groups [7–10]. Such a large database is not yet available for cooperative clinical studies. This research will take several years to mature and epidemiological databases are limited by the heterogeneity of treatment. Meanwhile, clinical oncologists are confronted with another situation. Given the ageing of the population, the prognosis and tolerance to treatment need to be balanced for comorbidity. Study designers feel an increasing need to include comorbidity in their projects and require readily available methods to do so. This would also greatly enhance the transferability of the study data to the community, as discussed above. Here is where well validated scales with known metrological performance are adequate. They will allow head-to-head comparison of studies, as well as large-scale meta-analyses on similarly treated patients rendered possible by data collection in compatible formats. The four indexes discussed below have been chosen because they are the ones for which there are, by far, the most data available in the published literature. Each has been used in at least half a dozen published studies, by different investigators. These indexes represent effective tools for a measurement of comorbidity in clinical oncology studies and should allow, in the next few years, a large data set to be built from prospective studies. Evidently, one should be aware that these indexes will not constitute the last step on the road of measuring comorbidity in cancer patients, but are precious instruments to progress along that road.

3. Review of the indexes

Although qualitative definitions are largely used in epidemiological studies, graded indexes tend overall to offer a higher risk discrimination and are preferred in

clinical studies [3,7,11]. All four indexes discussed here use a grading system. One index (the Charlson) weighs precise diseases differently, two indexes offer progressive severity grading within several categories of diseases (the Kaplan–Feinstein and the Index of Coexistent Diseases), one index finally offers progressive grading of comorbidity within each organ system, either by type of disease, or several levels of severity of the same disease (Cumulative Illness Rating Scale: CIRS). An overview of the characteristics of these indexes is presented in Table 1.

The literature relevant to each index was extracted by Medline searches and cross-references. Expert opinion was sought including that of the authors of the indexes. Several elements are also derived from the author's direct experience in rating comorbidity, first in sepsis, then in cancer patients.

4. Charlson Comorbidity Index (Charlson)

4.1. Description

The Charlson is probably the most widely used comorbidity index to date [12]. It was designed by Mary Charlson and colleagues in 1987. They used data from an internal medicine inpatient service and analysed the mortality at 1 year as a function of various comorbidities. As a result, a list of 19 conditions (certain of them representing two degrees of severity of the same condition) was designed. Any disease generating a relative risk of death $\geqslant 1.2$ was retained and weighted. If the relative risk was $\geqslant 1.2$ and < 1.5, the weight was 1; if $\geqslant 1.5$ and < 2.5, the weight was 2; if $\geqslant 2.5$ and < 3.5, the weight was 3; and the two conditions with a weight of 6 or more were weighted 6. The total score is calculated. It can then be collapsed into four ordinal categories: 0, 1–2, 3–4 and $\geqslant 5$ points. The index was validated in a cohort of breast cancer patients, with the 10-year mortality rate as an endpoint. In the validation cohort, the Charlson was adjusted for age, using the following formula: each decade of age, starting at 50 years of age, was counted as an extra point.

4.2. Clinical experience

As mentioned above, the Charlson is widely used (reviewed in [3]). It is valid in predicting mortality risk over a period of a few weeks to 10 years in conditions ranging from breast cancer to spine surgery [8,12–14]. It is correlated also with such outcomes as postoperative complications, length of hospital stay and discharge to a nursing home [8]. It has been validated in older cancer patients [6], where it also correlates with progression-free survival [15]. Its performance in predicting mortality is in the range of that of the CIRS and the Kaplan–Feinstein scales [12,16]. Potential limitations in oncology include the fact that the index ignores several comorbidities that may be relevant in designing the treatment of cancer patients, such as haematopoietic disorders other than malignancies, polyneuropathy or moderate renal dysfunction.

Table 1
Construction of the major comorbidity scales reviewed in this article

Scale	Type	Items and rating	How constructed	Inter-rater reliability	Test–retest reliability	[Ref.]
Charlson	Weighted	19 diseases weighted 1 to 6 Total: 0-30[b]	Internal medicine patients: 1 year mortality	0.159–0.945[a]	0.86–0.92	[6,7,12,17,18]
Charlson/age	Composite	Original Charlson + each decade above 50 as 1 point	Same as Charlson			
Cumulative Illness Rating Scale (CIRS)	Weighted	13 or 14 organ system categories, rated 0–4 Total: 0–52 or 56[b]	Comprehensive listing of diseases weighted by clinician estimate or manual	0.76–0.91[c]	0.95[c]	[6,16,25,28,30,33]
Index of Coexistent Disease (ICED)	Composite	Disease severity subindex: 14 diseases (0–4) Functional severity subindex: 12 conditions (0–2) Total: 0–3	Breast cancer patients: anticipated outcome 2 years after hospitalisation	0.57–0.71	0.93	[34,35]
Kaplan–Feinstein	Weighted	12 conditions (10 diseases, locomotive function, and alcoholism): 0–3 Total: 0-3	Diabetics: diseases that might be expected to impair survival	0.82	N/A	[7,43]

[a] See text for comments.
[b] Alternative scoring strategies available.
[c] Total score.

4.3. Metrological performance

The Charlson has a good inter-rater and test–retest reliability. The inter-rater reliability was 0.74 (95% lower bound estimate (LBE) 0.60) by intraclass correlation coefficient (ICC) in older cancer patients [6]. Its test–retest reliability is 0.86 (95% LBE 0.72) in the same population. In another study of older breast cancer patients, the weighted kappa was 0.945 for inter-rater agreement [7]. In surgical patients, the test–retest reliability by ICC was 0.92 [17]. A study in stroke patients found an astonishingly low inter-rater correlation (ICC 0.159) [18]. However, this may be due to the very narrow range of scores in the sample tested for the ICC (data not shown).

In most series, especially in cancer patients, in whom the primary disease is generally excluded (four of the Charlson items relate to cancer), the distribution of the Charlson scores is highly skewed (Fig. 2). The range in cancer patients is short, with very few patients rating 3 or more [6,12]. In Charlson's original series, the progression of the predictive risk of death is fairly regular. The published incremental risks for the age-corrected version are 1.45–2.4 for each point [12,19]. In

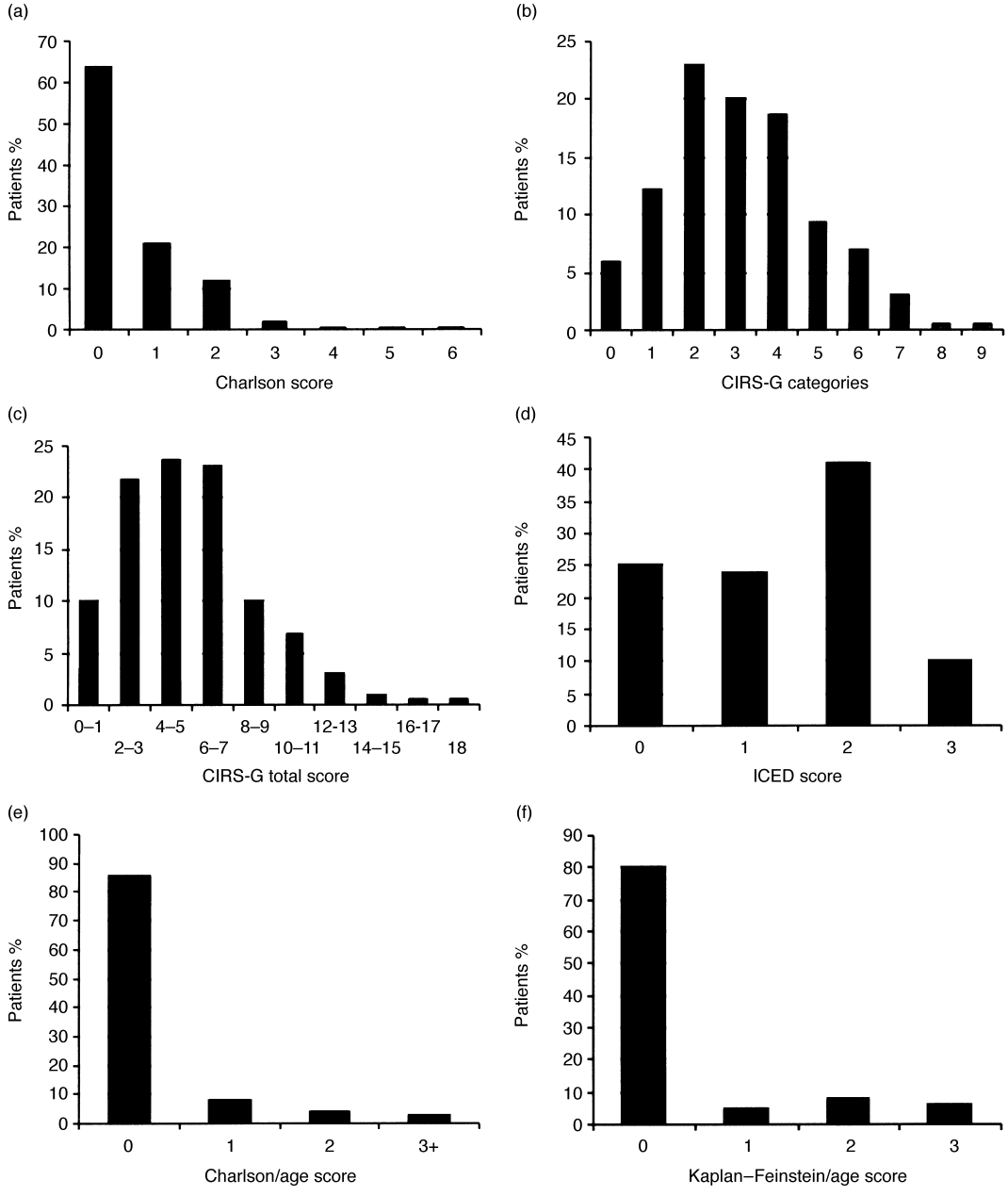

Fig. 2. Distribution of comorbidity scores in sample populations of cancer patients. (a) Charlson; (b) and (c) CIRS-G: number of categories and total score (outpatient older cancer patient population) [6]; (d) ICED (postmenopausal breast cancer patients from several institutions) [37]; (e) Charlson/age; (f) Kaplan–Feinstein + age (breast cancer patients from one institution) [12].

multivariate models where age is separated from the Charlson score, the incremental risk for the Charlson is 1.13–1.4 per point [20–23]. In a sample of older cancer outpatients, 36% had a positive score on the Charlson scale. The median score was 0, and the range 0–6 (20% of maximum possible score) (Fig. 2) [6]. Estimates of the predictive ratios for specific outcomes, patient groups and study settings can be extracted from the author's parallel review [3].

4.4. Ease of use

The Charlson is very easy to fill, especially if scores are preprinted (see Appendix A). The rating criteria are fairly easy to memorise for a frequent user and the list is short. Its ease of use is without doubt part of its success.

4.5. Cross-compatibility

The Charlson has been adapted to databases via the ICD-9 codes and therefore is also widely used in epidemiological studies [3,8,9,24]. The correlation between chart-derived and ICD-9 code-derived Charlson is, however, fair to moderate: 0.36–0.47 [7,10].

The Charlson can also be extracted fairly easily from a CIRS-G score, given a few precautions. Owing to differences in scope and weighting of diseases, the level of correlation is moderate. It is 0.39 between the Charlson and the CIRS-G in one study [6], and 0.51 between the Charlson and the CIRS in another [16]. A self-administered questionnaire has been derived from the Charlson, however, its correlation with a chart-based Charlson was only 0.63 [17].

4.6. Data preservation

Only the diseases listed in the Charlson are preserved. They are well defined, except for cancers, which are more generic.

5. The Cumulative Illness Rating Scale (CIRS)

5.1. Description

The CIRS was first designed by Linn and colleagues in 1968 [25]. It is aimed at a comprehensive recording of all the comorbid diseases of a patient. Its principle is to class comorbidities by organ system affected, and rate them according to their severity from 0 to 4, in a way similar to the Common Toxicity Criteria grading (none, mild, moderate, severe, extremely severe/life-threatening) [26]. Within each category, if two diseases are present, the disease with the highest severity is counted. The scale can then be summarised as a total number of categories involved, total score, mean score, or number of grade 3 or 4 diseases. Linn and colleagues did not define precise diseases/rating associations, and relied on the physician's judgement. Later authors have added slight modifications to the list of organ systems or, in trying to enhance inter-rater reliability, have designed a rating manual [27]. As a result, the CIRS has 13 or 14 organ systems subdivisions (14 in recent publications). These are: cardiac, vascular (in recent versions, subdivided either between vascular and haematopoietic (CIRS-G [28]), or vascular and hypertension [29,30]), respiratory, eyes, ears, nose, throat and larynx (EENT), upper GI, lower GI, liver, renal, other genito-urinary (GU), musculoskeletal/integuments, neurological, endocrine/metabolic and psychiatric. An adaptation that is particularly interesting for geriatric oncologists is the CIRS-Geriatric (CIRS-G) designed by Miller and colleagues, with a multidisciplinary designed rating manual aimed at a geriatric population (and, therefore, detailing several geriatric problems in the list) [27,28].

5.2. Clinical experience

There is also a large experience with the CIRS in clinical series (reviewed in [3]). The CIRS scores correlate with mortality, hospitalisation rates and duration, hospital re-admission, medication usage, abnormal laboratory test results, functional disability and patient morale in geriatric populations [28–32]. The CIRS and functional disability are independent predictors of mortality in elderly persons [28,20–31]. The CIRS-G has been validated in older cancer patients [6], where it also correlates with progression-free survival [15]. It correlates well with post-mortem findings [33]. Its prognostic performance compares very well with the Charlson [16]. Potential limitations in an oncology setting are correlated to its inclusiveness. Diseases relevant for a specific outcome may be confounded by less significant diseases.

5.3. Metrological performance

The CIRS has a good inter-rater and very good test–retest reliability. In Linn and colleagues' original study the inter-rater correlation was >0.82 (Kendall's W) [25]. In a surgical series, the inter-rater reliability of the total score was 0.8 [16]. In geriatric outpatients, the CIRS-G inter-rater correlation by ICC was 0.78 for the total score (95% LBE 0.55), and 0.81 for the number of categories endorsed (95% LBE 0.61). For inpatients, it was 0.88 (95% LBE 0.85) for the total score, and 0.83 (95% LBE 0.78) for the number of categories [28]. In a study in older cancer patients, the CIRS-G inter-rater reliability was 0.76 (95% LBE 0.63) for the total score, 0.72 (95% LBE 0.57) for the mean score, 0.67 (95% LBE 0.50) for the number of categories rated and 0.59 (95% LBE 39%) for the number of grade 3/4 diseases. The test–retest reliability in these patients was 0.95 for

the total score (95% LBE 0.91), 0.90 for the number of categories (95% LBE 0.79), 0.57 for the mean score (95% LBE 0.26) and 0.87 for the number of grade 3/4 diseases (95% LBE 0.75) [6]. The total categories and total scores are, therefore, the most reliable variables. The behaviour of the mean score is somewhat more erratic and quite unstable. The number of grade 3 and 4 diseases provides important qualitative information. However, its inter-rater reliability is somewhat low for correlation studies [6]. The shape of the association of CIRS with mortality has been less studied than for the Charlson, although it seems to progress correctly through the spectrum of scores [3,30]. In a sample of older cancer patients, 94% had some degree of comorbidity on the CIRS-G scale, which has also a wider range of variability than the Charlson scale [6]. The distribution of total scores and total categories was a skewed normal one in older cancer patients (Fig. 2). The median total score was 5 (range: 0–18: 33% of maximum possible), and the median number of categories 3 (range: 0–9: 67% of maximum possible). Estimates of the predictive ratios for specific outcomes, patient groups and study settings can be extracted from the author's parallel review [3].

5.4. Ease of use

Rating the CIRS requires more training than the Charlson, in order to assess the severity of diseases. The CIRS-G necessitates a working familiarity with the manual, but such a tool can alleviate the level of medical training required for rating [27]. A trained rater can rate a patient in 5–10 min from a medical record. In order to render the rating easier the author and Gregory Gulick, MA, have designed a software program. Even so, its user-friendliness does not match that of the Charlson.

5.5. Cross-compatibility

A Charlson score can be easily extracted from the CIRS, if one takes the precaution of writing the diagnoses considered on the data sheet, including creatinine value if renal insufficiency is present. Due to differences in scope and weighting of diseases, the level of correlation is moderate. It is 0.39 between the Charlson and the CIRS-G in one study [6], and 0.51 between the Charlson and the CIRS in another [16].

5.6. Data preservation

By allowing recording of diseases on the scoring sheet and requiring grading of diseases, the CIRS allows extensive data preservation, independent of the chart. This ability to record each disease presented is the major strength of the CIRS.

6. The Index of Coexistent Diseases (ICED)

6.1. Description

The ICED was developed by Greenfield and colleagues in 1987 to address issues of intensity of care [34]. It consists of two subscales: physical and functional. In ICEDs present version, the physical subscale rates comorbidities from 0 to 4 in severity (the same principle as the CIRS), and regroups them in 14 categories: organic heart disease, ischaemic heart disease, primary arrhythmias and conduction problems, congestive heart failure, hypertension, cerebral vascular accident, peripheral vascular disease, diabetes mellitus, respiratory problems, malignancies, hepatobiliary disease, renal disease, arthritis and gastro-intestinal disease. The diseases are graded according to a manual. The functional subscale contains 12 domains of functional impairment, rated 0–2. The scales are then summarised each by the highest score obtained, and both scores are lumped together to form an overall severity score ranging from 0 to 3. Some publications may differ slightly in the number of disease categories and rating [34,35].

6.2. Clinical experience

The ICED has been mostly used to study the correlation of comorbidity with treatment patterns in cancer patients (reviewed in [3]). It has been shown to correlate with the intensity of treatment in breast and prostate cancer, as well as with the use of axillary node dissection in breast cancer [34,36–37]. It also correlated with postoperative complications and functional outcome in hip replacement patients [38]. It correlated with survival in patients with prostate cancer and benign prostatic hyperplasia [39,40]. It did not correlate with hospital readmission in a small series of veteran patients [41].

6.3. Metrological performance

In Greenfield's original article, the agreement between raters was complete in 73.3% of cases for the overall disease value, 56.7% for the overall functional status, 66.7% for the combined index. It was 90% for the number of variables rated [34]. In a series analysing its performance in older orthopaedic patients, the ICED had an excellent test–retest reliability (ICC 0.93), but a moderate inter-rater reliability (ICC 0.569–0.7067) [35]. This appeared to be due more to the physical than the functional part. The shape of the association of ICED with mortality has been less studied than for the Charlson, although it seems to progress correctly through the spectrum of scores [3,40]. The distribution of the combined index is more even than that of the Charlson or the Kaplan–Feinstein (Fig. 2) [34,37].

6.4. Ease of use

Like the CIRS-G, the ICED needs a rating manual and a rater with some medical knowledge [42]. Its rating times are comparable with those of the CIRS-G.

6.5. Cross-compatibility

The ICED data are not directly translatable in other comorbidity scales but can be analysed separately from functional items. Some data of its functional scale can be used for comparison with geriatric functional scales such as Katz's Activities of Daily Living. The integration of comorbidity and functional status in one scale is the originality of the ICED and contributes to its predictive ability [40].

6.6. Data preservation

Only the diseases and functions listed in the ICED are preserved. They are well defined.

7. The Kaplan–Feinstein index

7.1. Description

The Kaplan–Feinstein was developed by these two authors in 1974 [43]. It consists of a list of conditions "that might be expected to impair a patient's long-term survival". These conditions are regrouped in 12 categories (hypertension, cardiac, cerebral or psychic, respiratory, renal, hepatic, gastro-intestinal, peripheral vascular, malignancy, locomotor impairment, alcoholism and miscellaneous) and rated 0–3 according to severity. The severity criteria are well defined. The number and severity of diseases are then summed in an overall comorbidity grade from 0 to 3.

7.2. Clinical experience

The index has also been used in many studies in various settings (reviewed in [3]). It correlates with mortality in patients with several medical conditions, including breast and prostate cancer patients [12,40,43–45]. It has been integrated in predictive scores of cancer outcome for prostate and head and neck tumours [44,46].

7.3. Metrological performance

The inter-rater reliability was good at 0.82 (weighted kappa) in a study of older breast cancer patients [7]. No data are available on test–retest reliability. The correlation with mortality was studied by Charlson and colleagues. For each level of Kaplan–Feinstein, it was 2.0 (95% CI: 1.6–2.4). The distribution of scores is skewed to the left with 80% of breast cancer patients scoring 0 (Fig. 2) [12].

7.4. Ease of use

The rating instructions are simpler than those of the CIRS and the ICED and closer to the simplicity of the Charlson.

7.5. Cross-compatibility

The Kaplan–Feinstein data are not directly translatable in other comorbidity scales.

7.6. Data preservation

Only the diseases and functions listed in the Kaplan–Feinstein are preserved. They are well defined.

8. Practical implementation

In the author's and other clinicians' experience, comorbidity indexes are usually easiest to fill on the basis of the initial study history and physical examination report, and the routine laboratory closest to that date. A direct attempt at implementation at bedside most often results in a doubling of services to the patient without clearly demonstrated benefit. Patient-filled comorbidity reports are fairly good for simple items, but their correlation with physician's history taking is not particularly high (0.45–0.63) [17,47]. In addition, this correlation is dependent on the education level [17]. In a study by Katz and colleagues the predictive power was comparable with the Charlson scale. In Silliman and Lash's study, the conclusions are limited by the fact that highly truncated versions of the Charlson and the Satariano index were used [47]. Comparison has also been made between chart-derived and administrative data (ICD-9 codes)-derived comorbidity scores, with a better or equal performance obtained for chart-derived scores [7,10] and correlation between the two was only moderate (0.30–0.47). Given these limitations, the author of the present article suggests the chart record method for clinical studies, as close as possible to the examination of interest, in order to be able to elucidate missing or unclear information. In a clinical study setting, the initial assessment and laboratory are usually quite detailed, and should include or refer to a precise past medical history and substance abuse history. For the rating, the tumour of interest, as well as its complications or those of treatment, are usually not counted [6,7,12,39,48,49]. The tumour-related symptoms are often included in the tumour staging (e.g. Hodgkin's

'B symptoms', or renal insufficiency in myeloma). The treatment-related effects are highly variable over short periods of time and are best accounted for by the Common Toxicity Criteria [26]. The index to apply should be carefully chosen in the function of the study aim, but should be selected amongst validated indexes (such as the ones mentioned in this article), in order to enable cross-study comparisons (as discussed at the beginning of this article). Different indexes can give a very different picture of a patient's comorbidity, both quantitatively and qualitatively. In a study comparing the Charlson and the CIRS-G in older cancer patients, 36% rated positively on the Charlson, and 94% on the CIRS-G [6]. The most frequent diseases according to Charlson were second tumour (10%) and diabetes (7%), and according to the CIRS-G were locomotive/tegumental problems (43%), vascular conditions (36%), genito-urinary diseases (31%), cardiac conditions (30%) and breast and endocrine diseases (29%). The indexes should be rated by trained raters, who need to have some medical education: physicians, nurse practitioners, physician assistants, research nurses or medical students can be used. The inter-rater and test–retest scores mentioned above have been obtained between persons with different medical training [6,28]. Training takes approximately 20 charts under supervision, and then a senior rater available for specific questions (usually an MD). In prospective studies (clinical trials or cohort databases), data can be entered on accrual, and a raw list of the diseases considered should be kept (e.g. in the CIRS-G, this can be done on the data sheet or the computer history window). In prospective cohort studies, the assessment time(s) should be carefully chosen, so that they correspond with a time when extensive data are collected. For example, at the time of the initial visit or at admission. An assessment at the time of initial outpatient visit has proven highly effective in Moffitt's Senior Adult Oncology Program cohort over a period of 5 years and more than 800 patients. For multicentric trials, two solutions can be adopted. For very simple indexes, such as the Charlson, the rating can be decentralised with adequate initial training and instructions. For more complicated indexes, such as the CIRS, or as a general alternative, this author suggests a centralised rating. The initial examination report and the initial laboratory data are sent to the data centre (eventually via a formatted data collection sheet), where trained raters calculate the scores and enter them in the central database. This has several advantages: the centralised raters can be more easily trained, the rating is more uniform and rapid, and the raters have easier access to a consulting physician (for example, an investigator familiar with the scales). Quality control is easier for the investigators. The original data are also easier to access for future retrospective reviews.

9. Research issues

The measurement of the influence of comorbidity in (older) cancer patients is still in its infancy. Although there is now clear evidence of the high prevalence and the influence on survival of comorbidity, much remains to be explored. The first question is: Do only a few specific diseases matter, or is the overall burden of disease (a more 'geriatric' understanding) important? One may expect some diseases, such as myocardial infarction, dementia or stroke, to have a strong impact on prognosis. However, it is also true that older patients have a general decrease in their functional reserve that leads to a 'domino effect' when these systems are under stress. This general decrease may be noticeable through an accumulation of minor dysfunctions at baseline more than through one well compensated condition.

A second, related, issue is: how do comorbidities cumulate in determining patients' outcome? Are they simply additive, synergistic or does the incremental weight decrease with the number of diseases? How do they interact with cancer-related events? Whilst a study by Satariano and Ragland does not show an interaction on mortality in breast cancer, a study by Newschaffer and associates suggests there may be a small one (1.17, $P = 0.12$) [48,50]. A study by Fried and coworkers on paired diseases showed a grossly additive pattern on disability when two diseases are paired. There may be an additional effect of further accompanying diseases that remains to be clarified [2].

A third issue is: are the diseases that predict mortality the same as those that predict functional decline, toxicity from treatment or decreased quality of life? Totally similar or totally dissimilar lists are unlikely. Models may develop more likely with a common stem of diseases (small or large), and several endpoint specific branches, in a cancer QOL scale-like manner (see, for example, the FACT or EORTC QLQ systems). Integrating weighting of diseases in such a model may, however, be difficult, and even more so if comorbidity does not prove simply additive. Therefore, models may also develop with a less closely fitting, but more generally applicable weighted grid similar to the CIRS, or a model with a list of systems impaired or specific conditions and columns of modulated weights according to the outcome of interest.

A fourth, very important issue is to elucidate the level of external validity of therapeutic oncological trials. Whereas in younger patients, the patients engaged into clinical trials are representative of the majority of the population, such is not the case as age advances. Presently, little information is available to allow rational transfer of results from, for example, randomised trials to a less healthy population. Even patients with a very good ECOG PS can present significant comorbidity

and minor functional impairments [6]. Evaluating comorbidity could facilitate the transfer of trial results to general practice. A reliable evaluation of comorbidity may also help to broaden accrual into clinical trials, stratifying for comorbidity level.

Finally, once the above points have been elucidated, one may be able to start integrating and testing comorbidity as influencing decision-making, and design differences in therapeutic strategies according to comorbidity burden (such as, for example, targeted use of haematopoietic growth factors in patients at risk).

Several retrospective and epidemiological studies have been conducted with mortality as an endpoint. They provide very helpful notions on a population scale. However, the information from such studies, although very useful as a screening, has limits, especially when it comes to account for confounding variables such as functional status. Non-lethal endpoints such as toxicity of treatment or functional impairment and independence are difficult to address with such studies. Therefore, an essential part of our knowledge needs to come from prospective clinical trials. These should record comorbidity in a comprehensive manner until we can further define the way comorbid diseases interact in prognosis. Such trials should use well validated comorbidity scales such as those described in this article, in order to allow larger-scale meta-analyses, which will probably be the only way to extract the role of particular diseases from other confounding variables. For that purpose, indexes using an internal grading of diseases, as imperfect as it may be, have two advantages: (a) they ask for a more precise definition of the comorbidity level than a qualitative description; and (b) they allow secondary block by block modifications of the weighting according to the outcomes of interest.

10. Conclusions

Comorbidity is an important problem in older cancer patients, and validated tools are available to measure it. Much remains to be learned about the best way to measure and sum it, and the profile of its prognostic value, especially for endpoints other than mortality. A large part of this information will come through prospective studies and meta-analytical techniques, and therefore every effort should be made to use validated indexes, rather than *ad hoc* lists. This article reviews four such indexes. All have been used by many authors in many different settings, the Charlson being the most widely used. The Charlson is simple and highly suitable for vast cohort studies but may under-detect significant problems resulting in non-lethal endpoints. In contrast, the CIRS gives a very accurate profile of comorbidity prevalence but may over-detect minor problems that may confound its prognostic ability, although head-to-head studies with the Charlson have demonstrated no such effect on the correlation with mortality (indeed the CIRS may be a slightly better index in this respect) [16]. The CIRS is the most detailed, but also, with the ICED, the most complicated to rate of the four indexes presented. The author and Moffitt's SAOP are presently using both the Charlson and the CIRS-G scales in parallel in their studies to analyse further their performance in older cancer patients. In addition, the Kaplan–Feinstein index has shown reproducible results in a way similar to the Charlson [3,12] and offers a more detailed grading of some comorbidities than the Charlson, whilst remaining simple to use. The ICED includes both a physical and a functional subset. It can be used to extract some functional information from medical records. It can be very interesting for studies where a distinction between functional status data and comorbidity is not necessary, and where a global 'host cofactor' measurement is sought. Its structure still allows the extraction of pure comorbidity information afterwards. None of these indexes represents the 'ultimate and final word' in comorbidity measurement. However, their widespread use in prospective oncological studies will allow more tightly fitting tools to be derived based on comprehensive and reliable comorbidity data that are presently cruelly lacking.

A good measurement and understanding of comorbidity, as well as its interaction with other health problems of the older cancer patient, will be the key to future progress in geriatric oncology, notably when it comes to expanding cooperative study results to the general population of older cancer patients.

Appendix A. Charlson Comorbidity Index (+optional age addition) [12]

Rating instructions: enclosed
Rating helps: weights included on scale
Option: age adjustment
Author's 1999 address: Dr Mary Charlson, Cornell Medical College, 515 E 71st Street, New York, NY 10021, USA
Tel.: +1-212-746-1607; E-mail address: mecharl@mail.med.cornell.edu

CHARLSON COMORBIDITY INDEX

Comorbidity	Present	Points
Myocardial infarct		1
Congestive heart failure		1
Peripheral vascular disease		1
Cerebrovascular disease (except hemiplegia)		1
Dementia		1
Chronic pulmonary disease		1
Connective tissue disease		1
Ulcer disease		1
Mild liver disease		1
Diabetes (without complications)		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2nd Solid tumor (non metastatic)		2
Leukaemia		2
Lymphoma, Multiple myeloma ...		2
Moderate or severe liver disease		3
2nd Metastatic solid tumor		6
AIDS		6

Comments:

Total points: _____

Optional extension

Age	Present	Score
50–59		1
60–69		2
70–79		3
80–89		4
90–99		5

Total combined score (comorbidity + age): _____

Rules for filling Charlson comorbidity scale

(according to Appendix of Ref. [12]. Adaptation: do not count non-melanotic skin cancers or *in situ* cervical carcinoma)

Myocardial infarction	History of medically documented myocardial infarction
Congestive heart failure	Symptomatic CHF with response to specific treatment
Peripheral vascular disease	Intermittent claudication, peripheral arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm ($\geqslant$6 cm)
Cerebrovascular disease (except hemiplegia)	History of TIA, or CVA with no or minor sequellae
Dementia	Chronic cognitive deficit
Chronic pulmonary disease	Symptomatic dyspnoea due to chronic respiratory conditions (including asthma)
Connective tissue disease	SLE, polymyositis, mixed CTD, polymyalgia rheumatica, moderate to severe RA
Ulcerative disease	Patients who have required treatment for PUD
Mild liver disease	Cirrhosis without PHT, chronic hepatitis
Diabetes (without complications)	Diabetes with medication
Diabetes with end organ damage	Retinopathy, neuropathy, nephropathy
Hemiplegia (or paraplegia)	Hemiplegia or paraplegia
Moderate or severe renal disease	Creatinine >3 mg/dl (265 μmol/l), dialysis, transplantation, uremic syndrome
2nd solid tumour (non metastatic)	Initially treated in the last 5 years. Exclude non-melanomatous skin cancers and *in situ* cervical carcinoma
Leukaemia	CML, CLL, AML, ALL, PV
Lymphoma, MM...	Non-Hodgkin's lymphoma (NHL), Hodgkin's, Waldenström, multiple myeloma
Moderate or severe liver disease	Cirrhosis with PHT $+/-$ variceal bleeding
2nd metastatic solid tumour	Self-explaining
AIDS	AIDS and AIDS-related complex Suggested: as defined in latest definition

CHF, congestive heart failure; TIA, transient ischemic attack; CVA, cerebro-vascular accident; SLE, systemic lupus erythematosus; CTD, connective tissue disease; RA, rheumatoid arthritis; PUD, peptic ulcer disease; PHT, portal hypertension; CML, chronic myeloid leukaemia; CLL, chronic lymphoid leukaemia; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; PV, polycythemia vera.

Scoring

The total score can be classified into four categories as a prognostic for mortality: 0, 1–2, 3–4, >4.

The mortality rates are age-dependent. To integrate scoring for age, simply add the age-related scores and the score can be categorised as above [19].

Appendix B. Cumulative Illness Rating Scale (Geriatric) [28]

Rating instructions: manual [27] or software available at Dr Miller's or Dr Extermann's address
Rating helps: ability to write down diseases on scale, summary scoring rule on scale
Author's 1999 address: Dr Mark D. Miller, MD, Associate Professor of Psychiatry, WPIC, University of Pittsburgh Medical Center, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA
Tel.: +1-412-624-1886; E-mail address: millermd@msx.upmc.edu

Scoring Sheet

CUMULATIVE ILLNESS RATING SCALE FOR GERIATRICS (CIRS-G)
Miller, Paradis, and Reynolds 1991

PATIENT _____ AGE _____
RATER _____ DATE _____

Instructions: Please refer to the CIRS-G manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. (Use reverse side for more writing space).

RATING STRATEGY
0- No problem
1- Current mild problem or past significant problem
2- Moderate disability or morbidity/requires "first line" therapy
3- Severe/constant significant disability/"uncontrollable" chronic problems
4- Extremely severe/immediate treatment required/end organ failure/severe impairment in function

	SCORE
HEART	_____
VASCULAR	_____
HAEMATOPOIETIC	_____
RESPIRATORY	_____
EYES, EARS, NOSE, THROAT AND LARYNX	_____
UPPER GI	_____
LOWER GI	_____
LIVER	_____
RENAL	_____
GENITOURINARY	_____
MUSCULOSKELETAL/INTEGUMENT	_____
NEUROLOGICAL	_____
ENDOCRINE/METABOLIC AND BREAST	_____
PSYCHIATRIC ILLNESS	_____
TOTAL NUMBER OF CATEGORIES ENDORSED	_____
TOTAL SCORE	_____
Severity index: (total score/total number of categories endorsed)	_____
Number of categories at level 3 severity	_____
Number of categories at level 4 severity	_____

Appendix C. Cumulative Illness Rating Scale (Original) [25]

Rating instructions: on sheet
Rating helps: none or see CIRS-G version
Author's 1999 address: retired

Note: The original version is presented here because it is the common root of the modern variants. The article author's personal suggestion is to use the CIRS-G version.

CUMULATIVE ILLNESS RATING SCALE [25]

PATIENT _____ AGE _____
RATER _____ DATE _____

Instructions: Please refer to the CIRS-G manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. (Use reverse side for more writing space).

RATING STRATEGY
0- None
1- Mild
2- Moderate
3- Severe
4- Extremely severe

	SCORE
HEART	_____
VASCULAR	_____
RESPIRATORY	_____
EYES, EARS, NOSE, THROAT AND LARYNX	_____
UPPER GI	_____
LOWER GI	_____
HEPATIC	_____
RENAL	_____
GENITOURINARY	_____
MUSCULOSKELETAL/INTEGUMENT	_____
NEUROLOGICAL	_____
ENDOCRINE/METABOLIC	_____
PSYCHIATRIC ILLNESS	_____
TOTAL SCORE	_____

Appendix D. Index of Coexistent Disease [34]

Rating instructions: manual available at Dr Greenfield's or Dr Extermann's address [42]
Rating helps: see above
Author's 1999 address: Sheldon Greenfield, MD, The Health Institute, New England Medical Center, 750 Washington Street, Box 345, Boston, MA 02111, USA
Tel.: +1-617-636-5000; E-mail address: sheldon.greenfield@es.nemc.org

Index of Coexistent Disease (ICED)

COMORBIDITY INDEX WORKSHEET

NAME _____ HOSPITAL _____
ID# _____ STUDY ID# _____
AGE _____ SEX _____ CA ICD9# _____

DIAGNOSIS	IDS
Organic heart disease	1 2 3 4
Ischaemic heart disease	1 2 3 4
Primary arrhythmias & conduction problems	1 2 3 4
Congestive heart failure	1 2 3 4
Hypertension	1 2 3 4
Cerebral vascular accident	1 2 3 4
Peripheral vascular disease	1 2 3 4
Diabetes mellitus	1 2 3 4
Respiratory problems	1 2 3 4
Malignancies	1 2 3 4
Hepatobiliary disease	1 2 3 4
Renal disease	1 2 3 4
Arthritis	1 2 3 4
Gastro-intestinal disease	1 2 3 4

PHYSICAL IMPAIRMENT		
CIRCULATION 0 1 2	RESPIRATION 0 1 2	NEUROLOGICAL 0 1 2
MENTAL STATUS 0 1 2	URINARY 0 1 2	FECAL 0 1 2
FEEDING 0 1 2	AMBULATION 0 1 2	TRANSFER 0 1 2
VISION 0 1 2	HEARING 0 1 2	SPEECH 0 1 2

GROUPING SYSTEM

Peak Intensity of Coexistent Disease(s)	Peak Intensity of Physical Impairment	ICED Levels
0	0	0
0	1	0
1	0	1
2	0	1
1	1	2
2	1	2
3+	any (0–2)	3
any (0–4)	2	3

Total score:_____

Appendix E. Kaplan–Feinstein scale [43]

Rating instructions: included
Rating helps: none particular
Authors' 1999 address: Dr Moreson H. Kaplan and Dr Alvan R. Feinstein, Yale University School of Medicine, New Haven, Connecticut, USA
Tel.: Kaplan: +1-203-432-0039; Feinstein +1-203-785-4146; E-mail address: moreson.kaplan@yale.edu

KAPLAN–FEINSTEIN SCALE

PATIENT _____ AGE _____

RATER _____ DATE _____

Cogent co-morbid ailment	Score
Hypertension	123
Cardiac	0 1 2 3
Cerebral or psychic	0 1 2 3
Respiratory	0 1 2 3
Renal	0 1 2 3
Hepatic	0 1 2 3
Gastro-intestinal	0 1 2 3
Peripheral vascular	0 1 2 3
Malignancy	0 1 2 3
Locomotor impairment (regardless of cause)	0 1 2 3
Alcoholism	0 1 2 3
Miscellaneous	0 1 2 3

Total score: _____

Scoring rules for Kaplan–Feinstein scale

Cogent co-morbid ailment	Grade 3	Grade 2	Grade 1
Hypertension	Severe or malignant; papilloedema; encephalopathy; or diastolic pressure 130 mmHg or higher	Diastolic pressure 115–129 mmHg; or at any level below 130, with secondary cardiovascular or symptomatic effects such as headaches, vertigo, epistaxis	Diastolic pressure 90–114 mmHg, without secondary effects or symptoms
Cardiac	Within past 6 months: congestive heart failure, myocardial infarction, significant arrhythmias, or hospitalisation required for angina pectoris or angina-like chest pain	Congestive heart failure more than 6 months ago; or angina pectoris not requiring hospitalisation	Myocardial infarction more than 6 months ago; ECG evidence of coronary disease; or atrial fibrillation
Cerebral or psychic	Recent stroke, comatose state or suicidal state	Old stroke, with residua; recent transient ischaemic attacks; or recent episode of status epilepticus	Old stroke without residua; past transient ischaemic attacks; or frequent epileptic seizures
Respiratory	Marked pulmonary insufficiency (i.e. cyanosis, CO_2 narcosis); or recurrent status asthmaticus	Moderate pulmonary insufficiency (i.e. dyspnoea on slight exertion); recurrent asthmatic attacks with chronic obstructive pulmonary disease	Mild pulmonary insufficiency; recent active tuberculosis; chronic lung disease manifested only on X-rays or function tests; or recurrent asthmatic attacks without underlying lung disease
Renal	Uraemia; renal decompensation with secondary anaemia, oedema, hypertension	Azotemia, manifested by elevated BUN (>25 mg/dl) and/or creatinine (>3.0 mg/dl) without secondary effects; nephrotic syndrome; recurrent renal infections; hydronephrosis	Proteinuria (tests of 3+ or 4+ on two or more urinalyses, or excretion of >1 g on 24 h urine collection); recurrent lower urinary tract infections or renal stones
Hepatic	Hepatic failure (ascites, icterus, encephalopathy); or oesophageal varices	Compensated hepatic failure (cutaneous spiders, palmar erythema, hepatomegaly or other clinical evidence of chronic liver disease)	Chronic liver disease manifested on biopsy or by persistently elevated BSP (>15% retention) or bilirubin (>3 mg/dl)
Gastro-intestinal	Recent major bleeding controlled by 6 or more units of blood transfusion	Moderate bleeding, requiring transfusion but less than 6 units of blood; recent acute pancreatitis; or chronic malabsorption syndrome	Slight bleeding, not requiring transfusion; episodes of symptomatic cholelithiasis; chronic pancreatitis; or peptic ulcer
Peripheral vascular	–	Recent amputation or gangrene of extremity	Old amputation; intermittent claudication
Malignancy	Uncontrolled	Controlled (i.e. successful previous resection or other therapy); Kaposi's sarcoma	–
Locomotor impairment (regardless of cause)	Bed-to-chair existence	Moderately impaired (confined to home, nursing home, or convalescent setting)	Slightly impaired (some limitation of activity)

(continued on next page)

Scoring rules for Kaplan–Feinstein scale *(continued)*

Cogent co-morbid ailment	Grade 3	Grade 2	Grade 1
Alcoholism	Severely decompensated (i.e. more than one episode of delirium tremens or alcoholic seizures)	Moderately decompensated (i.e. single episode of delirium tremens or seizures); recurrent hospitalisation for alcohol-associated ailments such as gastritis or pancreatitis; nutritionally caused cachexia or anaemia; or significant behaviour problems	Mildly decompensated (i.e. "Drinking problem"); may have had hospitalisations for acute intoxication but no documented alcohol-associated ailments
Miscellaneous	Uncontrolled systemic "collagen disease" (e.g. lupus erythematosus)	Controlled systemic "collagen disease"	Recurrent epistaxis requiring transfusion; chronic active infection not specified elsewhere

BUN, blood urea nitrogen; BSP, brome sulfone phtaleine.

Scoring rules

The total score ranks from 0 to 3.

If several ailments are present, the ailment with the highest rank defines the score.

Exception: if two or more grade 2 ailments are present, the total score is 3.

References

1. Yancik R, Ries LA. Cancer in older persons. *Cancer* 1994, **74**, 1995–2003.
2. Fried LP, Bandeen-Roche K, Kasper JD, Guralnik JM. Association of comorbidity with disability in older women: the Women's Health and Aging Study. *J Clin Epidemiol* 1999, **52**, 27–37.
3. Extermann M. Measurement and impact of comorbidity in older cancer patients. *Crit Rev Oncol Hematol* 2000, in press.
4. Monfardini S, Sorio R, Hoctin Boes G, Kaye S, Serraino D. Entry and evaluation of elderly patients in European Organization for Research and Treatment of Cancer (EORTC) new-drug-development studies. *Cancer* 1995, **76**, 333–338.
5. Trimble EL, Carter CL, Cain D, Freidlinn B, Undergleider RS, Friedman MA. Representation of older patients in cancer treatment trials. *Cancer* 1994, **74**, 2208–2214.
6. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol* 1998, **16**, 1582–1587.
7. Newschaffer CJ, Bush TL, Penberthy LT. Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. *J Clin Epidemiol* 1997, **50**, 725–733.
8. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992, **45**, 613–619.
9. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol* 1993, **46**, 1075–1090.
10. Kiezsak SM, Flanders WD, Kosinski AS, Shipp CC, Karp H. A comparison of the Charlson Comorbidity Index derived from medical record data and administrative billing data. *J Clin Epidemiol* 1999, **52**, 137–142.
11. Yancik R, Wesley MN, Ries LAG, *et al*. Comorbidity and age as predictors of risk for early mortality in male and female colon carcinoma patients. *Cancer* 1998, **82**, 2123–2134.
12. Charlson ME, Pompei P, Ales K, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987, **40**, 373–383.
13. Charlson ME, Sax FL, McKenzie CR, Fields SD, Braham RL, Douglas RG. Assessing illness severity: does clinical judgement work? *J Chron Dis* 1986, **39**, 439–452.
14. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. *J Am Med Assoc* 1998, **279**, 1187–1193.
15. Chen H, Overcash J, Extermann M, Cantor A, Balducci L. Comprehensive geriatric assessment in elderly cancer patients: impact on overall survival and progression-free survival. Poster P76. *Am Geriatric Soc Meeting*. Philadelphia, PA, 19–23 May 1999.
16. Rochon PA, Katz JN, Morrow LA, *et al*. Comorbid illness is associated with survival and length of hospital stay in patients with chronic disability. *Med Care* 1996, **34**, 1093–1101.
17. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? *Med Care* 1996, **34**, 73–84.
18. Liu M, Domen K, Chino N. Comorbidity measures for stroke outcome research: a preliminary study. *Arch Phys Med Rehabil* 1997, **78**, 166–172.
19. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a comorbidity index. *J Clin Epidemiol* 1994, **47**, 1245–1251.
20. Chin MH, Goldman L. Gender differences in 1-year survival and quality of life among patients admitted with congestive heart failure. *Med Care* 1998, **36**, 1033–1046.
21. Knight EL, Kiely DK, Fish LC, Marcantonio ER, Minaker KL. Atrial natriuretic peptide level contributes to a model of future mortality in the oldest old. *J Am Geriatr Soc* 1998, **46**, 453–457.
22. Covinsky KE, Kahana E, Chin MH, Palmer RM, Fortinsky RH, Landefeld CS. Depressive symptoms and 3-year mortality in older hospitalized medical patients. *Ann Intern Med* 1999, **130**, 563–569.
23. Skiest DJ, Rubinstein E, Carley N, Gioiella L, Lyons R. The importance of comorbidity in HIV-infected patients over 55: a retrospective case–control study. *Am J Med* 1996, **101**, 605–611.
24. D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. *Methods Inf Med* 1993, **32**, 382–387.

25. Linn BS, Linn MW, Gurel L. Cumulative Illness Rating scale. *J Am Geriatr Soc* 1968, **16**, 622–626.
26. Common Toxicity Criteria Version 2.0, National Institutes of Health, National Cancer Institute, April 1999. http://ctep.info.-nih.gov/ctc3/default.htm.
27. Miller MD, Towers A. A manual of guidelines for scoring the cumulative illness rating scale for geriatrics (CIRS-G). University of Pittsburgh, May 1991.
28. Miller MD, Paradis CF, Houck PR, *et al*. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 1992, **41**, 237–248.
29. Parmelee PA, Katz IR, Lawton MP. The relation of pain to depression among institutionalized aged. *J Gerontol* 1991, **46**, P15–P21.
30. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. *J Am Geriatr Soc* 1995, **43**, 130–137.
31. Keller BK, Potter JF. Predictors of mortality in outpatient geriatric evaluation and management clinic patients. *J Gerontol* 1994, **49**, M246–M251.
32. Di Iorio A, Longo AL, Miltidieri Costanza A, *et al*. Characteristics of geriatric patients related to early and late readmission to hospital. *Aging (Milano)* 1998, **10**, 339–346.
33. Conwell Y, Forbes NT, Cox C, Caine ED. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. *J Am Geriatr Soc* 1993, **41**, 38–41.
34. Greenfield S, Blanco DM, Elashoff RM, Ganz P. Patterns of care related to age of breast cancer patients. *J Am Med Assoc* 1987, **257**, 2766–2770.
35. Imamura K, McKinnon M, Middleton R, Black N. Reliability of a comorbidity measure: the Index of Coexistent Disease (ICED). *J Clin Epidemiol* 1997, **50**, 1011–1016.
36. Bennett CL, Greenfield S, Aronow H, Ganz P, Vogelzang NJ, Elashoff RM. Patterns of care related to age of men with prostate cancer. *Cancer* 1991, **67**, 2633–2641.
37. Guadagnoli E, Shapiro C, Gurwitz JH, *et al*. Age-related patterns of care: evidence against ageism in the treatment of early-stage breast cancer. *J Clin Oncol* 1997, **15**, 2338–2344.
38. Greenfield S, Apolone G, McNeil BJ, Cleary PD. The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement. *Med Care* 1993, **31**, 141–154.
39. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term survival among men with conservatively treated localized prostate cancer. *J Am Med Assoc* 1995, **274**, 626–631.
40. Krousel-Wood MA, Abdoh A, Re R. Comparing comorbid-illness indices assessing outcome variation: the case of prostatectomy. *J Gen Intern Med* 1996, **11**, 32–38.
41. Waite K, Oddone E, Weinberger M, *et al*. Lack of association between patient's measured burden of disease and risk for hospital readmission. *J Clin Epidemiol* 1994, **47**, 1229–1236.
42. Greenfield S, Apolone G. Assessment of Comorbidity: the Index of Coexistent Disease (ICED). (Rating manual) New England Medical Center, Boston, MA, 1991.
43. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *J Chron Dis* 1974, **27**, 387–404.
44. Clemens JD, Feinstein AR, Holabird N, Cartwright S. A new clinical-anatomic staging system for evaluating prognosis and treatment of prostatic cancer. *J Chron Dis* 1986, **39**, 913–928.
45. Pompei P, Charlson ME, Ales K, McKenzie CR, Norton M. Relating patient characteristics at the time of admission to outcomes of hospitalization. *J Clin Epidemiol* 1991, **10**, 1063–1069.
46. Piccirillo JF. Inclusion of comorbidity in a staging system for head and neck cancer. *Oncology* 1995, **9**, 831–836.
47. Silliman RA, Lash TL. Comparison of interview-based and medical-record based indices of comorbidity among breast cancer patients. *Med Care* 1999, **37**, 339–349.
48. Newschaffer CJ, Bush TL, Penberthy LE, Bellantoni M, Helzlsour K, Diener-West M. Does comorbid disease interact with cancer? An epidemiologic analysis of mortality in a cohort of elderly breast cancer patients. *J Gerontol* 1998, **53**, M372–378.
49. Zincke H, Bergstrahl EJ, Blute ML, *et al*. Radical prostatectomy for clinically localized prostate cancer: long-term results of 1,143 patients from a single institution. *J Clin Oncol* 1994, **12**, 2254–2263.
50. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med* 1994, **120**, 104–110.