Multimorbidity measures were poor predictors of adverse events in patients aged ≥80 years: a prospective cohort study

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Abstract

Objectives: To assess and compare the ability of two measures of multimorbidity and a simple disease count (DC) to predict health outcomes in a population of patients aged ≥80 years.

Study Design and Setting: A prospective, observational, and population-based cohort study including 567 individuals [3.0 years (standard deviation ± 0.25) follow-up].

Results: Of the patients, 37.6% were reported with five or more diseases. Multimorbidity was measured by means of a modified Charlson comorbidity index [mCCI; median score, 5 (range, 4–15)], Cumulative Illness Rating Scale [CIRS; median score, 4 (range, 1–11)], and a simple DC of 22 selected chronic conditions [median score, 4 (range, 0–13)]. All measures were independently related to mortality [adjusted hazard ratio (HR) mCCI, 2.5 (confidence interval [CI]: 1.5, 4.1); CIRS, 2.1 (CI: 1.4, 3.2); DC, 2.1 (CI: 1.4, 3.2)] and hospitalization [adjusted HR DC, 2.3 (CI: 1.7, 3.1); mCCI, 2.1 (CI: 1.5, 3.0); CIRS, 1.9 (CI: 1.5, 2.6)] but not to functional decline. Areas under the curve for mortality and hospitalization were all below 0.70. Net reclassification improvements did not indicate that any one measure provided a significant benefit over the others.

Conclusion: In this population, the mCCI, CIRS, and unweighted DC predicted mortality and hospitalization but not functional decline. There is no clear advantage of using one measure over another. © 2015 Elsevier Inc. All rights reserved.

Keywords: Multimorbidity; Measurement; Mortality; Hospitalization; Functional decline; Older persons

1. Introduction

Aging populations are associated with increases in the prevalence of chronic disease and dependence. In clinical care, patients with multiple conditions (multimorbidity) are the rule rather than the exception [1,2], and studies have primarily focused on patients with a single disease [3,4]. Thus, the results of these studies may not apply to patients with multiple conditions [5,6]. To tailor the care to this growing group of patients, interest in multimorbidity research is rapidly growing. However, this research is challenging, as the concept of multimorbidity is difficult to define and measure [7]. Various measures have been developed, but researchers are unsure on which instrument to choose [8,9].

Most studies have used simple disease counts (DCs), but weighted scores that allocate different weights to different diseases, such as the Charlson comorbidity index (CCI) [10] and the Cumulative Illness Rating Scale (CIRS) [11–13], have also been developed and validated. Experts in the field have suggested that researchers use an index that is valid for predicting the specific outcome of interest, but few studies have directly compared the performance of different measures [9]. Moreover, although most measures were originally developed and validated for a single outcome, multimorbidity impacts several health-related outcomes and measures of multimorbidity may not be equally valid across different outcomes [14,15].
What is new?

- Weighted multimorbidity measures are not superior to a simple disease count to predict mortality, hospitalisation and functional decline in the oldest age group.
- In general, measures of multimorbidity have a limited ability to predict adverse outcomes in this population.

It is unclear whether more complicated measures of multimorbidity are really of added value in multimorbidity research or whether simple counts can also be used with acceptable validity across health outcomes. The present study compares the ability of two multimorbidity measures [a modified CCI (mCCI) and the CIRS] and a simple DC to predict mortality, hospitalization, and functional decline in persons aged 80 years and older. These measures were appropriate to compare because DCs are the easiest measure to use in clinical research, the CCI is the most established measure in multimorbidity research, and the CIRS is the most comprehensive measure.

2. Methods

2.1. Study population

The BELFRAIL study (BF<sub>80+</sub>) was designed as a prospective, observational, and population-based cohort study to evaluate subjects aged 80 years and older living in Belgium. All the participants in the study provided informed consent, and the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain of Brussels approved the study. The study protocol and the sampling methods have previously been described in detail [16]. In short, between November 2008 and September 2009, 567 individuals were included in the study. Only three exclusion criteria were used: known severe dementia, palliative situations, and medical urgency. At baseline (T0), the patient’s general practitioner (GP) recorded sociodemographic data and medical history information. A clinical research assistant (CRA) performed an extensive examination that included performance testing and questionnaires. A second CRA visit was performed 19.6 ± 2.5 months after patient enrollment (T1). Detailed follow-up on mortality and hospitalizations was collected from the participants’ GPs until 3.0 ± 0.25 years after baseline (T2) (Fig. 1).

2.2. Baseline multimorbidity

The GPs reported the medical histories of their patients as free text. These histories included both active medical problems and important antecedents, such as myocardial infarction and pulmonary embolism. The GPs also completed a structured questionnaire that asked about the presence or absence of 22 chronic conditions (vide infra). Multimorbidity was measured by means of a simple DC, an mCCI, and the CIRS. The simple DC was the sum of the diseases that were included in the structured questionnaire. To calculate the mCCI and the CIRS, two researchers (P.B., and O.D.) assessed and coded the medical history of each patient. In cases of discrepancy between the first and the second researcher’s codes, the patient’s case was discussed with a third researcher (B.V.) until consensus was reached.

2.2.1. Disease count

The unweighted DC included hypertension, lipid disorder, angina pectoris, cardiomyopathy, myocardial infarct, transient ischemic attack, cerebrovascular accident (CVA), peripheral arterial disease, an episode of decompensated heart failure, an episode of atrial fibrillation, known valvular disease, thyroid disease, respiratory impairment [either asthma or chronic obstructive pulmonary disease (COPD)], Parkinson’s disease, arthritis, osteoarthritis, documented osteoporosis, cancer, depression, renal insufficiency, locomotor sequelae of CVA, and diabetes.

2.2.2. The modified Charlson comorbidity index

The CCI includes 19 chronic diseases that are weighted based on their association with mortality [10]. For the present study, the CCI was slightly modified because connective tissue disease could not be reliably assessed and various stages of liver disease, cancer, and diabetes could not always be differentiated. Consequently, the mCCI assigned the following weights: 1 point: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease (COPD or asthma), all liver diseases, and all cases of diabetes; 2 points: hemiplegia, renal disease, and all cancers with no metastases mentioned in the medical history; 6 points: human immunodeficiency virus and metastatic cancer.

2.2.3. The Cumulative Illness Rating Scale

The CIRS uses a scoring system that includes 14 body systems, and the scale can be validly reproduced based on a chart review [11]. Based on the medical history of the patient, each body system is assigned a severity score (1, no problem; 2, current mild problem or past significant problem; 3, moderate disability or morbidity; or 4, severe problem). The CIRS comorbidity index (CIRS-CI) [12] is based on the number of body systems that present a severity score of at least 3, so the score can range from 0 to 14. Within this study sample, 58 chronic conditions were observed in the patients’ medical histories. The conditions were categorized into the appropriate body systems according to the CIRS scoring manual that was published by Hudon [12].
2.3. Outcome measures

2.3.1. Mortality and hospitalization

All-cause mortality and the time to first hospitalization at T2 were used as outcome measures.

2.3.2. Functional decline

Functional decline was assessed by means of activities of daily living (ADL) decline, physical decline, and mental decline, which were determined based on the difference between the baseline assessment and the assessment at T1.

2.3.2.1. ADL decline. The ADL assessment includes self-reported difficulty climbing stairs, walking 5 minutes outdoors without resting, getting up from and sitting down in a chair, dressing and undressing oneself, using transportation, and caring for one’s toenails. The answers vary between 1 (“no, I cannot do this”) to 5 (“yes, I can do this without any problems”). The total score ranges between 6 and 30 and is calculated by summing the scores for all activities [17,18]. A relevant decline was determined using the Edwards-Nunnally index, which determines the probability of substantial individual change. Based on the reliability of the ADL scale and the 95% confidence interval (CI) of the mean score at T0, the Edwards-Nunnally index determines whether a significant change has occurred between T0 and T1 [19].

2.3.2.2. Physical decline. Physical decline was defined as a decline in gait speed or grip strength. To determine gait speed, the respondents were asked to walk 3 m, turn...
2.3.2.3. Mental decline

Mental decline was defined as a relevant decline in performance on the Mini-Mental State Examination (MMSE) [20] or a shift in the short version relevant decline in performance on the Mini-Mental State Examination; GDS-15 score [21,22]. A relevant decline in MMSE performance was determined using the Edwards-Nunnally index [19]. For the GDS-15, a decline was determined as a shift from a score of less than 5 to a score of greater than 5.

2.4. Statistical analyses

To describe the characteristics of the cohort, descriptive statistics (means, standard deviations, and frequencies) were calculated for the baseline and outcome variables. The Spearman rank correlations were used to determine the agreement among the mCCI, CIRS, and DC. Levels of multimorbidity were defined based on the distribution of each measure in the sample and clinical sense: level 1: mCCI and CIRS less than 4 and DC less than 3; level 2: mCCI between 5 and 6, CIRS equal to 4, and DC between 3 and 4; and level 3: mCCI greater than 6, CIRS greater than 4, and DC greater than 5. Kaplan–Meier curves were used to assess the relationship with mortality. Cox proportional hazard regression models (adjusted for age and gender) were used to estimate hazard ratios (HRs) for mortality and hospitalizations across levels of multimorbidity. Logistic regression models (adjusted for age and gender) were used to estimate odds ratios for ADL decline, physical decline, and mental decline across levels of multimorbidity. A stepwise approach was used to further compare the predictive ability of the mCCI, CIRS, and DC; when an independent relationship was found between a measure of multimorbidity and a specific outcome, areas under the curve (AUCs) were used to determine the optimal cutoff point (with the highest sensitivity and specificity) of the specific measure in relation to the specific outcome. Based on these cutoff points, net reclassification improvements (NRIs) [23] were calculated to directly compare the ability of the different measures to predict the outcomes. The data analysis was performed using the software SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 13.2.2 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Baseline population characteristics

The BELFRAIL cohort included 567 individuals with a mean age of 84.7 ± 3.7 years (range, 80–101 years). At the time of inclusion, 62.8% (n = 356) of the sample was female and 37.6% (n = 213) suffered from five or more chronic diseases (range, 1–16). The most frequent disorders were hypertension (66.6% of the population) and osteoarthritis (57.1% of the population). Multimorbidity was measured by means of the mCCI [median score, 5 (range, 4–15)], the CIRS [median score, 4 (range, 1–11)], and a simple DC of 22 selected chronic conditions [median number of conditions, 4 (range, 0–13)]. Table 1 summarizes the frequency distribution of the mCCI scores, CIRS scores, and DC. The Spearman rank correlations among the mCCI, CIRS, and DC indicate that there was a stronger agreement between the CIRS and DC [Spearman rank correlation, 0.68 (CI: 0.39, 0.53)] than between the mCCI and DC [Spearman rank correlation, 0.66 (CI: 0.64, 0.72)]. The CIRS and mCCI had the lowest agreement score [Spearman rank correlation, 0.46 (CI: 0.39, 0.53)].

3.2. Mortality

There was no loss to follow-up for mortality. During the follow-up period, 131 (23.1%) patients died. For the patients with the highest levels of multimorbidity, the Kaplan–Meier curves (Fig. 2) indicate that the survival rate at T2 ranged from 66.6% (mCCI) to 68.2% (CIRS), whereas for the patients with the lowest levels of multimorbidity, the survival rate ranged from 82.9% (DC) to 86.7% (mCCI). Adjusted for age and gender, the Cox proportional hazard regression model showed that this pattern was consistent for all three measures. For the highest level of multimorbidity, the adjusted hazard ratios (HRs) ranged from 2.1 (CI: 1.4, 3.2) for the CIRS and DC to 2.5 (CI: 1.5, 4.1) for the mCCI (Table 2). The areas under the curve (AUCs) for mortality were generally poor (<0.70); the highest AUC was reported for mCCI [0.63 (CI: 0.57, 0.68); Table 3]. The NRI values reported in Table 4 show that no one measure was significantly better at predicting mortality than the others.

<table>
<thead>
<tr>
<th>Table 1. Baseline population characteristics</th>
</tr>
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<tbody>
<tr>
<td><strong>Age in yr, mean ± standard deviation</strong></td>
</tr>
<tr>
<td>84.7 ± 3.7</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
</tr>
<tr>
<td>356 (62.8)</td>
</tr>
<tr>
<td><strong>Living at home, n (%)</strong></td>
</tr>
<tr>
<td>320 (89.9)</td>
</tr>
<tr>
<td><strong>Charlson comorbidity index, n (%)</strong></td>
</tr>
<tr>
<td>4 (26%)</td>
</tr>
<tr>
<td><strong>Cumulative Illness Rating Scale, n (%)</strong></td>
</tr>
<tr>
<td>275 (48.5)%</td>
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<tr>
<td><strong>Unweighted disease count, n (%)</strong></td>
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<tr>
<td>246 (43.4)</td>
</tr>
<tr>
<td><strong>Activities of daily living, ADL at T0, median (spread)</strong></td>
</tr>
<tr>
<td>25 (6)</td>
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<tr>
<td><strong>Gait speed at T0 (m/s), median (spread)</strong></td>
</tr>
<tr>
<td>0.59 ± 0.26</td>
</tr>
<tr>
<td><strong>Grip strength at T0, median (spread)</strong></td>
</tr>
<tr>
<td>21.1 (10.9)</td>
</tr>
<tr>
<td><strong>MMSE at T0, median (spread)</strong></td>
</tr>
<tr>
<td>28 (3)</td>
</tr>
<tr>
<td><strong>GDS-15 &gt; 5 at T0, n (%)</strong></td>
</tr>
<tr>
<td>115 (20.6)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADL, activities of daily living; MMSE, Mini-Mental State Examination; GDS, geriatric depression scale.
3.3. Hospitalization

Follow-up data about hospitalizations were available for 560 patients. For 285 (50.9%) patients, at least one hospitalization was reported (range, 1–9). Multimorbidity was an independent predictor of hospitalization. For the highest level of multimorbidity, the adjusted hazard ratios (HRs) ranged from 1.9 (CI: 1.5, 2.6) for the CIRS to 2.3 (CI: 1.7, 3.1) for the DC (Table 2). The AUCs for hospitalization were generally poor (<0.70); the highest AUC was reported for the DC [0.63 (CI: 0.58, 0.67)] Table 3. The NRI values reported in Table 4 show that no one measure was significantly better at predicting hospitalization than the others.

3.4. Functional decline: ADL decline, physical decline, and mental decline

Follow-up data on ADL, physical decline, and mental decline could not be obtained for the full cohort (Fig. 1), as 73 patients had died at T1 and 64 participants refused to be assessed by the CRA at T1. ADL decline was documented in 100 (23.8%) patients. Physical decline was documented in 183 (44.7%) patients, and mental decline was demonstrated in 97 (24.2%) patients. Logistic regression models (adjusted for age and gender) showed no relationship between the two measures of multimorbidity or a simple DC and ADL decline, physical decline, or mental decline (Table 2).

4. Discussion

In the oldest patients, the mCCI, CIRS, and unweighted DC predicted mortality and hospitalization but not functional decline. However, the AUCs for mortality and hospitalization showed that the predictive abilities of the two multimorbidity indexes and the simple DC were limited. Furthermore, none of the measures were clearly superior to the others.

4.1. Comparison with other studies

Most previous studies on multimorbidity have been performed with administrative databases or electronic patient records [24–27]. Consequently, previous studies have used measures, such as the CCI and DCs, that can be easily extracted from large databases. The CIRS requires judgment about individual patients and is not suitable for automated data extraction. The present study is the first to compare the more comprehensive CIRS with a mCCI and a simple DC outside a hospital setting.

<table>
<thead>
<tr>
<th>Measure of multimorbidity</th>
<th>Mortality Hazard ratio (95% CI)a</th>
<th>Hospitalization Hazard ratio (95% CI)a</th>
<th>ADL decline Odds ratio (95% CI)a</th>
<th>Physical decline Odds ratio (95% CI)a</th>
<th>Mental decline Odds ratio (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson comorbidity index</td>
<td>0–4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>1.8 (1.1, 2.9)</td>
<td>1.3 (1.0, 1.8)</td>
<td>1.1 (0.7, 2.0)</td>
<td>1.0 (0.6, 1.5)</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>2.5 (1.5, 4.1)</td>
<td>2.1 (1.5, 3.0)</td>
<td>1.4 (0.7, 2.6)</td>
<td>1.6 (0.9, 2.8)</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale</td>
<td>0–3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.8 (1.2, 2.9)</td>
<td>1.8 (1.4, 2.5)</td>
<td>1.2 (0.7, 2.1)</td>
<td>0.7 (0.4, 1.1)</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>2.1 (1.4, 3.2)</td>
<td>1.9 (1.5, 2.6)</td>
<td>1.3 (0.8, 2.2)</td>
<td>1.2 (0.7, 1.9)</td>
</tr>
<tr>
<td>Unweighted disease count</td>
<td>0–3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4–5</td>
<td>1.5 (1.0, 2.2)</td>
<td>1.7 (1.3, 2.3)</td>
<td>1.2 (0.7, 2.0)</td>
<td>1.3 (0.8, 2.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>2.1 (1.4, 3.2)</td>
<td>2.3 (1.7, 3.1)</td>
<td>1.0 (0.5, 1.8)</td>
<td>1.6 (0.9, 2.6)</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; CI, confidence interval.
a All models adjusted for age and gender.
In terms of the CCI and DC, our results are consistent with the findings of Perkins [24] and Brilleman [25], who demonstrated that a DC and the CCI were similar in their abilities to predict the use of health services, costs, and mortality. For functional decline, Di Bari et al. [28] have found that the DC and CCI could predict functional loss. However, the patients in this cohort were younger, they were independent in terms of ADL at the time of inclusion and the follow up time was considerably longer (4 years instead of 1.5 years) which may all explain for the differing results. In our study, the follow-up period may have been too short to assess functional decline. However, the prevalence of decline was still considerable (up to 44.7% for physical decline).

Although we found a relationship between the different measures of multimorbidity and mortality and hospitalization, the role of multimorbidity in the oldest age group appears to be limited (the AUCs were all less than 0.70.) Stronger relationships may be found in younger populations. However, Brilleman and Salisbury [29] have previously demonstrated that measures of multimorbidity added little value in predicting 3-year mortality in a younger population (95,372 patients aged 18 years and older). This result was confirmed for the subgroup aged 65 years and older.

Longitudinal studies of the oldest individuals are important because the number of elderly individuals is expanding. Moreover, this population is a unique group in terms of high levels of comorbidity and disability, and the factors that influence survival are not completely understood. Multimorbidity scores may help to define the sickest patients, but these scores do not directly lead to the detection of individuals who are susceptible to functional decline, hospitalization, or mortality. The fact that patients’ complexity in old age extends beyond somatic diagnoses has been determined previously. The concept of frailty deserves consideration in relation to multimorbidity, as frailty has been considered to be an overall marker of risk for poor health outcomes in aging populations [30–32]. Unfortunately, there is no consensus about how frailty should be measured and operationalized. As many as 30 criteria have been proposed to identify or predict frailty in aging adults [30]. Using different conceptual and operational definitions, these criteria have been included in various frailty models [33].

Brilleman and Salisbury [29] have stated that measures of multimorbidity may be especially useful to decide whether interventions, such as hip prosthesis and valvular surgery, are useful for older patients. Our results suggest that merely numerical multimorbidity measures, such as the mCCI and the CIRS or a simple DC, will not sufficiently capture the clinical complexity of these patients. Van den Akker et al. have identified important psychosocial factors, including negative life events, external locus of control, and social networks. Mental illness and socioeconomic deprivation are also likely relevant. This will also be the topic of future research in the BELFRAIL study.

4.2. Strengths and limitations of the study

The BELFRAIL study included a comprehensive clinical assessment of multimorbidity and a comprehensive assessment of functional status (including both patient-reported and objective measures) in a unique and representative cohort of primary care patients aged 80 years and older. Although longitudinal studies in the oldest age groups are susceptible to methodological challenges related to the age of the participants in the study, the hospitalization and mortality data of the present study were nearly complete, and drop-out was minimized because the assessments of functional status were performed at the participants’ homes.

The primary strength of this study was that the assessment of multimorbidity was based on data reported by the GP, which is important because the GP has the most comprehensive view of the health status of the patient. Consequently, this study was able to use the CIRS, which requires individual clinical judgment about each patient’s history. As such, this was the first study to assess whether the more complex and time-consuming (but comprehensive) CIRS is superior to other measures of multimorbidity.
in the primary care setting. However, even when reported by the GP of the patient, a medical history may not completely capture the impact of diseases on the individual patient. Patients or (informal) caregivers would likely have added substantial information about the impact of certain diseases on individual patients. Inclusion of information from the patient or (informal) caregivers may improve the CIRS and make the measure superior to the DC and CCI.

There is currently no gold standard multimorbidity measure [1,2,8,9,34]. The existing instruments are characterized by high heterogeneity, and there is no consensus about which instrument to choose or which chronic conditions to include. Most authors do not explain why they make a specific choice, which strongly suggests that in many studies, the choice is made for pragmatic reasons, such as the availability of data. Therefore, we have specifically compared a self-selected DC, a mortality-weighted mCCI and an individually weighted and comprehensive CIRS. Because a modified CCI was used in the current study, it is possible that the predictive abilities of the real CCI have been underestimated by the mCCI. Therefore, the results should be interpreted with caution, and the findings should be confirmed in other data sets using the original CCI, before generalizing our results for the use of the CCI in the oldest age group. Furthermore, there is no consensus about the interpretation or cutoff values for the various measures of multimorbidity. Therefore, different strategies were used to compare the measures across outcomes. The DC, mCCI, and CIRS were used as categorical variables in the regression modeling, continuous variables in the AUC calculations, and dichotomous variables in the NRI calculations. This study did not incorporate health-related quality of life, which has been linked to mortality [35].

5. Conclusion

This study suggests that adverse events in the oldest age groups cannot be predicted solely on the basis of the number of somatic diagnoses. This result was confirmed for a simple DC and two different measures of multimorbidity, including the CIRS, which is the most comprehensive multimorbidity measure available.

To capture the complexity of individual patients in the oldest age groups, future research should continue to search beyond somatic disease and multimorbidity for concepts and measures that integrate diseases and functional status, including environmental and personal factors that affect individual patients [36]. Additional research is needed to better understand the interactions between frailty and chronic conditions. The integration of patient-reported measures will probably be vital [37].

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Author contributions: P.B. (family physician, PhD student) is the main author of the study. She was responsible for the analyses and the writing of the manuscript. B.V. (family physicians, PhD) has been involved in the design of the study, data collection, and assisted both in the data analysis and writing of the manuscript. G.V.P., C.M., W.A., D.L., and O.D. have all been actively involved in the data collection and were involved in the development of the research questions of the article and strategies for data analysis. A.D.S. and J.D. (both family physicians, PhD, Professor) were supervising the data analysis and writing of the manuscript. J.D. is the leading researcher of the BELFRAIL study.

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