Does Co-morbidity Provide Significant Improvement on Age Adjustment when Predicting Medical Outcomes?*

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1. Introduction

In hospitalized populations, co-morbidity (either acute or chronic illness) is associated with adverse patient outcomes such as postoperative complications and in-hospital mortality [1–9]. Consequently, in clinical settings, co-morbidities influence how a clinical decision is made or how a treatment strategy is planned. For example, unlike in randomised controlled trials (RCT), allocation of patients to an elective surgical procedure such as total joint replacement (TJR) or non-TJR alternative therapies is not random and therefore patients selected for different therapies (i.e. surgery versus non-surgery) may differ considerably [10, 11]. Often patients with clinical indications for TJR are never proposed for elective surgery because of medical concerns regarding worse outcomes. This potential selection for surgery may be present if, for instance, factors such as advanced age or co-morbidities exclude patients from undergoing the surgical procedure [12]. Therefore, since in clinical practice (or in observational studies) randomisation is usually not feasible, presence of co-morbidity must be accounted for in any non-RCT study. The lack of randomisation inherent in observational epidemiological studies necessitates adjusting for differences in patients’ underlying health status. Co-morbidities necessitate adjusting for differences in observational epidemiological studies necessitates adjusting for differences in patients’ underlying health status.
Co-morbidity assessment is one means of adjusting for differences in patients’ underlying health status, although it is important to recognize that co-morbidity is only one dimension of health status; others include age, gender, functional status, and psychological, cognitive, and psychosocial functioning [13]. Of these, age and gender are the most widely confounders adjusted for in epidemiological studies. Age—sometimes considered the simplest co-morbidity score—has often been used as an indicator of co-morbidity [14]. Although age may be a poor approximate of co-morbidity, it is recorded uniformly in all hospital patient databases, and methods used to adjust for age are similar. In contrast, co-morbid conditions may be under- or over-reported in electronic hospital patient data or hospital morbidity data (HMD), and therefore the predictive performance of HMD-based co-morbidity may largely depend on the accuracy of these routinely collected data. As a result, researchers have often questioned whether the predictive accuracy of statistical models improves when an HMD-based co-morbidity score is added to a model that initially adjusts for age [13–15]. Melfi et al. used the Deyo adaptation of the Charlson index in assessing 30-day mortality in 249,744 Medicare patients who had had a total knee replacement, reported that an increase in the co-morbidity index of one point increased the probability of dying by 17%. However, the addition of this HMD-based co-morbidity adjusting index showed a marginal and non-significant improvement in model discrimination [C (concordance) statistic of 0.653 compared with C = 0.645 of baseline model] [15]. In a much smaller prospective study, Poses et al. used Charlson Index to predict in-hospital death among 227 patients who were hospitalized for suspected bacteraemia with positive blood cultures [13]. The index was independently associated with increased mortality in a model that also accounted for age and clinical data (OR = 1.2, 95% CI: 1.1–1.4). However, the reported area under the receiver operating curve (ROC) or AUC (area under curve) for a model that included the co-morbidity index was C = 0.64, not very different from the AUC for a model that only adjusted for age (C = 0.61).

In a previous validation analysis of the Western Australia (WA) HMD on an elderly population belonging to the Health In Men Study (HIMS), we found good to acceptable sensitivities and positive predictive values (PPVs) for major operations (e.g., both sensitivity and PPV of 0.92 for TJR) and major morbidity (e.g., sensitivity of 0.90 and PPV of 0.78 for any cancer and sensitivity of 0.69 and PPV of 0.80 for past myocardial infarction) [16]. In another analysis [17], we identified 819 men, also belonging to the HIMS cohort, who had a primary elective total joint replacement due to osteoarthritis, and these men are the focus of the current analysis. The objective of this retrospective cohort study was to assess whether HMD-based co-morbidity provided significant improvement on age adjustment when predicting length of stay in hospital, 90-day readmission, and 1- and 2-year all-cause mortality following an elective total joint replacement. We used the Charlson co-morbidity index (CCI) [18] and Elixhauser’s co-morbidities [19] to measure and control for the effects of co-morbid illness because, among the International Classification of Diseases (ICD) coding algorithms, these are the most widely used risk-adjustment methods in hospital electronic data. Besides these two, we also used number of co-morbidities as a risk adjustment method.

2. Methods
2.1 Data Sources and Study Population

The study population was described previously [3, 17]. Briefly, the study integrated longitudinal clinical data from a population-based cohort of men belonging to the Health In Men Study with validated hospital morbidity data and mortality records. The linkage enabled us to retrieve for each participant any significant morbidity, as recorded in HMD, in the period 1970 through 2007 [16]. All 12,203 study participants, who were willing to participate in the original study, were retrospectively followed from baseline screening (1996–1999) until they experienced their first TJR or died or were right censored at the end of follow-up (March 2007) [17]. Electronic record linkage with WA hospital morbidity data was used to identify in the target population admissions to hospital for TJR, length of stay of index TJR-admission, and readmission to hospital within 90 days of the procedure. Mortality following TJR was ascertained through linkage with the WA mortality records.

2.2 WA Linked Data System

The HMD system is a core part of the WA Linked Data System [20] and includes demographic, diagnostic, and procedural information on all patients discharged from all public and private hospitals in WA. The HMD database allows the inclusion of up to 21 diagnoses and 11 procedure codes for each hospitalization. These data have 21 quality-of-data checks that are built into the provision of data from all hospitals and there are periodic audits of random selections of hospital-assigned codes to ensure quality and validity of the data [20].

2.3 Co-morbidity Adjustment Methods

The calculation of the Charlson co-morbidity index and Elixhauser’s method was based on all reported conditions in admissions that preceded the index TJR-admission. Both ICD-9-CM (Clinical Modification) and ICD-10-AM (Australian Modification) coding algorithms were utilised in order to capture all conditions recorded in the dataset in the period 1970 through 2007. Charlson index has had many adaptations. For this analysis, we used the latest adaptation introduced by Quan et al [21], while applying the original Charlson weights to build the final score [18]. The 17 co-morbid conditions that constitute Charlson index are assigned with different weights of 1, 2, 3, or 6 depending on the condition. These weights are then summed to give a total score that forms the index. The coding algorithms used to calculate the Charlson index and Elixhauser’s co-morbidities are presented in Appendixes 1a and 1b. Number of co-morbidities was the count of the unique co-morbidities detected by diagnosis codes as recorded in the electronic database for each study participant.
2.4 Statistical Analysis

Postoperative length of stay in hospital (continuous variable), all-cause 90-day readmission to hospital (dichotomous variable), and one-year and two-year mortality (dichotomous variables) were modelled separately using Cox proportional hazards regression, as a function of age in baseline models and as a function of age and each of the co-morbidity-adjustment methods. For our outcomes, we evaluated the predictive performance of each of the 16 models using Harrell’s C statistic [22], which indicated a model’s discriminatory power. Harrell’s C statistic takes values from 0 to 1, with 1 indicating a perfect prediction and 0.5 a chance prediction. The difference in the statistical performance between the models that included age alone and those that also included the co-morbidity adjustment method was assessed by measuring the difference in the Harrell’s C estimates between pairs of models applied to the same patient data using Bootstrap analysis with 1000 replications. Bootstrapping also generated bias-corrected confidence intervals for our study estimates. The proportional hazard assumption of the Cox models was tested using Schoenfeld residuals. All analyses were performed using Stata statistical program (version 12, StataCorp, College Station, TX).

Ethical approval for the study was obtained from the Human Research Ethics Committee of The University of Adelaide. All analyses used de-identified data.

3. Results

As reported previously [17], of the 12,203 men who participated in the baseline screening 819 (6.7%) had an elective total joint replacement. Mean age at the time of surgery was 76.3 (SD 4.6) years (range 66–89 years) and mean HMD-based Charlson co-morbidity index (CCI) was 1.3 (SD 1.7) (range 0–13), with 137 (17%) having a CCI of “3 or more”. Compared to CCI of “0”, those with CCI of “3 or more” were significantly older and smoked more years (►Table 1), and were more likely to stay longer in hospital, be readmitted and die post surgery (►Table 2). Body weight and socioeconomic status were similar among the groups with different Charlson co-morbidity indices.

In the multivariable analyses, Charlson co-morbidity index was not associated with length of stay or with readmission but with mortality. For every one point increase in CCI, 1-year and 2-year mortality increased by 37% and 30%, respectively (►Table 3). Number of co-morbidities was not associated with any of the study outcomes (results not shown) without any significant improvement in model discrimination (►Table 4). In predicting both 1- and 2-year mortality following primary elective TJR, model discrimination significantly improved by 16% (P = 0.02) and 13% (P = 0.02), respectively, when Charlson co-morbidity index was added to a model that included age. Elixhauser’s method outperformed the other two providing significant improvement on age adjustment in all outcomes. For the prediction of readmission to hospital, neither age nor Charlson index showed good model fit. The proportional hazards assumption was not violated by any of the variables in all Cox models.

4. Discussion

In a population based cohort we have found that the predictive performance of co-morbidity derived from electronic hospital data is outcome and risk-adjustment method specific. In all study outcomes, number of co-morbidities was not a valid risk adjustment tool. Charlson co-morbidity...
Co-morbidity Predicting Medical Outcomes

Abbreviation: C diff (Harrell’s C difference); CI (confidence interval); LOS (length of stay)

Table 3 Hazard ratios* by various outcomes post an elective total joint replacement

<table>
<thead>
<tr>
<th>Covariates by outcome</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of stay following TJR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.05 – 1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HMD-based Charlson Index</td>
<td>1.04 (0.99 – 1.08)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>90-day all cause readmission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.98 – 1.06)</td>
<td>0.3</td>
</tr>
<tr>
<td>HMD-based Charlson Index</td>
<td>1.09 (0.98 – 1.19)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>1-year mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.23 (1.10 – 1.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HMD-based Charlson Index</td>
<td>1.37 (1.23 – 1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>2-year mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.15 (1.07 – 1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HMD-based Charlson Index</td>
<td>1.30 (1.18 – 1.43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: HMD (hospital morbidity data), TJR (total joint replacement)
* The Hazard ratios (HRS) were determined by a multivariable Cox proportional hazards model that accounted for age and HMD-based Charlson index run separately for each outcome listed in table 3.

As the general population ages and obesity becomes more prevalent, the proportion of patients presenting for elective total joint replacement will increase [23]. As the general population ages and obesity becomes more prevalent, the proportion of patients presenting for elective total joint replacement will increase [23]. The association of age and obesity with increased co-morbidity is well documented [24]. A study that reviewed hospital discharge, outpatient and primary care patient files of a random sample of 1,217,103 Americans aged 65 years and older found that 82.0% of the subjects had one or more chronic conditions, while 65.0% had multiple chronic conditions [25]. A case-control study assessed the presence of co-morbidity in patients with osteoarthritis (OA) matched 11,375 individuals who had consulted general practitioners for OA in 60 sites in England and Wales during a one-year study period with controls without OA. After adjusting for age, sex, and social class, patients who consulted for OA had higher levels of co-morbidity than controls (OR 2.35; 99% CI: 2.16 – 2.55) [26]. As a result, surgeons are more likely to confront patients with co-morbid conditions, and these need to be accounted for when assessing medical outcomes but often it is not clear how to measure co-morbidity or which method to use as indicated in a systematic review of co-morbidity adjustment methods [27].

Since HMD-based co-morbidity adjustment methods such as the Charlson Index have no "Criterion Standard", researchers often assess the preference of one method over another by how each predicts worse health outcomes [13 –16]. Often the predictive ability of these adjusting methods may vary between studies, between treatments and between study populations, as their overall performance may be affected by various factors such as accuracy of the data. This is especially true because hospital electronic databases have been initially designed for billing purposes and not for use with co-morbidity adjustment measures. That is, such databases may reflect the intensity of resource utilization more accurately than they reflect a patient’s health status [28]. Prior research has shown that coding practices for billing purposes may vary among hospitals and are influenced by...
factors including hospital characteristics, and physician documentation [29, 30]. Furthermore, a patient's co-morbid conditions may not be fully captured if these were retrieved from a single index admission [16]. Often, some co-morbid diagnoses may not be relevant to the principal diagnosis when the patient received medical care and thus not recorded during that particular admission. Consequently, the predictive ability of these co-morbidity adjustment methods is limited by the availability and accuracy of the data. Besides accuracy of HMD, the performance of these measures may be influenced by factors including the prevalence of co-morbidity in the study population (e.g., younger versus older study populations) [31] and the outcome studied, as demonstrated in our study.

Melfi et al. showed that a simple count of the unique diagnosis codes listed on the discharge summary was predictive of hospital length of stay and 30-day mortality following a total knee replacement, performing better than Charlson Index with  \( C = 0.733 \) for the mortality model [15]. Unlike these authors, our study has found that number of co-morbidities is not a valid adjustment method observed in all of our study's outcomes. A clear advantage in this simple adjusting method is the fact that number of the coded diagnoses may not be affected by miscoding of diagnosis [32]; however, a simple count does not account for the degree of severity inherent in different conditions and also this method of adjustment may be influenced by the general under-reporting of diagnoses which is not uncommon in hospital electronic databases [33].

For the prediction of readmission to hospital, neither age nor Charlson index showed good model fit. Improvement in model discrimination was observed only after Elixhauser's method, containing 30 co-morbid conditions, was used. This may be partially explained by the fact that younger and healthier patients are often more likely to be initially selected for TJR [17]. Therefore, both age and major co-morbid conditions forming the Charlson index may play a less significant role in affecting postoperative readmission. Besides the extended Elixhauser's co-morbidities, such a readmission may be more associated with the presence of other factors such as postoperative complications [7] and administrative determinants (e.g. hospital type which may indicate hospital policy of readmission threshold) [34, 35] than with age and co-morbidity.

Strengths of this study include its population-based provenance, the longitudinal design and the data linkage with various data sources. However, the study has some limitations. Hospital electronic data systems may be disadvantaged by under-coding or over-coding, and coding practices may be different across hospitals. We had no access to patients’ charts and therefore, we could not validate the HMD-recorded co-morbidities against these charts. Similarly, our study population was relatively old and our findings may not be generalizable to other younger patient populations.

In conclusion, this study has shown that co-morbidity derived from hospital electronic data provides significant improvement on age adjustment mainly when predicting mortality following an elective surgical procedure. This may indicate that adjusting for age alone is insufficient and that co-morbid illnesses can have a substantial influence on patient outcomes, and, without adequate adjustments, their effects can confound observed variations in patient outcomes. Currently, both Charlson Index and Elixhauser's risk adjustment methods include only co-morbid conditions. Since co-morbidity is just one dimension of health status, further research is needed to incorporate into such scores other important dimensions of health including socio-demographic and socio-economic factors and psychosocial functioning.

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Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mnatzaganian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design (GM, JEH), analysis and interpretation of data (GM, PR).

References


