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Risk factors for in-hospital post-hip fracture mortality

Steven A. Frost [a,b,c], Nguyen D. Nguyen [a], Deborah A. Black [d], John A. Eisman [a,e], Tuan V. Nguyen [a,e,*]

[a] Osteoporosis and Bone Biology, Garvan Institute of Medical Research, Sydney, NSW, Australia
[b] University of Western Sydney, Sydney, NSW, Australia
[c] Liverpool Hospital, Sydney, NSW, Australia
[d] Faculty of Health Sciences, University of Sydney, Sydney, NSW, Australia
[e] School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW, Australia

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ABSTRACT

Introduction: Approximately 10% of hip fracture patients die during hospitalization; however, it is not clear what risk factors contribute to the excess mortality. This study sought to examine risk factors of, and to develop prognostic model for, predicting in-hospital mortality among hip fracture patients.
Methods: We studied outcomes among 410 men and 1094 women with a hip fracture who were admitted to a major-teaching-hospital in Sydney (Australia) between 1997 and 2007. Clinical data, including concomitant illnesses, were obtained from inpatient data. The primary outcome of the study was in-hospital mortality regardless of length of stay. A Log-binomial regression model was used to identify risk factors for in-hospital mortality. Using the identified risk factors, prognostic nomograms were developed for predicting short term risk of mortality for an individual.
Results: The median duration of hospitalization was 9 days. During hospitalization, the risk of mortality was higher in men (9%) than in women (4%). After adjusting for multiple risk factors, increased risk of in-hospital mortality was associated with advancing age (rate ratio [RR] for each 10-year increase in age: 1.91 95% confidence interval [CI]: 1.47 to 2.49), in men (RR 2.13; 95% CI 1.41 to 3.22), and the presence of comorbid conditions on admission (RR for one or more comorbid conditions vs. none: 2.30; 95% CI 1.52 to 3.48). Specifically, the risk of mortality was increased in patients with a pre-existing congestive heart failure (RR 3.02; 95% CI: 1.65 to 5.54), and liver disease (RR 4.75; 95% CI: 1.87 to 12.1). These factors collectively accounted for 69% of the risk for in-hospital mortality. A nomogram was developed from these risk factors to individualize the risk of in-hospital death following a hip fracture. The area under the receiver operating characteristic curve of the final model containing age, sex and comorbid conditions was 0.76.
Conclusion: These data suggest that among hip fracture patients, advancing age, gender (men), and pre-existing concomitant diseases such as congestive heart failure and liver disease were the main risk factors for in-hospital mortality. The nomogram developed from this study can be used to convey useful prognostic information to help guide treatment decisions.

Introduction

Hip fracture is one of the most serious consequences of osteoporosis, because it is relatively common in the elderly population, and is associated with increased risk of mortality [1–3]. Approximately 10% of women and 5% of men aged 60 years or above will sustain a hip fracture during their remaining lifetime [4]. Several studies have shown that approximately 20% of women and 30% of men die in the first year following a hip fracture [2], with men having a higher risk of mortality than women [5]. Worldwide, approximately 1.6 million hip fractures occur in elderly men and women each year, making it one of the most important public health burdens in the world [6].

Virtually all patients with hip fracture are hospitalized. A recent meta-analysis has suggested that the risk of mortality during the first 3 months after a hip fracture (including during hospitalization) is highest, with men having greater risk than women [7]. Indeed, the risk of in-hospital mortality has been estimated to range between 4 and 12% [5,8–10]. However, it has not been clear which risk factors are associated with increased risk of in-hospital mortality. While pre-existing co-morbidity seems to be associated with increased risk of post hip-fracture mortality [9,11,12], its relative importance in the prognosis of in-hospital mortality has not been documented.

Knowledge of risk factors for mortality in hip fracture patients during hospitalization is critically important, because such knowledge can be translated into prognostic information, which can help allocate

* Corresponding author at: Osteoporosis and Bone Biology, Garvan Institute of Medical Research, St Vincent's Hospital, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia. Fax: +61 2 9295 8241.
E-mail addresses: s.frost@uws.edu.au (S.A. Frost), n.nguyen@garvan.org.au (N.D. Nguyen), deborahblack@usyd.edu.au (D.A. Black), j.eisman@garvan.org.au (J.A. Eisman), t.nguyen@garvan.org.au (T.V. Nguyen).

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clinical care resources and risk counseling for patients and their relatives. Such knowledge can also help identify high-risk patients for early intervention to reduce their risk of death after hospital discharge. The present study sought to examine risk factors, and to develop a prognostic model for predicting absolute risk of in-hospital mortality among hip fracture patients.

Materials and methods

Setting and patients

The study was undertaken in a large teaching hospital in the south west of Sydney (Australia) that has approximately 55,000 admissions each year. Study participants were an inception cohort of 1504 women and men aged 50-years or older at the time of admission, with a fracture of the femur between January 1st 1997 and December 31st 2007. The study protocol and procedure were approved by the South Western Area Health Service Human Research Ethics Committee.

Ascertainment of outcome and risk factors

The primary outcome of this study was in-hospital mortality. In-hospital mortality was defined as death occurring during the index hospital stay for hip-fracture. Fracture of the femur was defined as an admission with a principal diagnosis of fracture of femur (ICD-10-AM S72.0–S72.9).

Comorbidities at the time of admission for hip fracture were ascertained from patients' electronic medical record. A Charlson comorbidity index was calculated [13]. A full list of International Classification of Disease (ICD-version 10) codes used to identify comorbid conditions [14,15] and calculation of a Charlson index are presented in the Appendix A. Patient's age was determined from the date of admission and date of birth.

Data analysis

Relative risks of in-hospital death associated with baseline characteristics of hip fracture patients at admission were estimated using a log-binomial regression model [16,17]. The estimates from these models are rate ratios and this method was chosen due to mortality in some subgroups being greater than 10%, in which case odds ratios from a logistic regression model over-estimate the actual relative risk [18]. Both crude and adjusted relative risks of in-hospital death are presented with 95% confidence intervals. Potential effect-modification was assessed using interaction-terms between all factors (none were statistically significant at the 0.05 level). We estimated the proportion of the in-hospital mortality that may be attributed to baseline characteristics of hip fracture patients by using the method of partial attributable risk (pAR) using the pARccs package [19].

Development of prognostic model

Using risk factors identified from the initial analysis, we then developed a prognostic nomogram for predicting the absolute risk of death during hospitalization. The bootstrap-based backward deletion algorithm with *P*-value of 0.20 was used to determine predictors of mortality. In this algorithm, small bootstrap samples (n = 50) from the entire sample were repeatedly selected and the predictors that were statistically significant (at the level of $P = 0.2$) in at least 60% of the bootstrap samples were included in the final model [20]. The discriminatory ability of the final prognostic model to assign higher risk to those hip fracture patients who did die during hospitalization was assessed using the area under the receiver operating characteristic curve (AUC) [21]. In order to assess the concordance between predicted and observed probability of mortality (i.e., calibration), we used the bootstrap method. In this method, a sub-sample of 50-patients was used to create a training model that was then applied to the whole data set to estimate biases between the observed and predicted rates of the outcome. This was repeated 200 times to create a distribution of bias between predicted and observed rates. The resulting estimate of bias between predicted and observed frequencies of in-hospital death is referred to as the maximum calibration error [20]. To further assess the performance of the final model we compared reclassification of individuals using a simple model containing age and sex alone, with the final model which also considered comorbid conditions [22,23]. The Design package by Frank Harrell was used to develop the nomogram [24]. All analyses were undertaken using the R statistical environment (version 2.10) [25].

Results

Between January 1st 1997 to December 31st 2007, 1504 patients with a hip fracture (410 men and 1094 women) were admitted to the study hospital; among whom, 83 (6%) died during the hospitalization. The median duration of hospital stay was 9 days, 75% of patients having stayed in the hospital for less than 16 days. There was no significant difference in hospital length of stay between survivors and non-survivors.

Baseline clinical and demographic characteristics of hip fracture patients are shown in Table 1. The rate of mortality in men (9%) was higher than in women (4%, $P<0.001$). Non-survivors were more likely to have been admitted to hospital in the previous 12 months than survivors (40% vs. 23%; $P = 0.002$). In both genders, non-survivors

Table 1
Baseline clinical characteristics of hip fracture patients classified by survival status.

Characteristics	Non-survivors (n = 83)	Survivors (n = 1421)	*P*-value
Age (y), mean (SD)	84 (7)	80 (10)	<0.001
Sex			<0.001
Male	36 (43)	374 (26)	
Female	47 (57)	1047 (74)	
Fracture type			0.58
Cervical	39 (47)	694 (49)	
Pertrochanteric	36 (43)	632 (44)	
Subtrochanteric	8 (10)	95 (7)	
Last hospital admission			0.002
None in last 12-months	50 (60)	1093 (77)	
Within 28-days	9 (11)	60 (4)	
1–6 months	12 (14)	142 (10)	
6–12 months	12 (14)	126 (9)	
Charlson Index			<0.001
0 (None)	37 (45)	960 (68)	
1–2	11 (13)	242 (17)	
3–4	15 (18)	127 (9)	
5 or more	20 (24)	92 (6)	
One or more comorbid condition	46 (55)	467 (33)	<0.001
Comorbid condition			
Myocardial infarction	10 (12)	64 (5)	0.002
Congestive heart failure	25 (30)	106 (7)	<0.001
Peripheral vascular disease	5 (6)	49 (3)	0.22
Cerebral vascular disease	12 (14)	102(7)	0.015
Dementia	20 (24)	194 (14)	0.008
Pulmonary disease	12 (14)	113 (8)	0.037
Connective tissue disease	2 (2)	24 (2)	0.62
Peptic ulcer disease	8 (10)	58 (4)	0.016
Liver disease	6 (7)	15 (1)	<0.001
Diabetes	18 (22)	143 (10)	<0.001
Hemi-/paraplegia	5 (6)	59 (4)	0.41
Renal disease	14 (17)	67(5)	<0.001
Malignant conditions	6 (7)	41 (3)	0.25
Inflammatory bowel disease	3 (4)	29 (2)	0.33
Obesity	0 (0)	24 (2)	0.23
Pancreatitis	2 (2)	5 (0)	0.007
Alcoholism and alcohol related disease	0 (0)	23 (2)	0.24
Length of stay (days), median (IQR)	10 (5–18)	9 (6–16)	1.00

Values are number (%), unless otherwise specified.

were significantly older, and had more concomitant diseases than survivors. Approximately 24% of non-survivors had at least 5 concomitant diseases, which was almost 4 times higher than that in survivors (6%). The most common comorbid conditions among non-survivors were: congestive heart failure (30%), dementia (24%), renal disease (17%) and diabetes (22%).

The risk of in-hospital mortality increased with advancing age (*P*-value for trend <0.001). After adjusting for gender and pre-existing comorbid conditions, hip fracture patients aged 90 or above were 8.7 times more likely to die in hospital compared with those aged between 50 and 69 years (adjusted RR 8.70; 95% CI 2.67 to 28.4). Men had 2.4 times greater risk of in-hospital death compared to women (adjusted RR = 2.39; 95% CI 1.52 to 3.75). Having been admitted to the study hospital in the 12-month period prior to hip fracture was associated with an increased risk of death (RR 2.09, 95% CI 1.37 to 3.19); however, the risk was no longer significant after adjusting for age, gender, and preexisting comorbid conditions. The more comorbid conditions a patient had, the greater the risk of mortality. For example, the RR for death among those with 5 or more comorbid conditions was 4.09 times (95% CI 2.20 to 7.58) higher than among those with no documented comorbid conditions (Fig. 1).

Results of bootstrap analysis suggested that the following factors were independent predictors of in-hospital mortality: advancing age, male gender and comorbidities, including congestive heart failure, cerebral vascular disease, liver disease, renal disease and malignant conditions. Adjusted relative risks (as rate ratios) of in-hospital mortality due to factors retained in the final model are presented in Table 2. Absolute and partial attributable risks of in-hospital death are presented in Table 3. The absolute risk of in-hospital death was estimated to range from 2% (in women aged 50–79 years with no comorbid conditions on admission) to 18% (in men aged 80+ with a one or more comorbid conditions). Following adjustment for age and gender, the proportion of risk estimated to be attributable to having one or more comorbid conditions at admission was 32% (95% CI, 14 to 46). The partial attributable risk with a combination of gender, age and having at least one or more comorbid conditions was 69% (95% CI, 48 to 80). The AUC of the final model was 0.76, while a model that considered age and sex alone had an AUC of 0.69. When comparing a

Table 2
Risk factors for in-hospital mortality among hip fracture patients, multivariable analysis.

	Unit of comparison	Rate Ratio	(95% CI)	*P*-value
Age (y)	+10	2.06	(1.55–2.75)	<0.001
Men	vs. women	2.31	(1.47–3.63)	<0.001
Congestive heart failure	vs. no	3.00	(1.77–5.07)	<0.001
Cerebral vascular disease	vs. no	1.57	(0.83–2.98)	0.165
Liver disease	vs. no	4.79	(1.94–11.83)	<0.001
Renal disease	vs. no	1.69	(0.88–3.24)	0.115
Malignant conditions	vs. no	1.63	(0.69–3.86)	0.265

Note: Although renal disease and malignant conditions were not statistically significant in the multivariable model, these factors were selected due to the high probability (>60%) of being selected by the bootstrap method (see more details in Method section).

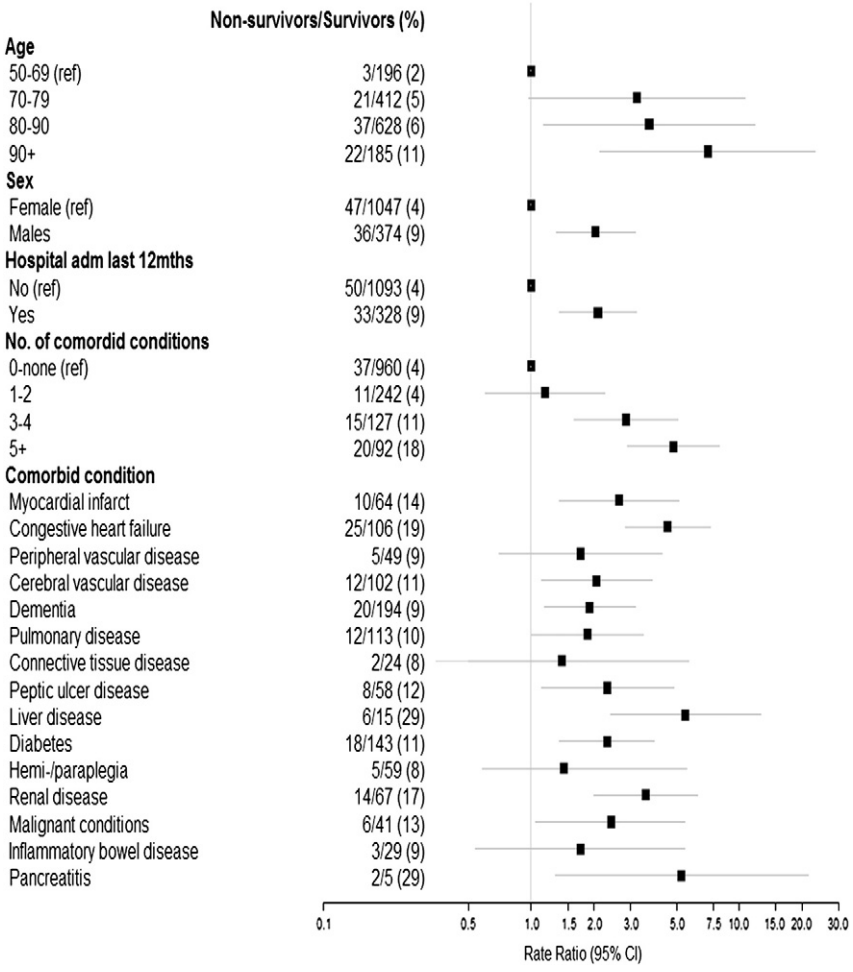

Fig. 1. Risk of in-hospital mortality. Crude rate ratios (solid squares) and 95% confidence intervals.

Table 3
Absolute and partial attributable risks of in-hospital mortality.

Gender	Age	Presence of at least one comorbidity[a]	Absolute (%) risk of death (95% CI)	Partial (%) attributable risk
Women	50–79	No	1.9 (0.9, 2.8)	Reference (0)
		Yes	4.3 (2.2, 6.4)	36.7
	80 +	No	3.7 (2.3, 5.1)	24.8
		Yes	8.4 (5.5, 11.3)	53.0
Men	50–79	No	4.1 (2.1, 6.1)	32.9
		Yes	9.3 (5.0, 13.7)	58.2
	80 +	No	8.0 (4.6, 11.4)	50.0
		Yes	18.2 (11.2, 25.2)	68.8

[a] Co-morbidity considered in this analysis included the following conditions: congestive heart failure, cerebral vascular disease, liver disease, renal disease, and malignant conditions.

model that considered age and sex alone with a model that also considered comorbid conditions, 17% of individuals were re-classified in risk status.

A nomogram was developed for predicting the risk of death based on these risk factors (Fig. 2). A clinical application of this nomogram can be illustrated by the following case: a 70-year old man with a history of congestive heart failure was admitted for hip fracture. Being a man, his gender-related score was 6 points (by drawing a vertical line from the "Men" axis to the "Point" axis); 70 years of age was equivalent to 10 points; and finally congestive heart failure was equivalent to 9 points; which yields a total score of 25. Locating the 25 points on the "Total Points" axis and draw a vertical line down to the "Risk of mortality" to estimate his in-hospital mortality which is ~10%, i.e., among men with his age and the medical condition, 1 in 10 will die in hospital after a hip fracture.

Discussion

Hip fracture is the most serious consequence of osteoporosis, because it is associated with increased risk of mortality. The risk of mortality is highest during the first year, particularly during the first 3 months, after the fracture [2], with between 20% and 30% of patients dying during this period. Because almost half of the risk of death during the first year is attributable to in-hospital death, the identification of individuals at high risk of mortality during this early post-fracture period could help to improve outcome of hip fracture by initiating appropriate and effective intervention.

The role of pre-existing comorbidity in post-hip-fracture mortality has not been consistently reported. In some settings, it has been found that pre-fracture comorbidity may account for much of the excess observed mortality following hip fracture [10,26], while in other settings, such an association has not been found [27]. In a large scale population-based study on elderly men and women of European background, the greatest portion of early-mortality was suggested to be attributable to the fracture-event itself [27].

Factors associated with increased risk for in-hospital mortality following hip-fracture has not been well-documented [5,28,29]. A previously risk-score based model has been developed for predicting in-hospital and 1-year mortality among hip fracture patients [5]. The risk factors considered in that study are largely similar to the present study's: advancing age, gender, and presence of comorbid conditions [5]. However, in terms of methodology, our model is different from the previous Jiang et al. model [5], which was based on the concept of risk stratification (i.e., continuous variables were categorized into sub-groups), whereas our model was based on the concept of individualization (i.e., the continuous nature of risk factors were preserved in order to increase the degree of uniqueness of an individual). With continuous variables, the more risk factors are considered, the greater likelihood of uniqueness of an individual's profile can be defined. Therefore, by modeling risk factors in their continuous scale, the present model can be uniquely tailored to an individual.

Although nomograms for individualizing prognosis have been widely used in cancer research [30–36] and sporadically in other clinical settings [37–40], their use in in-hospital settings has not been well documented. This study, therefore, offers an important innovation in the identification of elderly patients at risk of death during a hospital stay following hip-fracture. However, the utility of a prediction model is dependent on two important criteria: how well the model is calibrated, and could the model discriminate a high risk patient from a low risk patient. Our model satisfied both criteria, with

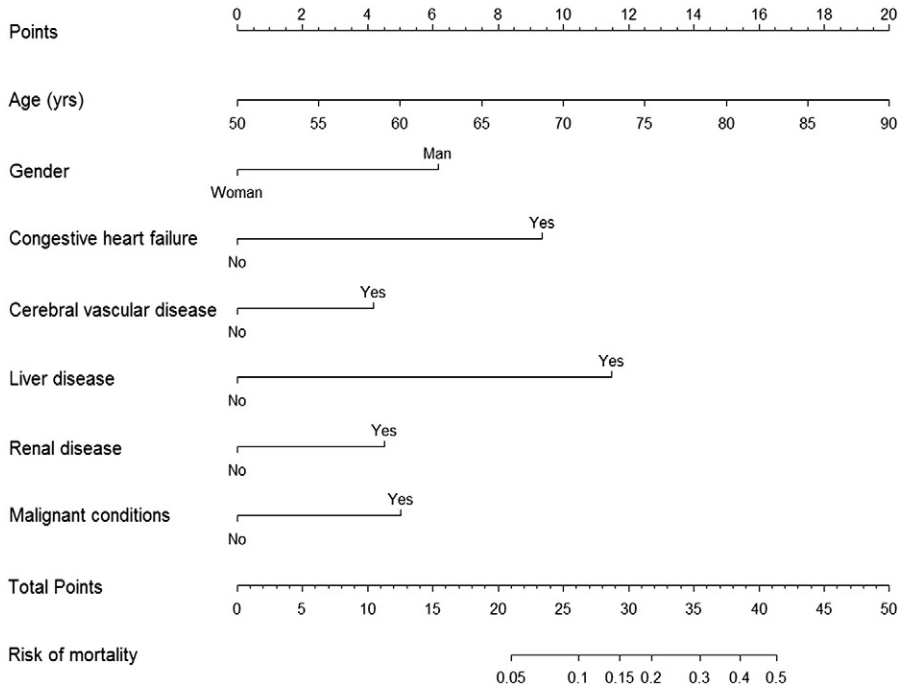

Fig. 2. Nomogram for predicting absolute risk of in-hospital mortality following a hip fracture admission.

a maximum calibration bias of only 4%, and an acceptable discrimination (AUC = 0.76) [41].

It should however be mentioned that not all individuals with high predicted risk of mortality will die, and conversely, not all individuals with low predicted risk of mortality will survive. Ideally, the predicted risk of mortality is used for stratifying individuals into distinctive groups for treatment allocation. For instance, zoledronic acid [42] given in this early post-fracture period has been shown to reduce 2-year risk of mortality in women and men by 30%. Our prognostic nomogram can be used as a guide for selecting appropriate patients for intervention, and to this end, it is important to derive a threshold for treatment decision. However, the threshold is a function of the test sensitivity, specificity, benefit and risk of treatment, which are not currently available. Therefore, further research is required to derive thresholds for the assessment of mortality risk and treatment decision. It has been suggested that patients with hip fracture treated with zoledronic acid had reduced risk of mortality by 28% [42]. If the probability of mortality is set at 5% and 10% as screening thresholds, we estimated that 62 and 135 individuals, respectively, need to be screened to prevent one death.

The present study's finding must be interpreted within the context of its strengths and potential weaknesses. A major strength of this study is that it is based on a large number of consecutive patients following hip fracture in elderly women and men over a 10-year period. Complete ascertainment of outcome was possible. Also the role of the study hospital as the major teaching and referral hospital for the population it serves ensured a wide capture of hip fracture patients. However, the data used in the analysis were based on administrative data collected routinely in the hospital setting. Therefore, there is potential for under-reporting of co-morbid conditions among patients which could result in underestimation of the effect of co-morbidity on mortality risk. Another potential weakness is the unknown final status of hip fracture patients who were transferred to other health care institutions following the admission to the study hospital. These patients, transferred to other health care facilities, may potentially represent a group at high-risk of early mortality. The final model may be biased by the misclassification of this small group of patient as surviving hospitalization; when in fact many may have died within another health care facility.

In summary, the results of the present study suggest that advancing age, being male, and pre-existing concomitant diseases, particularly as congestive heart failure and liver diseases, are important risk factors for in-hospital mortality after a hip fracture. The nomogram developed from this study can assist clinicians in conveying useful prognostic information to help guide treatment decision.

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Appendix A. Charlson comorbidity index and diagnostic codes

The Charlson index was estimated as a function of concomitant diseases with each being weighted by a coefficient as follows:

$$\text{AMI} + \text{CHF} + \text{PVD} + \text{DEM} + \text{CVD} + \text{CPD} + \text{RHE} + \text{PU} + \text{DM} + \text{HEP1} + \text{HP} \times 2 + \text{REN} \times 2 + \text{DMCC} \times 2 + \text{MAL} \times 2 + \text{HEP2} \times 3 + \text{MST} \times 6 + \text{HIV} \times 6$$

where AMI = acute myocardial infarction = AMI, CHF = congestive heart failure, PVD = peripheral vascular disease, CVD = cerebral vascular disease, DEM = dementia, CPD = chronic pulmonary disease, RHE = rheumatologic disease, PU = peptic ulcer disease, DM = diabetes, HEP1 = mild liver disease, HP = hemiplegia/paraplegia, REN = renal disease, DMCC = diabetes with chronic complications, MAL = malignancy, HEP2 = moderate or severe liver disease, MST = metastatic solid tumor, and HIV = human immunodeficiency disease or AIDS. Emergency department and in-patient diagnostic codes from July 1st 1996 were used to derive the Charlson Index and co-morbidity categories prior in-hospital admission. The derivation of ICD-10 Charlson Index's was based on a SAS macro to identify the cumulative Charlson Index up until the index admission for hip fracture.

Comorbid conditions (ICD-10 diagnosis codes)

Myocardial infarction: I21, I22, I23 and I25.2
Congestive heart failure: I50; I11.0; I13.0; I13.2
Peripheral vascular disease: I70; I71; I72; I73; I74; I77
Cerebrovascular disease: I60–I69; G45; G46
Dementia: F00–F03; F05.1; G30
Pulmonary disease: J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease: M05; M06; M08; M09; M30–36; D86
Peptic ulcer disease: K22.1; K25–K28
Liver disease: B15.0; B16.0; B16.2; B18; B19.0; K70–K74; K76.0; K76.6; I85
Diabetes: E10-E11
Hemi/paraplegia: G81; G82
Renal disease: I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61
Malignant conditions: C00–C96
Obesity: E65; E66
Pancreatitis: K85; K86.0; K86.1
Alcoholism and alcoholism-related conditions: F10; G31.2; G62.1; G72.1; I 42.6K29.2; R78.0; T51; Z72.1

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