Prognostic Impact of the Charlson Comorbidity Index on Mortality following Acute Pulmonary Embolism

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Key Words

Pulmonary embolism • Charlson score • Comorbidity

Abstract

Objectives: It was the aim of this study to determine the prognostic significance of the Charlson Comorbidity Index (CCI) following acute pulmonary embolism (PE) and assess the prognosis of patients without comorbidities (defined as a CCI score of 0). **Methods:** Outcomes of 1,023 consecutive patients admitted with confirmed PE were tracked after a median of 3.7 years (25–75th interquartile range 1.5–6.1 years). All were assigned a non-age-adjusted CCI score. **Results:** The median CCI score was 1.0 (interquartile range 0.0–3.0). Three hundred and fifty-one (34%) patients had a CCI score of 0. Only 1 (0.3%) of 31 in-hospital deaths occurred in patients with a CCI score of 0. Long-term mortality for these patients was similar to the population-derived age- and sex-matched mortality rate, and was significantly better than for those with a CCI score ≥ 1 (12.5 vs. 47.5%; $p < 0.0001$ adjusted for age and sex). In multivariate analysis, CCI (per 1-score increase) independently predicted in-hospital (hazard ratio 1.27, 95% confidence interval 1.09–1.49; $p = 0.003$) and post-discharge (hazard ratio 1.35, 95% confidence interval 1.29–1.42; $p < 0.0001$) death. The c statistics for the multivariate

prediction models for in-hospital (incorporating CCI score and serum sodium level) and post-discharge death (age, CCI score, hyperlipidemia, serum sodium and hemoglobin) were 0.738 and 0.788, respectively (both $p < 0.0001$). **Conclusion:** The CCI can be incorporated into risk models, with good discriminatory power, for predicting in-hospital and long-term outcomes following acute PE. Patients with a CCI score of 0 have a favorable long-term outcome following acute PE.

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Introduction

Patients presenting with acute pulmonary embolism (PE) frequently have significant underlying comorbidities such as chronic cardiopulmonary diseases and malignancy [1, 2]. While such comorbidities can predispose patients to acute PE [3], they may themselves also determine the patients' long-term prognosis [4]. It is not known how many patients are without significant comorbidities at the time of their PE presentation, and the outcome of these patients has not been described.

The Charlson Comorbidity Index (CCI) score is a measure of the burden of disease arising from multiple

comorbidities [5, 6]. It is a summary score based on the presence or absence of 17 medical conditions that include cardiovascular disorders, malignancies, chronic pulmonary and neurological diseases, connective tissue diseases and others. Whether the CCI score can be used to predict acute and long-term outcome in patients with acute PE is not known.

The current study aims firstly to determine whether the CCI score predicts in-hospital and long-term survival in a large cohort of patients with acute PE, and secondly, to investigate the survival outcome of patients with acute PE who are without comorbidities defined as a CCI score of 0.

Patients and Methods

Study Population

Consecutive patients admitted with a principle diagnosis of acute PE between January 2000 and December 2007 were identified retrospectively from a tertiary referral institution (Concord Hospital, Sydney, N.S.W., Australia). The medical records of all identified patients were then reviewed for formal confirmation of diagnosis of acute PE. Confirmed PE was defined according to published guidelines [7] and required both documented clinical diagnosis and/or treatment of acute PE by the attending physician and an imaging study consistent with the diagnosis (intermediate-high probability nuclear pulmonary ventilation-perfusion scintigraphy or computed tomography pulmonary angiogram showing thrombus within pulmonary arterial circulation). For those patients who presented on more than one occasion with acute PE during the study period (recurrent PE), only the initial presentation was included. Those patients who were non-local state residents (New South Wales) were excluded from the study to minimize incomplete tracking of long-term outcomes. This cohort has been described in detail previously [2, 8].

Data Collection

Details of the patients' admission history including the type of imaging modality used to diagnose PE (nuclear pulmonary ventilation-perfusion scintigraphy or computed tomography pulmonary angiogram), the admitting physician specialty, length of admission, comorbid illnesses, blood profiles during admission (serum sodium, creatinine, hemoglobin, and coagulation profiles), and in-hospital outcomes were recorded. The estimated glomerular filtration rate of each patient was derived from their serum creatinine, age and sex using the Modification of Diet in Renal Disease formula [9].

The overall comorbid status of each patient was quantified using the CCI [5, 6], which is a summation score based on 17 medical conditions with varying assigned weights (non-age adjusted). A score of 1 is given to each of the following conditions: myocardial infarction, cardiac failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes (without organ damage); a score of 2 for hemiplegia,

moderate to severe renal disease, any tumor (within last 5 years), lymphoma, leukemia, and diabetes with organ damage; a score of 3 for moderate to severe liver disease; and a score of 6 for metastatic solid tumor and acquired immunodeficiency syndrome. A value of 0 indicates no comorbidity, while higher values represent an increasing burden of comorbid illnesses.

Study Outcomes

The long-term outcome of the study cohort was tracked using a state-wide death registry database [2, 8]. A censored date, 30 June 2008, was predetermined to allow a minimum follow-up of 6 months. The primary outcome of the study was all-cause mortality. All death certificates were retrieved for review to ascertain the cause of death. Cardiovascular death was defined as death due to PE, acute myocardial infarction, heart failure, stroke, cardiac arrest and cardiac-related causes (when more than one cardiac cause of death was recorded). Non-cardiovascular death was defined as all other deaths not included in cardiovascular death. These included deaths due to malignancy, sequelae of sepsis and others. Patients with multiple potential causes of death on their death certificates were classified as 'undefined' and labeled as 'non-cardiovascular death' for the purposes of the present study. Each cause of death was coded independently by two reviewers (A.C.C.N. and L.K.) according to general principles set by the World Health Organization [10], and the reviewers were blinded to patient clinical details or comorbid illnesses during coding. Disparities were subsequently resolved by consensus.

The expected age- and sex-specific death rates for the local state residents were obtained from publicly available resources [11]. Population statistics of the same time period as our study (between 2000 and 2007) were chosen for contemporary comparison.

Statistical Analysis

All continuous variables underwent D'Agostino-Pearson omnibus normality testing to determine Gaussian distribution. Those that passed are expressed as the mean and 95% confidence interval (CI), while variables with skewed distribution are presented as the median with 25th and 75th interquartile range (IQR), unless stated otherwise. Categorical data are presented as frequency (percentage, 95% CI of the percentage). Comparison between groups used unpaired t test for parametric variables and the Mann-Whitney U test for nonparametric variables. Categorical variables were compared using χ^2 tests or Fisher's exact test. Kaplan-Meier survival methods were used to compare unadjusted survival rates. Univariate and multivariate logistic regression analysis was used to assess predictors of in-hospital death, while Cox proportional hazards regression analysis was used to assess predictors of post-discharge death. The univariate predictors that were assessed included age, sex, CCI score (as a continuous variable), other comorbidities not included in CCI, and laboratory parameters. Only univariate variables with $p < 0.10$ were included in the multivariate analysis. Discrimination performance was determined by the c statistic. The area under the receiver operating characteristic curve was used to assess the c statistic of the CCI score and the final multivariate logistic regression model in predicting in-hospital death, while the Harrell c statistic was used to assess the CCI score and the final multivariate Cox regression model in predicting post-discharge mortality [12]. To assess the calibration performance of multivariate mod-

els, the Hosmer-Lemeshow statistic was used, with a value of <20 and $p > 0.05$ indicating good calibration [13]. Analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, Ill., USA) and Prism 4.03 (GraphPad Software, La Jolla, Calif., USA). A two-tailed probability value $p < 0.05$ was considered statistically significant.

Ethical Considerations

The study complies with the Declaration of Helsinki and was approved by the institutional Human Research Ethics Committee (CH62/6/2008-009); because the study involved de-identified data, informed consent was not required.

Results

Study Cohort

Between 2000 and 2007, 1,112 patients were admitted with a diagnosis of PE to our institution. Of these, 89 were excluded from further analysis: 77 patients did not fulfill the criteria for confirmed PE, and 12 were non-local state residents. None of the non-local state residents died during their hospital admission. The final study cohort of 1,023 patients had a median follow-up of 3.7 (IQR 1.5–6.1) years.

The median age of the cohort was 71.6 (IQR 57.6–80.4) years, with more females ($n = 566$, 55%) than males ($n = 457$, 45%). A total of 860 patients had an abnormal nuclear ventilation-perfusion scintigraphic study consistent with PE, whilst 257 patients had their PE diagnosed on computed tomography pulmonary angiogram (102 patients received both imaging modalities).

Cohort Stratified by CCI

The median non-age-adjusted CCI score for the cohort was 1.0 (IQR 0.0–3.0) (fig. 1), with a higher score for males compared to females (mean 1.9, 95% CI 1.7–2.1, vs. mean 1.7, 95% CI 1.5–1.9, respectively; $p = 0.048$). Table 1 shows the study cohort stratified into those with a CCI score of 0 ($n = 351$) versus a CCI score ≥ 1 ($n = 672$). Those with a CCI score of 0 were younger, had more documented deep vein thrombosis, were less likely to receive an echocardiogram during admission, and had shorter admission for their PE compared to patients with a CCI score ≥ 1 . In addition, they were less likely to have atrial arrhythmias, hypertension or hyperlipidemia. There was no difference in the number of patients who presented as recurrent PE between the two groups. Significantly lower serum sodium, hemoglobin and glomerular filtration rate were noted in patients with a CCI score ≥ 1 than those with a 0 score.

Fig. 1. Frequency of study cohort based on CCI score.

In-Hospital and Post-Discharge Outcomes

There were 31 (3.0%, 95% CI 2.1–4.3) in-hospital deaths. Of the 992 who survived to hospital discharge, 332 died during follow-up, resulting in a total mortality of 363 patients (35.5%, 95% CI 32.6–38.5). Table 2 shows the short- and long-term all-cause mortality of the cohort stratified by their CCI scores. The total mortality for patients with a CCI score of 0 was 44 (12.5%, 95% CI 9.5–16.4) versus 319 (47.5%, 95% CI 43.7–51.3) for patients with a CCI score ≥ 1 ($p < 0.0001$). Compared to patients with a CCI score of 0, those with a CCI score ≥ 1 had a 16-fold [hazard ratio (HR) 16.4, 95% CI 2.2–120.4; $p = 0.006$] increased risk of in-hospital death following acute PE. This remained significant even after adjustment for age and sex (HR 14.3, 95% CI 1.9–106.8; $p = 0.009$).

After discharge, patients with a CCI score ≥ 1 continued to have worse survival outcome (HR 4.6, 95% CI 3.3–6.3; $p < 0.0001$) compared to patients with a CCI score of 0 (table 2; fig. 2). When adjusted for age and sex, the increased risk of death for patients with a CCI score ≥ 1 was more than 3-fold (HR 3.3, 95% CI 2.4–4.6; $p < 0.0001$) than that of patients with a CCI score of 0. Figure 2 also shows the post-discharge Kaplan-Meier actual survival curves of the study cohort compared to their expected survival derived from the age- and sex-matched general population, stratified by a CCI score of 0 versus a CCI score ≥ 1 . There was no difference between the actual and expected survival curves of patients with a CCI score of 0. In contrast, the actual survival of patients with a CCI score ≥ 1 was significantly poorer than their expected survival.

Table 1. Clinical parameters of the study cohort at baseline

Parameters	Study cohort (n = 1,023)	CCI = 0 (n = 351)	CCI ≥1 (n = 672)	p value
Median age, years	71.6 [57.6–80.4]	64.3 [48.0–77.1]	74.1 [64.1–81.5]	<0.0001
Males	457 (45, 42–48)	145 (41, 36–47)	312 (46, 43–50)	0.13
Documented DVT during admission	184 (18, 16–20)	80 (23, 19–27)	104 (15, 13–18)	0.005
Admitting physician specialty				
Internal medicine specialties	999 (97.6, 96.5–98.4)	340 (96.9, 94.5–98.2)	659 (98.1, 96.7–98.9)	0.28
Surgical specialties	19 (1.9, 1.2–2.9)	8 (2.3, 1.2–4.4)	11 (1.6, 0.9–2.9)	0.63
Emergency department	5 (0.5, 0.2–1.1)	3 (0.9, 0.3–2.5)	2 (0.3, 0.6–1.1)	0.35
Median length of hospital stay, days	7 [5–10]	6 [4–8]	7 [5–11]	<0.0001
Echocardiogram during admission	381 (37, 34–40)	108 (31, 26–36)	273 (41, 52–59)	0.002
<i>Imaging modality</i>				
Ventilation-perfusion scintigraphy	860 (84, 82–86)	296 (84, 80–88)	564 (84, 81–87)	0.93
High probability	758 (74, 71–77)	254 (72, 67–77)	504 (75, 72–78)	0.37
Intermediate probability	90 (9, 7–11)	35 (10, 7–14)	55 (8, 6–11)	0.35
Computed tomography pulmonary angiogram	257 (25, 23–28)	95 (27, 23–32)	162 (24, 21–27)	0.32
Main pulmonary artery	58 (6, 4–7)	21 (6, 4–9)	37 (6, 4–7)	0.78
Segmental and sub-segmental	186 (18, 16–21)	67 (19, 15–24)	119 (18, 15–21)	0.61
Both imaging modalities used	102 (10, 8–12)	43 (12, 9–16)	59 (9, 7–11)	0.08
<i>Other comorbid conditions not included in the CCI score^a</i>				
Recurrent pulmonary embolism	94 (9, 8–11)	31 (9, 6–12)	63 (9, 7–12)	0.82
Valvular heart disease	23 (2, 2–3)	5 (1, 1–3)	18 (3, 2–4)	0.27
Atrial fibrillation and/or flutter	157 (15, 13–18)	35 (10, 7–14)	122 (18, 15–21)	0.001
Prosthetic heart valve	9 (1, 0.4–2)	2 (1, 0.2–2)	7 (1, 0.5–2)	0.51
Hypertension	316 (31, 28–34)	64 (18, 15–23)	252 (38, 34–41)	<0.0001
Hyperlipidemia	142 (14, 12–16)	35 (10, 7–14)	107 (16, 13–19)	0.01
Current smoker	86 (8, 7–10)	33 (9, 7–13)	53 (8, 6–10)	0.48
Ex-smoker	177 (17, 15–20)	53 (15, 12–19)	124 (18, 16–22)	0.19
Sleep apnea	22 (2, 1–3)	5 (1, 0.6–3)	17 (3, 2–4)	0.27
<i>Blood profile during admission^b</i>				
Median serum sodium, mmol/l	139.0 [137.0–141.0]	139.0 [137.0–141.0]	139.0 [136.0–141.0]	0.003
Median estimated GFR, ml/min/1.73 m ²	75.7 [57.1–94.5]	82.3 [69.2–98.6]	70.5 [51.2–91.0]	<0.0001
Median serum hemoglobin, g/l	131.0 [118.0–143.0]	137.0 [126.0–147.0]	128.0 [113.0–140.0]	<0.0001
Median INR at time of admission	1.1 [1.0–1.2]	1.1 [1.0–1.1]	1.1 [1.0–1.2]	<0.0001
Median INR at time of hospital discharge	2.2 [1.8–2.7]	2.1 [1.7–2.6]	2.3 [1.9–2.8]	0.001

Categorical variables are presented as frequency, with percentages and 95% CIs in parentheses, or as medians with IQRs in brackets. DVT = Deep vein thrombosis; GFR = glomerular filtration rate; INR = international normalized ratio. Estimated glomerular filtration rate = $186 \times [(S_{CR}/88.4)^{-1.154}] \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$, where the estimated S_{CR} stands for serum creatinine concentration ($\mu\text{mol/l}$), and age is expressed in years.

^a Conditions included in the CCI are myocardial infarction, congestive cardiac failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary dis-

ease, connective tissue disease, peptic ulcer disease, liver disease (mild vs. moderate to severe), diabetes (with or without organ damage), hemiplegia, moderate to severe renal disease, any tumor (within the last 5 years), lymphoma, leukemia, metastatic solid tumor and AIDS.

^b Laboratory parameters were retrieved in 983/1,023 patients (96.1%) for serum sodium; estimated glomerular filtration rate in 980/1,023 (95.8%); serum hemoglobin in 983/1,023 (96.1%); international normalized ratio on admission in 948/1,023 (92.7%); international normalized ratio on discharge in 932/992 (94.0%).

Fig. 2. Kaplan-Meier survival curves of the study cohort following acute PE (after discharge), stratified by the CCI score (CCI score of 0 vs. ≥ 1). The thick line represents the actual survival curve of patients with a CCI score of 0, while the large dotted line represents the actual survival curve of patients with a CCI score ≥ 1 . In addition, the thin line represents the expected survival curve for the patients with a CCI score of 0, while the small dotted line represents the expected survival curve for the patients with a CCI score ≥ 1 . The expected survival curves were based on death rates of New South Wales residents in the year 2006, adjusted for age and sex (Australian Bureau of Statistics, <http://www.abs.gov.au>).

Table 3 shows the causes of death for the cohort. The main in-hospital cause of death was the index PE event. After discharge, PE was a relatively infrequent cause of death, and patients with a CCI score ≥ 1 demonstrated a greater proportion of deaths due to non-cardiovascular causes than did patients with a CCI score of 0 (65.1 vs. 58.1%; $p < 0.0001$).

Predictors of Mortality

Table 4 shows the univariate and multivariate predictors of mortality for the study cohort. The CCI score was a multivariate independent predictor of both in-hospital and post-discharge death following acute PE, such that for every 1-unit score increase in CCI, the risk for in-hospital death increased by 27% (HR 1.27, 95% CI 1.09–1.49; $p = 0.003$), and for post-discharge death, the risk increased by 35% (HR 1.35, 95% CI 1.29–1.42; $p < 0.0001$). In the final multivariate modeling, the c statistic for predicting in-hospital death was 0.74 ($p < 0.0001$; incorporating the CCI score and serum sodium level), while the c statistic for predicting post-discharge death following acute PE was 0.79 ($p < 0.0001$; incorporating age, CCI

Table 2. Short- and long-term outcome after acute PE

	CCI = 0 (n = 351)		CCI ≥ 1 (n = 672)	
	mortality	95% CI	mortality	95% CI
Short-term outcome				
In hospital	1 (0.3)	0.07–1.57	30 (4.5)	3.15–6.30
30 days	1 (0.3)	0.07–1.57	40 (6.0)	4.41–8.01
3 months	4 (1.1)	0.46–2.88	81 (12.1)	9.81–14.7
6 months	6 (1.7)	0.80–3.67	108 (16.1)	13.5–19.0
Long-term outcome				
1 year	14 (4.0)	2.40–6.58	153 (22.8)	19.8–26.1
3 years	27 (7.7)	5.35–11.0	246 (36.6)	33.1–40.3
5 years	37 (10.5)	7.75–14.2	286 (42.6)	38.9–46.3
Total mortality	44 (12.5)	9.48–16.4	319 (47.5)	43.7–51.3

Figures in parentheses are percentages.

score, hyperlipidemia, serum sodium and hemoglobin levels). For predicting the 30-day mortality, the c statistic incorporating the CCI score and serum sodium level was 0.77 (95% CI 0.69–0.86; $p < 0.0001$).

Table 3. Cardiovascular versus non-cardiovascular causes of death

Cause of death	CCI = 0		CCI ≥1	
	in hospital (total = 1)	after discharge (total = 43)	in hospital (total = 30)	after discharge (total = 289)
Cardiovascular causes	1 (100)	18 (41.9, 28.3–56.8)	25 (83.3, 66.3–92.5)	101 (34.9, 29.7–40.6)
Pulmonary embolism	1 (100)	2 (4.7, 1.4–15.5)	23 (76.7, 58.9–88.1)	14 (4.8, 2.9–8.0)
Acute myocardial infarction	0 (0)	6 (14.0, 6.6–27.4)	1 (3.3, 0.8–16.7)	25 (8.7, 5.9–12.5)
Heart failure	0 (0)	4 (9.3, 3.8–21.7)	0 (0)	23 (8.0, 5.4–11.7)
Stroke	0 (0)	4 (9.3, 3.8–21.7)	0 (0)	20 (6.9, 4.5–10.5)
Cardiac arrest	0 (0)	0 (0)	0 (0)	3 (1.0, 0.4–3.0)
Cardiac related ¹	0 (0)	2 (4.7, 1.4–15.5)	1 (3.3, 0.8–16.7)	16 (5.5, 3.5–8.8)
Non-cardiovascular causes	0 (0)	25 (58.1, 43.3–71.7)	5 (16.7, 7.5–33.7)	188 (65.1, 59.4–70.3)
Malignancy	0 (0)	4 (9.3, 3.8–21.7)	1 (3.3, 0.8–16.7)	85 (29.4, 24.4–34.9) ²
Sepsis	0 (0)	12 (27.9, 16.8–42.8)	2 (6.7, 2.0–21.4)	59 (20.4, 16.2–25.4)
Others	0 (0)	9 (20.9, 11.5–35.3)	1 (3.3, 0.8–16.7)	36 (12.5, 9.1–16.8)
Undefined	0 (0)	0 (0)	1 (3.3, 0.8–16.7)	8 (2.8, 1.4–5.4)

Figures in parentheses are percentages and 95% CIs. The 95% CI is not applicable to in-hospital death for patients with a CCI score of 0 (only 1 death) and those with no deaths reported.

¹ Cardiac-related cause of death is coded when more than one cardiac cause of death is recorded on the death certificate.

² Of the 85 deaths attributed to malignancy, 70 occurred in patients with known malignancy at the time of their index PE presentation (4/70 due to a new malignancy whilst 66/70 due to the underlying malignancy), and 15 in patients without baseline malignancy.

Discussion

The current study is the first to show that the CCI score predicts both in-hospital and long-term mortality in a large contemporary adult population hospitalized for acute PE. Despite a high overall long-term mortality rate for the cohort, we identified a subgroup of patients with a CCI score of 0 who had a very favorable acute and long-term survival outcome that was comparable to the expected age- and sex-matched mortality of the general population.

The CCI is a summation score of the burden of comorbidities [6]. It has been validated in predicting in-hospital mortality when applied to ICD-10 data [14] and shown to be a useful tool in predicting outcome in various disease states. Yang et al. [15] found the CCI score (odds ratio 11.8; CCI ≥5 versus 0) to be a significant independent predictor of hospital mortality in patients with sepsis. In patients with heart failure, an increasing CCI score was associated with increased long-term mortality (HR 1.26, 95% CI 1.19–1.35; $p < 0.0001$) [16]. Its usefulness in risk-stratifying patients with cancer has also been confirmed [17].

Cardiovascular diseases, chronic pulmonary diseases and malignancies are among the comorbidities included in the CCI score. These illnesses have previously been

found to be important baseline characteristics of patients presenting with venous thromboembolism [1, 18] and were predictors of long-term survival [1]. In addition to these chronic diseases, Heit et al. [1] also reported increasing age, smoking status, chronic renal disease and neurologic disease to be independent predictors of long-term survival in their large inception cohort of patients suffering from venous thromboembolism. In patients with acute PE, age >70 years, malignancy, congestive heart failure and chronic pulmonary disease were found to be independent predictors of all-cause mortality at 3-month follow-up [3]. These studies highlighted the importance of considering patients' comorbid status in influencing their outcome, especially mid to long term, after an acute PE. The current study extends previous reports by being the first to quantify the overall comorbidity burden using the CCI score after acute PE, and to correlate it with long-term survival in these patients.

In the current study, the CCI score and serum sodium were the two independent predictors of in-hospital mortality. Hyponatremia is associated with adverse prognosis following acute coronary syndrome [19], patients with chronic heart failure [20], chronic renal failure on hemodialysis [21], and others [22]. Scherz et al. [23] recently reported baseline hyponatremia to be a common phe-

Table 4. Predictors of all-cause mortality after acute PE

Clinical parameters	HR	p value
<i>Univariate analysis</i>		
<i>In-hospital death</i>		
Age, per 1 year	1.03 (1.00–1.05)	0.06
Male	1.17 (0.57–2.39)	0.67
CCI score, per 1 score	1.35 (1.18–1.54)	<0.0001
Valvular heart disease	1.47 (0.19–11.3)	0.71
Atrial fibrillation and/or flutter	1.64 (0.69–3.87)	0.26
Hypertension	0.91 (0.42–2.01)	0.82
Hyperlipidemia	0.66 (0.20–2.19)	0.50
Current smoker	0.36 (0.05–2.64)	0.31
Serum sodium, per 1 mmol/l	0.87 (0.81–0.93)	<0.0001
Estimated GFR		
per 1 ml/min/1.73 m ²	1.00 (0.98–1.01)	0.47
Serum hemoglobin, per 1 g/l	0.98 (0.97–1.00)	0.04
<i>Post-discharge death</i>		
Age, per 1 year	1.05 (1.04–1.06)	<0.0001
Male	1.13 (0.91–1.40)	0.29
CCI score, per 1 score	1.42 (1.36–1.48)	<0.0001
Valvular heart disease	1.08 (0.51–2.28)	0.84
Atrial fibrillation and/or flutter	1.70 (1.31–2.21)	<0.0001
Hypertension	1.01 (0.80–1.28)	0.91
Hyperlipidemia	0.76 (0.54–1.05)	0.098
Current smoker	0.57 (0.35–0.91)	0.02
Serum sodium, per 1 mmol/l	0.93 (0.91–0.96)	<0.0001
Estimated GFR		
per 1 ml/min/1.73 m ²	0.99 (0.98–0.99)	<0.0001
Serum hemoglobin, per 1 g/l	0.98 (0.97–0.98)	<0.0001
<i>Multivariate analysis¹</i>		
<i>In-hospital death</i>		
Age, per 1 year	1.02 (0.99–1.06)	0.13
CCI score, per 1 score	1.27 (1.09–1.49)	0.003
Serum sodium, per 1 mmol/l	0.89 (0.83–0.95)	0.001
Serum hemoglobin, per 1 g/l	1.00 (0.98–1.02)	0.64
<i>Post-discharge death</i>		
Age, per 1 year	1.04 (1.03–1.05)	<0.0001
CCI score, per 1 score	1.35 (1.29–1.42)	<0.0001
Atrial fibrillation and/or flutter	1.09 (0.83–1.43)	0.54
Hyperlipidemia	0.63 (0.44–0.88)	0.008
Current smoker	1.05 (0.64–1.70)	0.86
Serum sodium, per 1 mmol/l	0.97 (0.95–1.00)	0.02
Estimated GFR		
per 1 ml/min/1.73 m ²	1.00 (1.00–1.01)	0.68
Serum hemoglobin, per 1 g/l	0.99 (0.98–0.99)	<0.0001

Figures in parentheses are 95% CIs. GFR = Glomerular filtration rate.

¹ Only univariate variables with $p < 0.10$ were included in the multivariate Cox proportional hazards regression analysis (multivariate logistic regression analysis for in-hospital death). The c statistics for predicting in-hospital (incorporating CCI score and serum sodium level) and post-discharge death (incorporating age, CCI score, hyperlipidemia, serum sodium and hemoglobin levels) were 0.738 ($p < 0.0001$) and 0.788 ($p < 0.0001$), respectively; the Hosmer-Lemeshow χ^2 statistic for in-hospital death was 4.10 ($p = 0.85$) and 2.07 ($p = 0.98$) for post-discharge death.

nomenon amongst patients presenting with acute PE and was an independent predictor of 30-day mortality. Including this easily obtainable biochemical parameter to the CCI score gave rise to a risk model that predicted in-hospital death with good discriminatory power (c statistic of 0.74, 95% CI 0.63–0.85; $p < 0.0001$). The c statistic for predicting the 30-day mortality in the current study incorporating the CCI score and serum sodium level was 0.77. This compares favorably with the more complex Pulmonary Embolism Severity Index reported to predict 90-day mortality after acute PE with a c statistic of 0.78 (95% CI 0.70–0.86) [24]. Jimenez et al. [25] developed a simplified version of the Pulmonary Embolism Severity Index that incorporates age, cancer, chronic cardiopulmonary disease, heart rate, systolic blood pressure, and oxyhemoglobin saturation level, and demonstrated similar prognostic accuracy as the original risk model, with a c statistic of 0.75 (95% CI 0.69–0.80) for predicting 30-day mortality.

There is currently no risk model for predicting long-term outcome for patients who experienced an acute PE. We found that the CCI can predict in-hospital and short-term outcome after acute PE and can also be incorporated into long-term mortality risk modeling. The discriminatory power of CCI did not differ between in-hospital and post-discharge death (c statistic 0.74 vs. 0.73, respectively), but the HR after discharge was slightly higher (HR 1.35, 95% CI 1.18–1.54, vs. HR 1.42, 95% CI 1.36–1.48, respectively), suggesting that the impact of comorbidities influenced long-term prognosis more than in-hospital outcome in these patients. Multivariate risk modeling also showed differences in predictors between in-hospital versus post-discharge long-term outcome. While the CCI score and serum sodium level were predictors of both in-hospital and post-discharge death, a number of other variables only predicted death after discharge and were not independently predictive of in-hospital death. These include age, hyperlipidemia and serum hemoglobin. The current study not only confirms the acute prognostic importance of serum sodium in patients with acute PE [23], it also identifies that serum sodium during the index PE admission has important long-term prognostic influence for these patients. For every 1 mmol/l higher level of serum sodium on admission, there was a 3% lower risk for all-cause long-term mortality. The final multivariate risk model incorporating the CCI score, age, hyperlipidemia, serum sodium and hemoglobin levels demonstrated good discriminatory power in predicting post-discharge death with a c statistic of 0.79.

Although the present study demonstrated the prognostic usefulness of the CCI in patients with acute PE, a CCI score of 0 is not synonymous with the absence of risk factors for thromboembolic disease. This index does not include thrombophilia, drugs or recent surgery, and other predisposing factors for venous thrombosis. This could explain the 9% of patients with a CCI score of 0 who presented as recurrent PE. In addition, patients with the same CCI score may in fact have very different comorbidities. How acute PE interacts with patients' individual comorbidity to influence their outcome may be masked by using such an index. On the other hand, the only way to correlate patients' multiple comorbidities to their outcome following acute PE is by using an index such as the Charlson score. Not only did we show that the burden of comorbidities influenced the outcome, we were able to show a dose-dependent effect on mortality by considering the index as a continuous rather than categorical variable in our multivariate risk modeling. Although baseline serum sodium was also an independent predictor of mortality, how it influenced the outcome in these patients with acute PE is not clear. It may be a surrogate marker for poorly controlled comorbidities such as heart failure or renal failure. As serum sodium is also likely to be altered during admission by routine management such as the use of diuretics and fluid resuscitation, assessment of neurohormonal changes including catecholamines, renin, angiotensin II, aldosterone, vasopressin and brain natriuretic peptide levels, and the use of diuretics and fluids during acute PE may help establish a potential pathophysiological link between serum sodium and PE outcome.

The current study is limited by its single-center source of patients and its retrospective design, and thus, requires

validation in future prospective studies. Our outcome data were obtained from a state-wide death registry; thus, it is possible that some of the survivors died in other states. However, the estimated non-captured deaths during the study period are expected to be at most 0.6% based on known migration rates [11]. Although there were 90 patients who only had an intermediate probability of PE on their pulmonary ventilation-perfusion scintigraphy, 24 of these patients had other positive imaging studies for deep vein thrombosis and/or PE (6 had deep vein thrombosis on ultrasonography, 16 had thrombus seen on computed-tomography pulmonary angiogram and 2 patients had both). Excluding the remaining 66 patients did not alter the study results and conclusions.

In summary, the present study is the first to show that the CCI score can be incorporated into risk models to predict both in-hospital and long-term mortality in adult patients hospitalized with confirmed acute PE. In addition, patients with a CCI score of 0 appear to have a very favorable outcome, with long-term survival similar to the age- and sex-matched general population.

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Financial Disclosure and Conflicts of Interest

All authors declare that there is no conflict of interest.

References

- 1 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd: Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999;159:445–453.
- 2 Ng AC, Chung T, Yong AS, Wong HS, Chow V, Celermajer DS, Kritharides L: Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. *Circ Cardiovasc Qual Outcomes* 2011;4:122–128.
- 3 Goldhaber SZ, Visani L, De Rosa M: Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353:1386–1389.
- 4 Lee JW, Cha SI, Jung CY, Choi WI, Jeon KN, Yoo SS, Kim CH, Park JY, Jung TH: Clinical course of pulmonary embolism in lung cancer patients. *Respiration* 2009;78:42–48.
- 5 Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
- 6 Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S: An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer* 2004;4:94.
- 7 Torbicki A, Perrier A, Konstantinides S, et al: Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008;29:2276–2315.
- 8 Ng AC, Yong AS, Chow V, Chung T, Freedman SB, Kritharides L: Cardiac troponin-T and the prediction of acute and long-term mortality after acute pulmonary embolism. *Int J Cardiol* 2011, E-pub ahead of print.
- 9 Mathew TH: Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005;183:138–141.
- 10 National center for health statistics. Instructions for classifying the underlying cause-of-death, ICD-10. 2008:1–259. <http://www.cdc.gov/nchs/about/major/dvs/im.htm>.

- 11 Australian bureau of statistics. 2007. <http://www.abs.gov.au>.
- 12 Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–387.
- 13 Hosmer DW Jr, Lemeshow S: *Applied Logistic Regression*. New York, John Wiley & Sons, 1989.
- 14 Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA: New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57:1288–1294.
- 15 Yang Y, Yang KS, Hsann YM, Lim V, Ong BC: The effect of comorbidity and age on hospital mortality and length of stay in patients with sepsis. *J Crit Care* 2010;25:398–405.
- 16 Clarke B, Howlett J, Sapp J, Andreou P, Parkash R: The effect of comorbidity on the competing risk of sudden and nonsudden death in an ambulatory heart failure population. *Can J Cardiol* 2011;27:254–261.
- 17 Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL: Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol* 2011;29:1335–1341.
- 18 Klok FA, Zondag W, van Kralingen KW, van Dijk AP, Tamsma JT, Heyning FH, Vliegen HW, Huisman MV: Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. *Am J Respir Crit Care Med* 2010;181:501–506.
- 19 Goldberg A, Hammerman H, Petcherski S, Nassar M, Zdoroviyak A, Yalonetsky S, Kapelevich M, Agmon Y, Beyar R, Markiewicz W, Aronson D: Hyponatremia and long-term mortality in survivors of acute ST-elevation myocardial infarction. *Arch Intern Med* 2006;166:781–786.
- 20 Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Pina IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM: Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the escape trial. *Arch Intern Med* 2007;167:1998–2005.
- 21 Waikar SS, Curhan GC, Brunelli SM: Mortality associated with low serum sodium concentration in maintenance hemodialysis. *Am J Med* 2011;124:77–84.
- 22 Forfia PR, Mathai SC, Fisher MR, Houston-Harris T, Hemnes AR, Champion HC, Girgis RE, Hassoun PM: Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2008;177:1364–1369.
- 23 Scherz N, Labarere J, Mean M, Ibrahim SA, Fine MJ, Aujesky D: Prognostic importance of hyponatremia in patients with acute pulmonary embolism. *Am J Respir Crit Care Med* 2010;182:1178–1183.
- 24 Donze J, Le Gal G, Fine MJ, Roy PM, Sanchez O, Verschuren F, Cornuz J, Meyer G, Perrier A, Righini M, Aujesky D: Prospective validation of the pulmonary embolism severity index. A clinical prognostic model for pulmonary embolism. *Thromb Haemost* 2008;100:943–948.
- 25 Jimenez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, Otero R, Monreal M, Muriel A, Yusen RD: Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170:1383–1389.