DOI: 10.1002/pul2.70010

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI | WILEY

Comorbidity profiles and pulmonary embolism risk assessment: Leveraging the Charlson Comorbidity Index for improved prognostication in a national data set

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Funding information
Temple University Libraries Open Access Publishing Fund

Abstract

Current risk assessment of pulmonary embolism (PE) stratifies patients based on hemodynamic stability, clinical parameters of severity, right ventricular dysfunction and cardiac injury but fails to integrate a wide variety of comorbid conditions. The Charlson Comorbidity Index (CCI) predicts mortality based on patients' diseases and provides a system to quantify disease burden. The National Inpatient Sample (NIS) database (2016–2018) was used to identify patients with PE and calculate CCI score groups of 0, 1–2, 3–5, and ≥6 and stratify them by outcome. Of 561,625 patients with PE, 176,460 (31.4%) had CCI score of 0, 223,870 (39.8%) had CCI of 1–2, 102,305 (18.2%) had CCI of 3–5, and 58,990 (10.5%) had CCI ≥ 6. Higher CCI scores were associated with increased mortality: CCI 1–2 (adjusted odds ratio [aOR] 2.09), CCI 3–5 (aOR 3.12), CCI ≥ 6 (aOR 5.44) compared to CCI 0, along with stepwise increases in shock and mechanical ventilation with each increase in CCI score group. CCI scores ≥3 had increased length of stay (1.4–1.72 days) and increased total hospital costs ($3651–$4265) compared to CCI0. Patients with CCI ≥ 3 were less likely to receive systemic thrombolysis, catheter directed thrombolysis and mechanical thrombectomy. Acute PE in patients with elevated comorbidity scores is associated with higher morbidity and mortality, increased hospital resource utilization, and decreased usage of advanced therapies in a large cohort reflective of patients across the United States. Integration of comorbidities in risk assessment profiles identifies patients with higher short-term mortality which may guide management strategy.

KEYWORDS
advanced therapies, comorbidity assessment, pulmonary embolism, risk stratification

Abbreviations: CCI, Carlson Comorbidity Index; CDT, catheter directed therapy; HCUP, healthcare cost and utilization project; NIS, national inpatient sample; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index.

Pulmonary embolism (PE) is a frequent cause of inpatient hospitalization with a rising incidence over the recent decades given improved diagnostic tools and a higher index of suspicion.[1,2] At the same time there has been a significant decline in hospital length of stay, readmissions, and mortality.[1–3] Part of this improvement may be attributable to the current practice of early risk stratification to steer therapeutic management.[4] Guideline directed risk stratification mainly focuses on evaluating signs and symptoms of hemodynamic compromise, clinical parameters of PE severity, right ventricular dysfunction, and cardiac injury.[5] These factors assist in categorizing patients into early mortality risk groups which then help determine the treatment they receive.

Currently, a patient's underlying disease is most often assessed via the Pulmonary Embolism Severity Index (PESI) or its simplified form, the sPESI.[4,6] Patients with PESI III-IV or an sPESI of ≥1 immediately fall out of the low risk category by European Society of Cardiology early mortality risk classification.[5] While using the PESI score can reliably rule out patients at low risk of mortality, a large and heterogeneous group of patients fall into the intermediate risk category. Furthermore, the relationship between burden of comorbid disease and outcomes amongst patients with PE is unclear given that the current scoring system only accounts for chronic cardiac and pulmonary disease along with malignancy.[5] A more comprehensive risk model that factors in patients' comorbidities may improve stratification, especially in the PE intermediate risk group, and better inform treatment in patients with PE.

The Charlson Comorbidity Index (CCI) was designed as a method of quantifying patients' comorbid conditions and relating them to a patient's mortality,[7] and has been validated in studies using ICD-10 codes[8] and used to examine a widespread of disease states.[9–11] Our study aims to assess the impact of comorbidities, as defined by the CCI, on outcomes in acute PE irrespective of risk category. Enhanced risk stratification becomes increasingly important when selecting patients for advanced therapies outside of therapeutic anticoagulation.

METHODS

Data collection

Data was obtained from the National Inpatient Sample (NIS) database from 2016 to 2018. This database is a subdivision of the Healthcare Cost and Utilization Project (HCUP) managed by the Agency for Healthcare Research and Quality. The NIS is the US's largest publicly available administrative database. The NIS database represents around 20% of all US hospitalizations and includes information on the number of beds, ownership, hospital teaching status, US region, and state.

The CCI is a method for categorizing patients' comorbidities based on ICD diagnosis codes found in administrative data, such as hospital abstracts. It involves 17 comorbidities assigned variable amounts of points. History of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, and peptic ulcer disease were assigned 1 point. Hemiplegia, moderate to severe chronic kidney disease (on dialysis, posttransplant, uremic, or creatinine >3), leukemia and lymphoma were assigned 2 points. Liver disease was categorized from a scale of 0–3 (none, mild or moderate/severe). Diabetes was graded 0–2 (none/controlled, uncomplicated, end-organ damage). Solid tumor grading was assigned 0, 2 (localized), and 6 (metastatic). Age was graded on a scale from 0 to 4 (Age < 50, 50–59, 60–69, 70–79 and ≥80). The maximal combined score is 37 points.[7]

Study population

Using ICD-10-CM codes, we identified patients hospitalized with the primary diagnosis of nonseptic pulmonary embolism, ICD code I26 (excluding I26.01, and I26.90), along with treatments they received (Table S1). The Institutional Review Board at our institution evaluated this study and deemed it not to qualify as human subject research.

Study outcomes

The study's primary outcome was in-hospital mortality, while secondary outcomes included hospitalization costs, shock, and mechanical ventilation. We compared baseline comorbidities, primary payer, household income, hospital location, region, and teaching status among patients with CCI scores of 0, 1–2, 3–5, and ≥6.

Statistical analysis

The χ^2 test was used for categorical variables, while the Kruskal–Wallis one-way analysis of variance was employed for continuous variables. Categorical variables were reported as frequencies and percentages, while continuous variables were expressed using means and standard deviations (SDs). Regression models were

adjusted for age, sex, insurance type, median household income, hospital teaching status, and significant comorbidities. All p values were two-sided, with a cutoff of $p < 0.05$ used as the threshold for statistical significance. Statistical analysis was conducted using Stata 17.0 (StataCorp).

RESULTS

Baseline characteristics

There were 561,625 adult patients hospitalized with PE in the United States between 2016 and 2018 in the NIS database (Table 1). Of these, 176,460 (31.4%) patients had a CCI score of 0, 223,870 (39.8%) had a score of 1–2, 102,305 (18.2%) had a score of 3–5, and 58,990 (10.5%) had a score ≥6 (Table 1). Patients with CCI 0 were significantly younger, with mean (±SD) age of 55.8 (±17.2) compared to 63.8 (±16.1) for CCI 1–2, 69.5 (±13.7) for CCI 3–5, and 66.7 (±12.7) for CCI ≥ 6. Among these patients 51.9% were women. Asian patients with PE had the largest percentage of high comorbidity patients (19% of Asian patients had a CCI ≥ 6 as compared to 12% of whites and 10% of blacks and Hispanics) (Table 1). PE patients with higher CCI (≥3) also had a higher prevalence of comorbid conditions not included in the CCI score, including hyperlipidemia, atrial fibrillation, and tobacco use (Table 2).

Impact of CCI on therapeutic options

In terms of treatment, 2.9% of patients received systemic thrombolysis, 3.4% received catheter directed thrombolysis, 0.95% received thrombectomy (surgical or percutaneous) and 0.2% received ECMO (Figure 1). Patients with higher CCI scores (≥3) received advanced therapies less frequently. There were lower relative rates of systemic thrombolysis (2.9% for CCI 0, 2.8% for CCI 3–5, 2.1% for CCI ≥ 6, $p < 0.001$) and catheter directed thrombolysis (4% for CCI 0, 2.8% for CCI 3–5, 1.6% for CCI ≥ 6, $p < 0.001$). Thrombectomy was lower in CCI ≥ 6 (0.66%) as compared to CCI = 0 (0.89%) ($p < 0.001$). There was no significant difference in terms of ECMO utilization.

Impact of CCI on clinical outcomes in pulmonary embolism

Overall, the odds of in-hospital mortality were higher in PE patients with CCI of 1–2 (adjusted odds ratio [aOR], 2.04, 95% CI: 1.81–2.29, $p < 0.001$), CCI of 3–5 (aOR 3.23, 95% CI: 2.82–3.71, $p < 0.001$), CCI ≥ 6 (aOR 5.57, 95% CI: 4.89–6.36, $p < 0.001$) compared with PE patients without comorbidity (Figure 2). PE patients with higher CCI were more likely to develop shock and had higher rates of mechanical ventilation. From a resource utilization standpoint, PE patients with higher CCI had a longer adjusted length of stay, and increased hospitalization costs (Table 3).

DISCUSSION

Our study is the largest to date examining the association of PE patients' comorbidities, as measured by the CCI, with clinical outcomes, in a population reflective of the Unites States. In terms of our primary outcome, we saw a stepwise increase in mortality with rising CCI score in patients with PE. Overall, in-hospital mortality was 3.1%. Mortality in CCI 0 was 1.2%, CCI 1–2 was 2.7%, CCI 3–5 was 4.5%, and CCI ≥ 6 was 7.2%. When assessing adjusted odds ratio of mortality for patients with PE, as compared to CCI 0, CCI 1–2 had an OR of 2.04 (CI 1.81–2.29), CCI 3–5 3.23 (2.82–3.71), CCI ≥ 6 5.57 (4.89–6.36) with $p < 0.001$. While it may seem obvious that patients with higher disease burden have higher mortality, our study demonstrates the extent to which mortality increases.

Overall, we found that in patients with PE, a higher burden of comorbidities was associated with both worse patient and hospital centered outcomes. With an increasing CCI, along with the rise in-hospital mortality, there is a stepwise increase in shock and rates of mechanical ventilation, as well as prolonged hospital length of stay and increased charges and costs.

Our study contributes to the current literature as there are limited studies focusing on the burden of comorbidities and its relationship to outcomes in patients with PE. Ng and colleagues, examined the prognostic impact of CCI on mortality in PE, however it was a single center study consisting of only 1023 patients.[11] In comparing patient characteristics, we were able to see that baseline CCI scores were very similar between Ng and colleagues and our study (CCI 0: 31.4% vs. 34.3%, 1–2 39.8% vs. 39.5%, 3–5 18.2 vs. 17.5%, ≥6 10.5 vs. 8.7%). This allows for our study to further contribute to the study of PE and comorbid disease, as the NIS database allows analysis of a much larger patient cohort, consisting of 561,625 patients with PE, that is representative of patients across the United States over multiple years. Similarly, Keller and colleagues utilized the German Nationwide Inpatient Sample to show the increased gradient in mortality when patients admitted with PE

TABLE 1 Baseline characteristics of PE hospitalizations by CCI categories.

Characteristics Proportion	All patients (%)	CCI = 0 (%) 31.4	CCI 1–2 (%) 39.8	CCI 3–5 (%) 18.2	CCI ≥6 (%) 10.5	*p* Value
Age, years, mean ± SD	62.6 ± 16.6	55.8 ± 17.2	63.8 ± 16.2	69.5 ± 13.7	66.8 ± 12.7	<0.001
Female gender (%)	51.9	50.9	53.4	50.6	52.0	<0.001
Race (%)						<0.001
White	71.9	73.1	72.3	70.4	68.6	
Black	18.9	17.8	18.3	20.8	20.6	
Hispanic	5.8	5.7	6.2	5.4	6.4	
Asian or Pacific Islander	1.0	0.8	0.9	0.9	1.8	
Native American	0.4	0.3	0.4	0.4	0.4	
Other	2.1	2.1	2.0	1.9	2.2	
Disposition (%)						<0.001
Home	65.5	82.3	64.9	49.3	45.5	
Transfer to short term hospital	2.1	1.7	2.3	2.3	2.1	
Transfer to facility (skilled nursing facility, long term care hospital)	13.8	5.8	14.8	22.3	18.8	
Home with health aide	14.8	8.1	14.3	20.8	25.7	
Against medical advice (AMA)	0.8	0.8	0.9	0.8	0.5	
Died	3.1	1.2	2.7	4.5	7.2	
Advanced therapies (%)						
Systemic thrombolysis	2.9	2.9	3.2	2.8	2.1	<0.001
Catheter directed thrombolysis	3.4	4.0	3.8	2.8	1.6	<0.001
Surgical and percutaneous thrombectomy	0.95	0.89	1.1	0.97	0.66	<0.001
ECMO	0.2	0.1	0.2	0.2	0.06	0.033
Healthcare utilization						
Length of stay, days, mean ± SD	4.3 ± 4.7	3.3 ± 3.2	4.3 ± 4.6	5.5 ± 6.1	5.6 ± 5.6	<0.001
Charge of hospitalization in United States $, mean ± SD	46,631.5 ± 67,327.8	36,462.0 ± 46,883.4	47,248.8 ± 64,459.9	57,226.4 ± 95,445.9	56,428.2 ± 66,636.6	<0.001
Cost of hospitalization in United States $, mean ± SD	11,387.2 ± 14,657.7	8960.0 ± 9925.7	11,473.7 ± 14,078.4	13,822.4 ± 20,619.9	14,118.2 ± 15,070.9	<0.001

TABLE 2 Additional comorbidities of patients with PE hospitalizations by CCI categories.

Characteristics Proportion	All patients (%)	CCI = 0 (%) 31.4	CCI 1–2 (%) 39.8	CCI 3–5 (%) 18.2	CCI ≥6 (%) 10.5	*p* Value
Atrial fibrillation	12.5	6	12.9	21.3	15.7	<0.001
Hyperlipidemia	35.6	23.2	38.1	49.7	38.3	<0.001
Tobacco use	39.6	33.4	41.1	44	45.2	<0.001

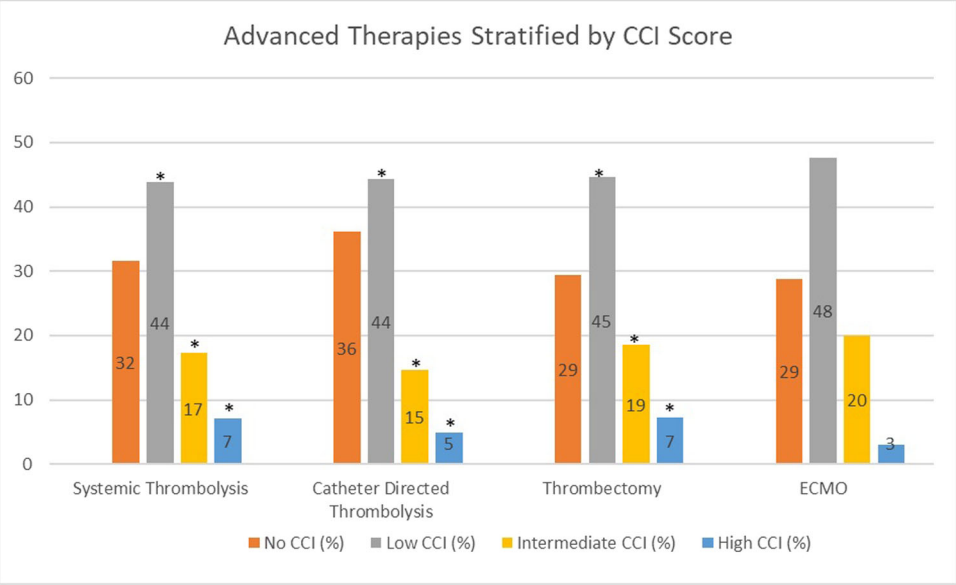

FIGURE 1 CCI distribution of patients with acute PE who underwent advanced therapies in percentages. No CCI = CCI 0, low CCI = CCI 1–2, intermediate CCI = CCI 3–5, high CCI = CCI ≥ 6. *Signifies $p < 0.001$.

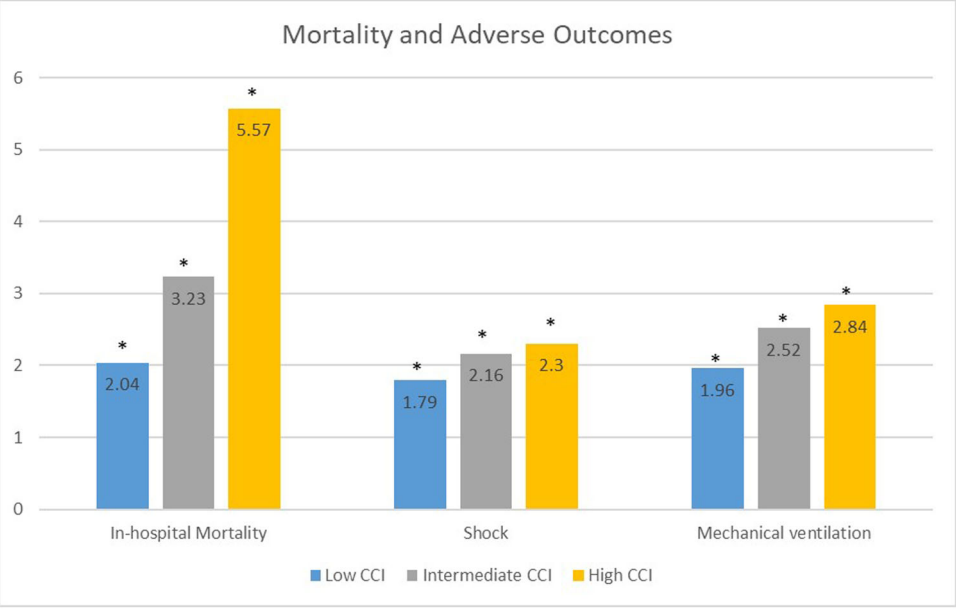

FIGURE 2 Adjusted odds ratio for the primary and secondary outcomes for patients with acute PE, as compared to patients with CCI = 0. No CCI = CCI 0, low CCI = CCI 1–2, intermediate CCI = CCI 3–5, high CCI = CCI ≥ 6. *Signifies $p < 0.001$.

TABLE 3 Univariate and multivariate linear regression model showing CCI as prognostic factors on adverse outcomes in PE hospitalizations.

Variables	Crude coefficient (95% confidence interval), comparing with CCI = 0				Adjusted coefficient (95% confidence interval), comparing with CCI = 0			
	CCI 1–2	CCI 3–5	CCI ≥ 6	*p* Value	CCI 1–2	CCI 3–5	CCI ≥6	*p* Value
Additional length of hospital stays (days)	1.06 (1.01–1.12)	2.20 (2.11–2.29)	2.29 (2.18–2.40)	<0.001	0.72 (0.66–0.79)	1.40 (1.30–1.51)	1.72 (1.60–1.83)	<0.001
Additional total hospitalization charges (in thousands)	10,800 (10,000–11,600)	20,800 (19,300–22,200)	20,000 (18,600–21,400)	<0.001	8600 (7600–9600)	14,900 (13,100–16,600)	15,300 (13,800–16,800)	<0.001
Additional total hospitalization costs (in thousands)	2500 (2300–2700)	4900 (4600–5200)	5200 (4900–5500)	<0.001	2100 (1900–2300)	3700 (3300–4000)	4300 (3900–4600)	<0.001

Note: Cost and charges rounded to the closest hundred.

were stratified by CCI scores.[12] Interestingly their study noted a higher proportion of high CCI patients (CCI 3–4: 28.8%, CCI > 4 47.8%), along with higher mortality by CCI group (CCI 0: 3.6%, CCI 1–2: 6.5%, CCI 3–4: 12.1%, CCI > 4: 22.1%). While there was some variation in cut-offs for CCI severity and the time period examined, this suggests that the United States population may not be generalizable to other parts of the world.

One potential application of these findings is to apply comorbidity scores to the risk assessment of low-risk PE. An important question in these patients is whether to discharge them from the emergency room on anticoagulation or admit them for further evaluation. Home therapy is preferred by patients, less expensive due to decreased hospitalization costs, and has been shown to be safe in select patients.[5,13,14] Despite this, home treatment remains relatively underutilized, and previous studies have seen greater than 80% of low risk PE patients hospitalized.[14,15] These results may be related to the treatment landscape at the time of the study, as direct oral anticoagulants had not yet become widespread. A more recent 2024 study by Watson and colleagues, however, examined emergency department visits for patients diagnosed with PE between 2012 and 2020 and still found that only 35.9% of low-risk patients were discharged from the ED setting, with discharge rates remaining relatively stable over time.[16] There are additional factors to consider such as provider comfort, ability to access close outpatient follow-up, and social factors, however, a patient's underlying conditions likely affects the decision to admit or discharge.

While calculations such as the PESI score or Hestia score have been used to identify patients who would tolerate home therapy, they are limited to malignancy, heart failure and chronic lung disease (PESI) or renal and liver dysfunction (Hestia) in terms of comorbidity assessment and may not capture the entirety of risk as perceived by the assessing physician. Previous studies have shown the ability to increase rates of home discharge by up to 11%, without increased adverse events, by using integrated clinical decision tools.[14] Future research will be needed to assess if integrating a comorbidity score index, that better captures risk profile, could similarly increase home discharges without significant adverse events.

Another significant finding in our study was the decreased utilization of advanced therapies in PE patients with higher CCI scores. This trend mirrors observations in the acute coronary syndrome population, where patients with higher CCI scores were less likely to receive guideline recommended drugs and reperfusion therapy, including percutaneous coronary intervention in patients with ST elevation myocardial infarction.[9,10] This

pattern undoubtedly stems from the concern that patients with more comorbidities are at higher risk of adverse effects due to the therapy. The crucial question, however, is whether the worse outcomes in patients with more comorbidities are solely attributable to their underlying conditions, or if the burden of disease contributes to less optimal treatment. A 2017 meta-analysis found that patients who underwent surgical thrombectomy had similar cardiovascular and noncardiovascular mortality at long-term follow-up.[17] This suggests that while longer term mortality in a patient with PE may be driven by comorbidities, those who meet criteria for intervention can do reasonably well. Interestingly, in the German cohort from Keller and colleagues, systemic thrombolysis and surgical embolectomy were performed at relatively similar rates between CCI groups (CCI 0 4.4%, CCI 1–2 4.9%, CCI 3–4 4.4%, CCI > 4 3.8% for thrombolysis, CCI 0–4 0.2%, CCI > 4 0.1% for surgical embolectomy) however there was no reporting for catheter directed therapies (CDT).[12] More studies will be required to determine the correct role of advanced therapies in high comorbidity patients, whether the risks outweigh the benefits, and how to identify an ideal candidate.

As the use of CDT continues to rise,[18] further data will be needed to assess if patients with high disease burden would benefit from these treatments. As we have shown, patients with multiple comorbidities are often not selected for advanced therapies but given their higher rates of short-term morbidity and mortality, they may derive the most benefit, should these therapies be shown to be safe and effective. Currently the exact role of CDT in patients with PE is still under investigation with guidelines only suggesting their usage in patients who have failed systemic thrombolysis or have a contraindication to these medications.[5,13] Initial data from prospective studies, though limited, has shown that CDT improves hemodynamics without an increased risk of bleeding,[19–23] however more data in real world populations is needed. Similar to patients with ACS, questions will continue to arise on the management of PE patients with high comorbidity burden, as overall PE incidence continues to rise.[1,2] Increased PE detection has yielded a larger group of patients in which more data is needed to guide treatment strategies, especially as the use of CDT increases.[1,18]

Although the current system utilizing the PESI score works well to distinguish low risk patients, a large swathe of PE patients currently fall into the intermediate risk category[24] and remain difficult to subcategorize. A recent systematic review and meta-analysis from 2022 by Sosa and colleagues examining the impact of PE Response Teams (PERT) on acute PE found that out of 3216 patients evaluated by PERT, 9.7% were high risk, 50.3% were intermediate and 37.9% were low risk.[25] Incorporating the CCI score may allow for a further breakdown of this large intermediate group, who comprise the majority of PERT evaluations, and remain challenging in terms of management. Further integration of comorbidities in risk assessment strategies identifies patients with higher short-term morality that may benefit from consideration of advanced therapies.

There are several limitations to this study. The NIS database utilizes ICD-10 codes and certain data such as the primary diagnosis of PE, CCI calculations (based on comorbidities), secondary outcomes (shock and mechanical ventilation), and interventions (systemic thrombolysis, catheter directed therapies, ECMO) depend on the accuracy of the original documentation. Vital signs, medications, laboratory data, and diagnostic studies are not included, and therefore PE risk category could not be determined. Certain measures of risk category could be extrapolated using ICD-10 codes for RV dysfunction; however, determining the chronicity and degree of dysfunction would be challenging. To minimalize confounding data and given the inherent limitations of administrative data sets, calculating risk groups from the available data was not pursued. Additionally, the CCI score was developed in 1987 and there are studies that suggest it would benefit from reevaluation with the current advancements in medicine.[26] It also does not incorporate certain factors that may be important such as hyperlipidemia, arrythmias such as atrial fibrillation, and tobacco use. While the weight of certain diseases has shifted over time, it does still provide a fairly comprehensive system for the standardization and comparison of patients.

Future research should specifically focus on separating PE patients by risk category and further stratifying them based on the extent of comorbid disease. The intermediate risk category would be the most amenable to study, given that it compromises the largest percentage of patients, and many questions remain on how to best manage this group. Additional studies would help to address if PE patients with elevated CCI scores and therefore higher mortality risk would benefit from a more aggressive upfront treatment approach. Long term follow-up comparing actual survival to expected survival will be useful, as it has been shown that PE patients with a CCI score of 0 approximate non PE patients with a CCI of 0 in terms of mortality, which is not seen in higher CCI scores.[11]

In conclusion, our study uses a large nationwide cohort of patients in the United States with acute PE to show the degree by which patients with higher burden of comorbidity have worse hospital and patient centered

outcomes. It also reveals that patients with higher CCI scores, and increased short term mortality, are less likely to receive any advanced therapies. While integrating the CCI score into daily practice may pose challenges due to its complexity compared to the sPESI, this study suggests a role of factoring in comorbidities to further define patients in risk stratification schemas and in the future may guide management and treatments.

AUTHOR CONTRIBUTIONS

Truong-An Ho is the guarantor of the article, taking responsibility for the integrity of the work from inception to the published article. Truong-An Ho, Si Li, and Parth Rali designed the research study. Si Li, Palakkumar Patel, and Yichen Wang performed data-analysis. Ka U. Lio, Si Li, Hammad Arshad, and Parth Rali helped revise the manuscript.

ACKNOWLEDGMENTS

Publication of this article was funded in part by the Temple University Libraries Open Access Publishing Fund.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was deemed to be exempt from institutional review board assessment as it was conducted using the National Inpatient Sample, a publicly available healthcare database that only contains deidentified patient information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ho T-A, Lio KU, Patel P, Wang Y, Arshad H, Li S, Rali P. Comorbidity profiles and pulmonary embolism risk assessment: leveraging the Charlson Comorbidity Index for improved prognostication in a national data set. Pulm Circ. 2024;14:e70010. https://doi.org/10.1002/pul2.70010