CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Categorization of Patients With Pulmonary Embolism by Charlson Comorbidity Index

Karsten Keller, MD,[a,b,c] Volker H. Schmitt, MD,[a,d] Omar Hahad, PhD,[a,d] Christine Espinola-Klein, MD,[a,b] Thomas Münzel, MD,[a,d] Philipp Lurz, MD,[a,d] Stavros Konstantinides, MD,[b,e] Lukas Hobohm, MD[a,b]

[a]*Department of Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Germany;* [b]*Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg-University Mainz, Germany;* [c]*Medical Clinic VII, Department of Sports Medicine, University Hospital Heidelberg, Germany;* [d]*German Center for Cardiovascular Research (DZHK), Partner Site Rhine Main, Mainz, Germany;* [e]*Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece.*

ABSTRACT

BACKGROUND: Short-term outcomes of pulmonary embolism are closely related to right ventricular dysfunction and patient's hemodynamic status, but also to individual comorbidity profile. However, the impact of patients' comorbidities on survival during pulmonary embolism might be underrated. Although the Charlson Comorbidity Index (CCI) is the most extensively studied comorbidity index for detecting comorbidity burden, studies analyzing the impact of CCI on pulmonary embolism patients' survival are limited.

METHODS: We used the German nationwide inpatient sample to analyze all hospitalized patients with pulmonary embolism in Germany 2005-2020 and calculated CCI for each patient, compared the CCI classes (very low: CCI = 0 points, mild: CCI = 1-2 points, moderate: CCI = 3-4, high severity: CCI >4 points) and impact of CCI class on outcomes.

RESULTS: Overall, 1,373,145 hospitalizations of patients with acute pulmonary embolism (53.0% females, 55.9% aged ≥70 years) were recorded in Germany between 2005 and 2020; the CCI class stratified them. Among these, 100,156 (7.3%) were categorized as very low; 221,545 (16.1%) as mild; 394,965 (28.8%) as moderate; and 656,479 (47.8%) as patients with a high comorbidity burden according to CCI class. In-hospital case fatality increased depending on the CCI class: 3.6% in very low, 6.5% in mild, 12.1% in moderate, and 22.1% in high CCI class ($P < .001$). CCI class was associated with increased in-hospital case fatality (odds ratio 2.014; 95% confidence interval, 2.000-2.027; $P < .001$).

CONCLUSION: Our study results may help practitioners to better understand and measure the association between an aggravated comorbidity profile and increased in-hospital case fatality in patients with pulmonary embolism.

KEYWORDS: Charlson Comorbidity Index; Comorbid; Comorbidity; Human resources; Mortality

Funding: No funding.

Conflicts of Interest: KK, VHS, OH, and TM report no conflicts of interest. CEK reports having lecture /consultant fees from Amarin Germany, Amgen GmbH, Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, MSD Sharp & Dohme, Novartis Pharma, Pfizer Pharma GmbH, and Sanofi-Aventis GmbH. PL has received institutional fees and research grants from Abbott Vascular, Edwards Lifesciences, and ReCor, honoraria from Edwards Lifesciences, Abbott Medical, Innoventric, ReCor, and Boehringer Ingelheim; and has stock options with Innoventric. SK reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol Myers Squibb/Pfizer. LH received lecture/consultant fees from Johnson & Johson, MSD, Boston Scientific, and Inari Medical, outside the submitted work.

Authorship: All authors contributed to the manuscript. KK: Writing – review & editing, original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization; VHS: Writing – review & editing; OH: Writing – review & editing; CEK: Writing – review & editing; TM: Writing – review & editing; PL: Writing – review & editing; SK: Writing – review & editing; LH: Writing – review & editing, Validation, Investigation, Conceptualization.

Requests for reprints should be addressed to Karsten Keller, MD, Department for Cardiology and Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Johannes Gutenberg-University Mainz Langenbeckstrasse 1, 55131 Mainz, Germany.

E-mail address: Karsten.Keller@unimedizin-mainz.de

https://doi.org/10.1016/j.amjmed.2024.04.025

INTRODUCTION

Pulmonary embolism is a cardiovascular life-threatening acute event afflicted by high morbidity and mortality.[1–6,10] While the annual incidence of pulmonary embolism has increased in the past two decades, the case fatality of this emergency event decreased in the same time.[3,7–10] Mortality caused by pulmonary embolism is strongly and closely related to the patient's hemodynamic status and cardiac involvement, including right ventricular dysfunction or myocardial injury, as well as the patient's comorbidity profile.[2–4,6,11–17] In that sense, the patient's comorbidity burden determines their capacity to face the strain of acute pulmonary embolism driven by right ventricular dysfunction and right heart injury, and the comorbidity burden of each patient can be understood and interpreted as the basis of the withstanding against the stress, adaptations, and complications resulting from the acute pulmonary embolism event.[2,18–20] Although scores such as the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI)[21–23] are already in use for prognosis prediction of acute pulmonary embolism,[19,21–29] the risk assessment of comorbid burden in acute pulmonary embolism is still under debate and developing.[6,19,20] The Charlson Comorbidity Index (CCI) is an established tool to assess the comorbidity burden of patients with different comorbidity profile and underlying diseases.[30] Thus, the aim of the present study was to identify the impact of comorbidity burden mirrored by CCI class on outcomes in pulmonary embolism patients.

CLINICAL SIGNIFICANCE

- Mortality of pulmonary embolism is strongly related to hemodynamic status, right ventricular dysfunction, and patients' comorbidity burden.
- The Charlson Comorbidity Index is an established tool to assess comorbidity burden of patients.
- The Charlson Comorbidity Index class impacts substantially on case fatality and major adverse cardiovascular and cerebrovascular events in pulmonary embolism independently of markers of hemodynamic compromise.
- Increase in Charlson Comorbidity Index class by 1 was associated with an approximate 2-fold risk of dying during the in-hospital stay.

METHODS

Data Source

The Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany) conducted and performed the statistical analysis on our behalf. The RDC provided aggregated statistics on the basis of SPSS codes (IBM SPSS Statistics for Windows, Version 20.0, 2011; IBM; Armonk, NY), which we had supplied to the RDC (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, Diagnosis Related Group [DRG] Statistics 2005-2020, own calculations).[3,31]

With this data analysis of the German nationwide inpatient sample, we aimed to investigate the impact of the comorbidity burden assessed by the CCI on case-fatality rate in acute pulmonary embolism (International Classification of Diseases [ICD] code I26) during the observational period between 2005 and 2020.

Study Oversight and Support

Because our study did not consist of direct access by the investigators to individual patient data, but only to summarized results provided by the RDC, approval by an ethics committee as well as patients' informed consent were not required, in accordance with German law/legacy.[3,31]

Coding of Diagnoses, Procedures and Definitions

During the year 2004, shortly after the turn of the millennium, diagnosis- and procedure-related remuneration was introduced in the German health care system. The coding of patient data on diagnoses, coexisting conditions, and surgeries, as well as on procedures/interventions according to the German Diagnosis Related Groups (G-DRG) system and transfer of these codes to the Institute for the Hospital Remuneration System, is mandatory for German hospitals to get their remuneration.[15,16] Patients' diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, with German modification (ICD-10-GM).[15,16] In addition, the surgical, diagnostical, and interventional procedures are coded according to OPS codes (Operationen- und Prozedurenschlüssel).

In the present analysis of the German nationwide inpatient sample, we identified all hospitalizations of patients with pulmonary embolism in Germany during the observational period between 2005 and 2020.

CCI Classes

Hospitalizations were categorized according to the calculated CCI class, and the impact of comorbidity burden (CCI class) on outcomes was investigated. The CCI is the most extensively studied comorbidity index.[32] The CCI classes were defined as very low severity of comorbid diseases with CCI of 0 points, mild severity of comorbid diseases with CCI values of 1-2 points, a moderate severity of comorbid diseases with a CCI of 3-4 points, and high severity of comorbid diseases when CCI is calculated with >4 points.[30,33]

Study Outcomes

The primary study outcome was defined as death from all causes during in-hospital stay (in-hospital death). Secondary study outcomes were major adverse cardiovascular and cerebrovascular events (MACCE, composite of all-cause in-hospital death, acute myocardial infarction [ICD code I21], or ischemic stroke [ICD code I63]), hemodynamic instability (defined as shock [ICD code R57] or cardiopulmonary resuscitation [OPS code 8-77]), right ventricular dysfunction (ICD code I26.0), occurrence of pneumonia (ICD codes J12-J18), and necessity of transfusion of blood components (OPS code 8-800).

Statistical Analysis

As mentioned above, for each hospitalization with pulmonary embolism, the CCI value was calculated and hospitalizations of patients with pulmonary embolism were categorized according to the CCI classes.[30,33] The differences between the CCI classes for the investigated categorical variables were tested statistically by Fisher's exact or chi-squared test, as appropriate. Temporal trends regarding annual and age-depending proportions of CCI classes, as well as absolute numbers of hospitalizations of the different CCI classes and of corresponding outcome rates, were analyzed by linear regression analyses. The results are presented as beta (β) estimates with the corresponding 95% confidence intervals (CI). In addition, we calculated logistic regression models to investigate associations between CCI classes and the mentioned outcomes, as well as adverse in-hospital events. To prove the independence of these findings from hemodynamic compromise, we further adjusted the logistic regression models for severe pulmonary embolism (defined as right ventricular dysfunction, tachycardia, shock, or cardiopulmonary resuscitation). Results were presented as odds ratios (OR) and 95% CI. Moreover, a receiver operating curve analysis was performed to analyze CCI as well as CCI class as predicting models for in-hospital case fatality. All statistical analyses were carried out using SPSS. Only P values of $< .05$ (2-sided) were statistically significant. Due to the explorative nature of the analysis, no adjustment for multiple testing was applied.

RESULTS

Overall, 1,373,145 hospitalizations of patients with pulmonary embolism were included in the present study between 2005 and 2020. Among these, 100,156 (7.3%) were categorized as very low severity of comorbid diseases according to CCI score (0 points), 221,545 (16.1%) as mild severity of comorbid diseases according to CCI score (1-2 points), 394,965 (28.8%) as moderate severity (3-4 points), and 656,479 (47.8%) as high severity (>4 points) (Table 1).

During the observational period, absolute numbers of hospitalizations of pulmonary embolism patients in all CCI classes increased from 2005 to 2020, but the increase was largest for the high severity class, mirroring the aging German population with aggravating comorbidity burden (Figure 1A). The proportion of pulmonary embolism patients in the high CCI class increased in the later years and with growing age (Figures 1B-D). Overall, patients' CCI class increased over time (β 0.097; 95% CI, 0.088-0.105; $P < .001$) and with age decade (β 1.131; 95% CI, 1.129-1.133; $P < .001$).

As shown in Table 1, patients' age and comorbidity burden increased significantly with CCI classes, thereby confirming the function of CCI calculation to evaluate comorbidity burden. While most pulmonary embolism patients in nearly all CCI classes were of female sex, the proportion of male patients exceeds female patients by approximately 20% in the CCI class with mild severity of comorbid disease. Length of in-hospital stay was not affected by comorbidity burden classified by CCI classes in the very low and mild severity CCI classes, but increased substantially with moderate and high severity of comorbid disease (Table 1). Interestingly, the rate of obese patients with pulmonary embolism was higher in CCI classes categorizing very low and mild severity of comorbid disease in comparison with CCI classes with larger comorbid burden.

Higher CCI classes were attributed to higher rates regarding the presence of risk stratification markers and markers of hemodynamic compromise. The rate of coded right ventricular dysfunction (very low: 19.3%, mild: 24.5%, moderate: 28.5%, high: 29.7%; $P < .001$) as well as occurrence of hemodynamic instability (very low: 4.0%, mild: 6.4%, moderate: 8.4%, high: 11.0%; $P < .001$) increased significantly with aggravating CCI class (Table 1).

While the reperfusion treatment of systemic thrombolysis was used slightly more often in patients of mild severity CCI class, surgical embolectomy was similarly widely used in the different CCI classes.

The in-hospital case-fatality rate increased significantly, from 3.6% in hospitalizations of pulmonary embolism patients with very low severity of comorbid diseases to 22.1% in the patients with high severity of comorbid diseases (very low: 3.6%, mild: 6.5%, moderate: 12.1%, high: 22.1%; $P < .001$). The case-fatality rate decreased in patients with high severity of comorbid diseases over time (Figure 2). In parallel, the rate of MACCE increased substantially with CCI classes (very low: 3.6%, mild: 7.3%, moderate: 13.8%, high: 27.1% severity of comorbid diseases, $P < .001$). In contrast, the occurrence of pneumonia was highest in the pulmonary embolism patients with the lowest CCI class (very low: 30.0%, mild: 23.9%, moderate: 21.2%, high: 25.0% severity of comorbid diseases; $P < .001$). Necessity regarding transfusion of blood constituents also increased with CCI classes (very low: 3.8%, mild: 5.4%, moderate: 8.0%, high: 17.1%, $P < .001$) (Table 1).

CCI class impacts all the investigated outcomes. An increase regarding CCI class by 1 was associated with an approximate 2-fold risk of dying during in-hospital stay (OR 2.014; 95% CI, 2.000-2.027; $P < .001$) and more than doubled the risk of suffering from a MACCE (OR 2.214; 95% CI, 2.200-2.228; $P < .001$). In contrast, the risk of

Table 1 Patients' Characteristics, Medical History, Presentation and Adverse in-Hospital Events of the 1,373,145 Hospitalizations of Patients with Acute Pulmonary Embolism 2005-2020 in Germany Stratified for Charlson Comorbidity Index Class

Parameters	Very Low Severity of Comorbid Diseases with Charlson Comorbidity Index 0 Points (n = 100,156; 7.3%)	Mild Severity of Comorbid Diseases with Charlson Comorbidity Index 1-2 Points (n = 221,545; 16.1%)	Moderate Severity of Comorbid Diseases with Charlson Comorbidity Index 3-4 Points (n = 394,965; 28.8%)	High Severity of Comorbid Diseases Charlson Comorbidity Index >4 Points (n = 656,479; 47.8%)	*P* Value
Age (years)	40.0 (31.0/45.0)	57.0 (51.0/63.0)	73.0 (66.0/78.0)	78.0 (70.0/83.0)	< .001
Age ≥70 y	0 (0%)	0 (0%)	262,474 (66.5%)	505,471 (77.0%)	<.001
Female sex	51,111 (51.0%)	90,601 (40.9%)	215,994 (54.7%)	369,778 (56.3%)	<.001
Length of in-hospital stay	7.0 (4.0/10.0)	7.0 (4.0/1.0)	9.0 (5.0/14.0)	11.0 (6.0/19.0)	<.001
Cardiovascular risk factors					
Obesity	10,951 (10.9%)	26,514 (12.0%)	36,630 (9.3%)	56,547 (8.6%)	<.001
Diabetes mellitus	0 (0%)	11,292 (5.1%)	46,150 (11.7%)	198,794 (30.3%)	<.001
Essential arterial hypertension	12,718 (12.7%)	78,300 (35.3%)	192,895 (48.8%)	318,846 (48.6%)	<.001
Hyperlipidemia	2930 (2.9%)	19,402 (8.8%)	52,835 (13.4%)	96,977 (14.8%)	<.001
Typical venous thromboembolism risk factors					
Surgery	32,829 (32.8%)	99,158 (44.8%)	190,995 (48.4%)	388,901 (59.2%)	<.001
Cancer	0 (0%)	4988 (2.3%)	30,923 (7.8%)	243,262 (37.1%)	<.001
Thrombophilia	3968 (4.0%)	5060 (2.3%)	3642 (0.9%)	3401 (0.5%)	<.001
Comorbidities					
Coronary artery disease	896 (0.9%)	11,886 (5.4%)	48,678 (12.3%)	126,133 (19.2%)	<.001
Peripheral artery disease	0 (0%)	1004 (0.5%)	5056 (1.3%)	33,618 (5.1%)	<.001
Stroke (ischemic or hemorrhagic)	0 (0%)	1291 (0.6%)	5620 (1.4%)	33,669 (5.1%)	<.001
Heart failure	0 (0%)	14,598 (6.6%)	49,907 (12.6%)	236,292 (36.0%)	<.001
Atrial fibrillation/ flutter	845 (0.8%)	10,047 (4.5%)	48,327 (12.2%)	147,845 (22.5%)	<.001
Chronic obstructive pulmonary disease	0 (0%)	6749 (3.0%)	32,869 (8.3%)	98,787 (15.0%)	<.001
Acute or chronic renal failure	805 (0.8%)	7664 (3.5%)	36,654 (9.3%)	249,353 (38.0%)	<.001
Risk stratification markers and deep venous thrombosis or thrombophlebitis					
Deep venous thrombosis or thrombophlebitis	44,969 (44.9%)	99,926 (45.1%)	152,037 (38.5%)	192,102 (29.3%)	<.001
Severe pulmonary embolism	21,498 (21.4%)	59,597 (26.8%)	123,506 (31.2%)	225,114 (34.2%)	<.001
Shock	1385 (1.4%)	5208 (2.4%)	12,950 (3.3%)	37,101 (5.7%)	<.001
Cardiopulmonary resuscitation	3313 (3.3%)	11,455 (5.2%)	25,997 (6.6%)	48,373 (7.4%)	<.001
Hemodynamic instability	4054 (4.0%)	14,141 (6.4%)	33,049 (8.4%)	71,936 (11.0%)	<.001
Right ventricular dysfunction	19,364 (19.3%)	54,260 (24.5%)	112,518 (28.5%)	195,119 (29.7%)	<.001
Syncope	1366 (1.4%)	3968 (1.8%)	10,141 (2.6%)	17,841 (2.7%)	<.001
Tachycardia	2393 (2.4%)	5526 (2.5%)	10,364 (2.6%)	22,636 (3.4%)	<.001
Reperfusion treatment					
Systemic thrombolysis	4378 (4.4%)	10,854 (4.9%)	17,257 (4.4%)	24,688 (3.8%)	<.001
Surgical embolectomy	174 (0.2%)	430 (0.2%)	608 (0.2%)	798 (0.1%)	<.001

Table 1 (*Continued*)

Parameters	Very Low Severity of Comorbid Diseases with Charlson Comorbidity Index 0 Points (n = 100,156; 7.3%)	Mild Severity of Comorbid Diseases with Charlson Comorbidity Index 1-2 Points (n = 221,545; 16.1%)	Moderate Severity of Comorbid Diseases with Charlson Comorbidity Index 3-4 Points (n = 394,965; 28.8%)	High Severity of Comorbid Diseases Charlson Comorbidity Index >4 Points (n = 656,479; 47.8%)	*P* Value
Adverse events during hospitalization					
In-hospital case-fatality	3597 (3.6%)	14,460 (6.5%)	47,607 (12.1%)	144,912 (22.1%)	<.001
MACCE	3597 (3.6%)	16,115 (7.3%)	54,329 (13.8%)	178,185 (27.1%)	<.001
Pneumonia	30,048 (30.0%)	53,054 (23.9%)	83,704 (21.2%)	164,029 (25.0%)	<.001
Transfusion of blood constituents	3842 (3.8%)	11,987 (5.4%)	31,718 (8.0%)	112,109 (17.1%)	<.001

MACCE = major adverse cardiovascular and cerebrovascular events.

developing pneumonia was lower with growing CCI class (OR 0.975; 95% CI, 0.972-0.979; $P < .001$). Importantly, these results were stable after adjustment for hemodynamic compromise (severe pulmonary embolism) (Table 2). The computed receiver operating curve analysis confirmed that CCI (0.666; 95% CI, 0.665-0.667; $P < .001$) as well as CCI class (0.604; 95% CI, 0.602-0.606; $P < .001$) were useful tools to predict in-hospital case fatality in patients with pulmonary embolism (Figure 3). Nevertheless, to prove the impact of CCI class on the different outcomes, we calculated additionally the impact of CCI class focusing on patients with severe pulmonary embolism only. In this crucial patient group, the impact of CCI class on the outcomes was also confirmed (Table 3).

DISCUSSION

Mortality in patients with pulmonary embolism is closely related to patients' hemodynamic status and cardiac complications, including right ventricular dysfunction or

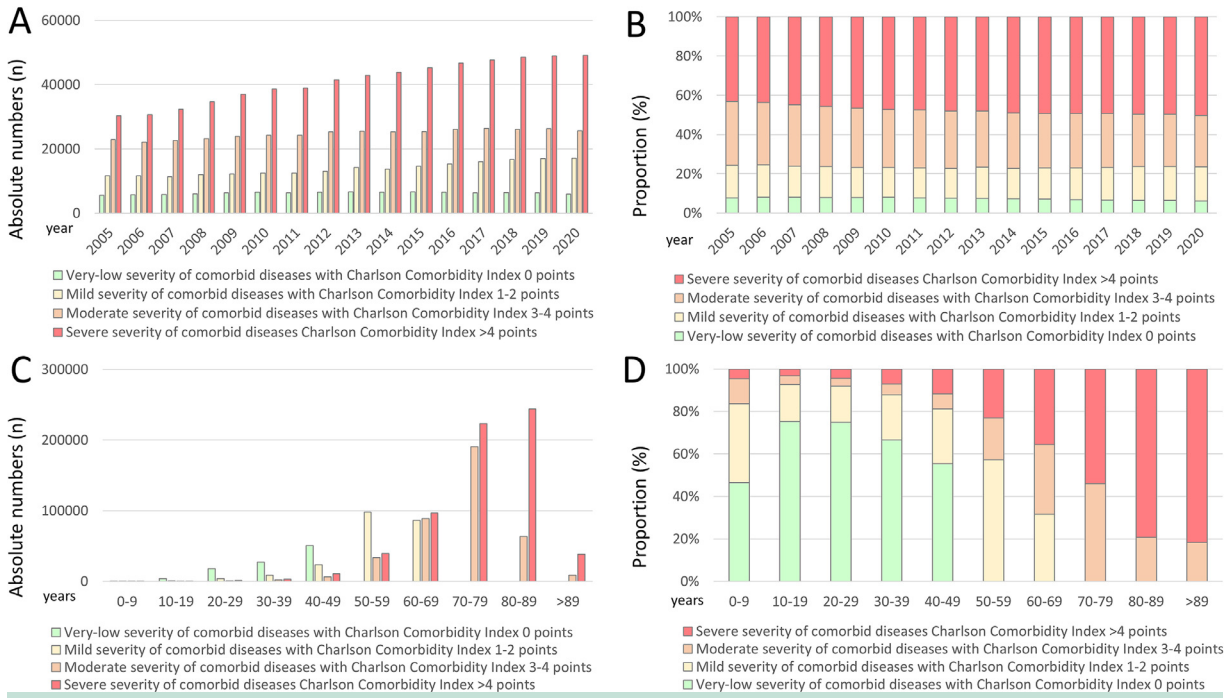

Figure 1 Temporal trends regarding total numbers and proportion of hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index Classes. **(A)** Annual trends regarding total numbers of hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index Classes. **(B)** Annual trends regarding proportions of the different Charlson Comorbidity Index Classes in hospitalized patients with pulmonary embolism. **(C)** Temporal trends regarding total numbers of hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index Classes stratified for age-decades. **(D)** Temporal trends regarding proportions of the different Charlson Comorbidity Index Classes stratified for age-decades in hospitalized patients with pulmonary embolism.

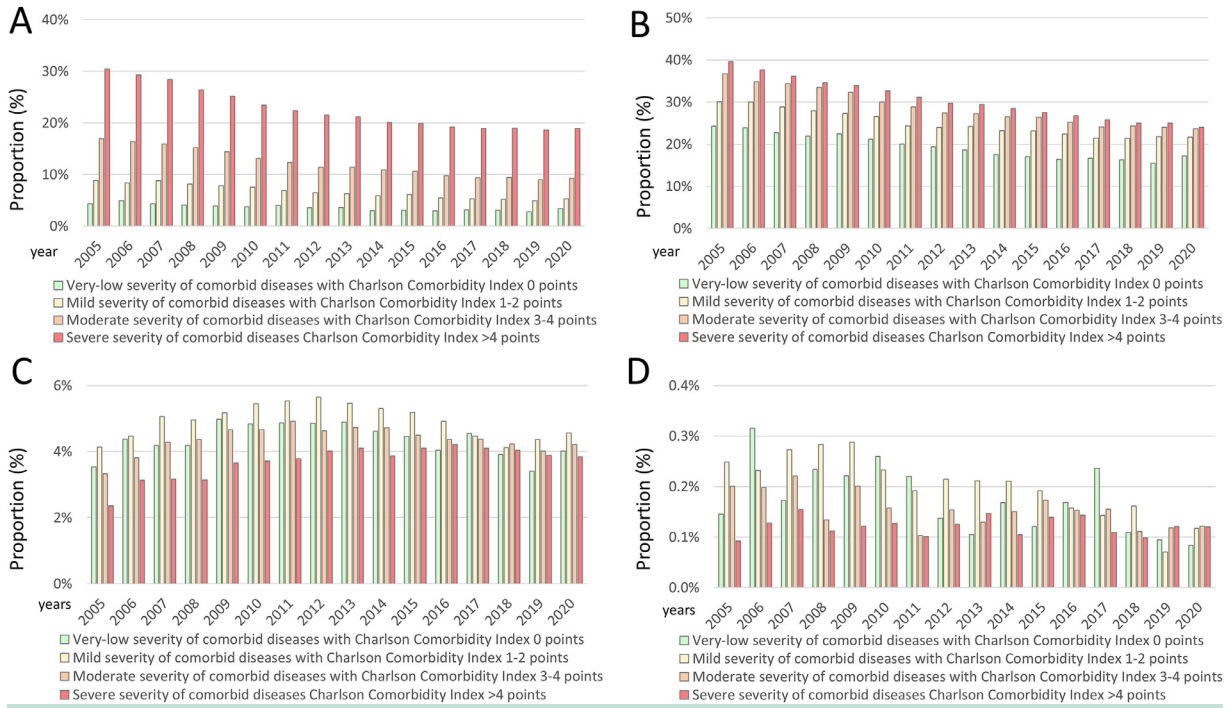

Figure 2 Temporal trends regarding proportion of hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index Classes. **(A)** Case-fatality rate of hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index Classes. **(B)** Rate of right ventricular dysfunction of hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index Classes. **(C)** Rate of systemic thrombolysis in hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index Classes. **(D)** Rate of surgical embolectomy in hospitalized patients with pulmonary embolism in the different Charlson Comorbidity Index classes.

Table 2 Impact of Charlson Comorbidity Index Class on Adverse In-Hospital Outcomes in All Patients with Pulmonary Embolism (Univariate and Multivariate Logistic Regression Model)

	Univariate Regression		Multivariate Regression Adjusted for Severe Pulmonary Embolism	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
In-hospital case-fatality	2.014 (2.000-2.027)	< .001	1.984 (1.970-1.997)	< .001
MACCE	2.214 (2.200-2.228)	< .001	2.202 (2.188-2.216)	< .001
Hemodynamic instability	1.376 (1.366-1.386)	< .001	—	—
Right ventricular dysfunction	1.166 (1.161-1.171)	< .001	—	—
Pneumonia	0.975 (0.972-0.979)	< .001	0.968 (0.964-0.972)	< .001
Transfusion of blood constituents	1.935 (1.921-1.950)	< .001	1.904 (1.890-1.918)	< .001

CI = confidence interval; MACCE = major adverse cardiovascular and cerebrovascular events; OR = odds ratio.

myocardial injury, as well as comorbidities.[2–4,6,11–17] However, the impact of patients' comorbidities on survival during the acute phase of pulmonary embolism might be underrated. Although the CCI is the most extensively studied comorbidity index for detecting comorbidity burden,[30,32,33] studies analyzing the impact of CCI on pulmonary embolism patients' survival are sparse.[34]

The results of our study clearly demonstrate that CCI class, as a mirror of each patient's comorbidity burden, impacts substantially on case fatality and MACCE rate in pulmonary embolism. In this context, it is of outstanding importance that the prediction of case fatality and MACCE is independent of markers of hemodynamic compromise (severe pulmonary embolism). An increase in CCI class by 1 was associated with an approximate 2-fold risk of dying during the in-hospital stay and more than a doubled risk of suffering from a MACCE.

The results of our study are in line with published literature indicating an important influence of comorbidity burden on survival:[35–41] The study of de Miguel-Díez et al[40] showed a significant increase of the in-hospital case fatality with inclining CCI on a nationwide level in 115,671 admitted patients with pulmonary embolism to Spanish hospitals during 2002-2011. In a second study of the same research group analyzing 241,821 patients with pulmonary embolism hospitalized in Spain from 2001-2018, CCI was once again an important predictor of short-term survival.[39] Notably, this relation between higher CCI and increased mortality

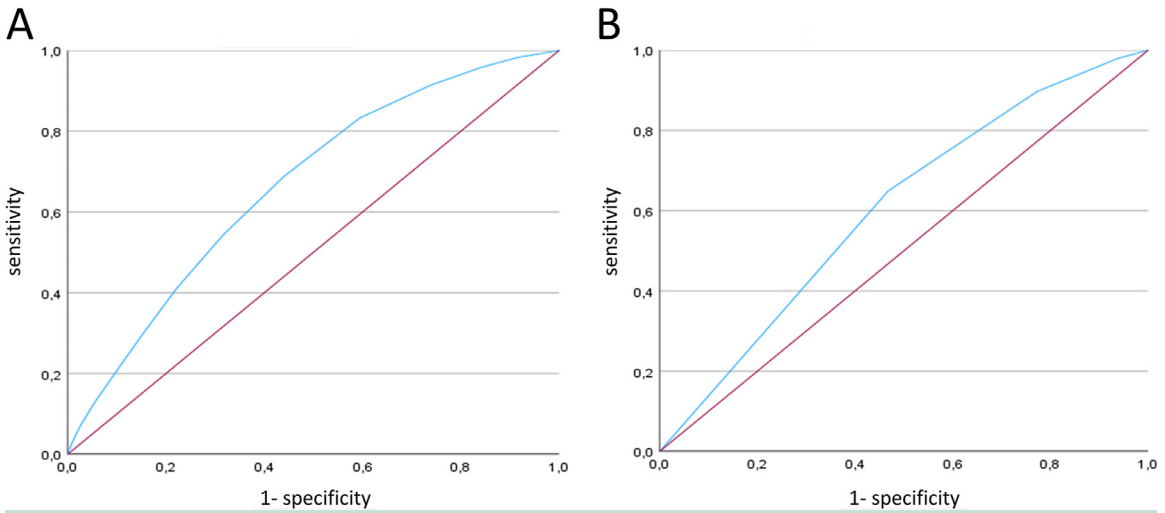

Figure 3 Receiver operating curve analysis for Charlson Comorbidity Index (**A**) and Charlson Comorbidity Index class (**B**) to predict in-hospital case-fatality in patients with pulmonary embolism.

Table 3 Impact of Charlson Comorbidity Index Class on Adverse In-Hospital Outcomes in Patients with Severe Pulmonary Embolism (Univariate Logistic Regression Model)

	Univariate Regression	
	OR (95% CI)	*P* Value
In-hospital case-fatality	1.658 (1.644-1.672)	<.001
MACCE	1.795 (1.780-1.810)	<.001
Pneumonia	1.135 (1.126-1.144)	<.001
Transfusion of blood constituents	1.727 (1.708-1.747)	<.001

CI = confidence interval; MACCE = major adverse cardiovascular and cerebrovascular events; OR = odds ratio.

was visible not only for the short-term, but also evident in studies elucidating the mid- and long-term course of patients with pulmonary embolism: In the study of Polo Friz et al,[36] the authors report that CCI >0 at the pulmonary embolism index event was associated with increased mortality at 3 and 6 months; and 1, 2, and 5 years after the index pulmonary embolism event compared with patients with a CCI of 0 as the reference group. In one further study of the same research group, CCI score was predictive for mortality after 90 days and 2 years in 162 hemodynamically stable patients with pulmonary embolism older than 65 years.[41] Another study including 368 patients with pulmonary embolism showed that a higher CCI score was afflicted by a higher mortality rate after 30 days and 1 year after the pulmonary embolism index event.[37] Notably, cancer had an exceptional role in these patients regarding survival.[37] In addition, Ng et al[35] showed that a CCI score was a strong and independent predictor for in-hospital and postdischarge mortality after a median follow-up of 3.7 years, and Golpe et al[38] reported that CCI score was predictive for pulmonary embolism patients' survival after a median follow-up of 2.97 years.

Thus, in summary, the individual comorbidity burden is very important for short-term survival during the acute pulmonary embolism event, but also regarding the mid- and long-term course. In relation to comorbidity burden, patients with pulmonary embolism frequently suffer from important comorbidities such as cancer or cardiovascular diseases, which are classified as risk factors for the development of pulmonary embolism but also significantly influence the outcome of pulmonary embolism.[18,34,42]

Patients' comorbidity profile/burden determines patients' capacities to encounter the strain of acute pulmonary embolism driven by right ventricular dysfunction and right heart injury, and therefore, constitutes the basis of withstanding the negative adverse effects of acute emergency pulmonary embolism.[2,18–20] The comorbidity burden of each patient can be understood and interpreted as the basis of withstanding against the stress, adaptations, and complications resulting from the acute pulmonary embolism event.

In this context, the development of pulmonary embolism has to be additionally considered, because the underlying mechanism of pulmonary embolism development seems also of outstanding importance for survival. In two-thirds of all pulmonary embolism cases, pulmonary embolism is the consequence of deep venous thrombosis rather than a separate clinical entity.[4,13,43] For pulmonary embolism without detected deep venous thrombosis, also termed as isolated pulmonary embolism, data from several studies suggest a key role of triggering comorbidities such as cancer,[44] atrial fibrillation,[45,46] myocardial infarction,[45] and heart failure[45,46] in the pathogenesis of thrombus formation.[4] These mentioned comorbidities play an exceptional role, not only regarding pulmonary embolism development, but also in pulmonary embolism survival.[4] Due to the fact that the CCI includes a large number of parameters, the CCI might be better than the PESI to evaluate the comorbidity burden of the pulmonary embolism patients. This will probably decrease specificity, but will increase sensitivity, which is crucial for identification of candidates for home treatment.

In accordance with our study results revealing an increase in the rates of higher CCI classes mirroring higher comorbidity burden of the admitted patients with pulmonary embolism in later years during the observational period, other studies also detected an increase in the CCI scores and, especially, of essential comorbidities such as arterial hypertension, diabetes mellitus, obesity, cancer, and chronic kidney disease over time in this crucial patient collective.[34,39,40] These observations unveil an increasing comorbidity burden in patients with pulmonary embolism, reflecting a mounting vulnerability of this crucial patient collective. For this, multiple reasons may come into consideration, including a progressively aging population, as with the present situation in Germany.

Because pulmonary embolism is a major public health problem with a high and increasing incidence worldwide,[3,34,40,47,48] our findings may help in understanding the role of patients' comorbidity burden on prognosis and the need for increased health care resources during their in-hospital stay.[34] Thus, we are of the opinion that these findings might support optimizing the management of patients with pulmonary embolism to save lives, but also to plan and to deliver sufficient health care capacities in light of pulmonary embolism patients' increasing comorbidity burden in recent years, and the further increase regarding aggravating comorbid profile in the following years in these patients to meet enormous health care challenges in the future.[35]

CONCLUSION

Our study results highlight an essential impact of the individual comorbidity burden on pulmonary embolism patients' short-term survival in this nationwide German inpatient sample. In this context, it is of outstanding importance that the prediction of case fatality and MACCE be independent of markers of hemodynamic compromise. The results may help increase understanding of the association between an aggravated comorbidity profile and increased in-hospital case fatality in patients with pulmonary embolism. In this context, the CCI can help to identify more patients at higher risk compared with more established scores due to its broader spectrum of variables.

ETHICAL STATEMENT

Because our study did not comprise direct access by the investigators to individual patient data but only an access to summarized results provided by the RDC, approval by an ethics committee as well as patients' informed consent were not required, in accordance with German law.

DATA SHARING

All code used in this study is publicly available online. The data used in this study are sensitive due to individual patient-level data and will not be made publicly available. The data are available at the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis; source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005-2020, and own calculations).

References

1. Konstantinides S, Goldhaber SZ. Pulmonary embolism: risk assessment and management. *Eur Heart J* 2012;33(24):3014–22.
2. Keller K, Beule J, Schulz A, Coldewey M, Dippold W, Balzer JO. Right ventricular dysfunction in hemodynamically stable patients with acute pulmonary embolism. *Thromb Res* 2014;133(4):555–9.
3. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. *Eur Heart J* 2020;41(4):522–9.
4. Keller K, Hobohm L, Münzel T, Ostad MA. Impact of concomitant deep or superficial venous thrombosis of the legs on survival of patients with pulmonary embolism. *Int J Cardiol* 2020;315:92–8.
5. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev* 2014;28(6):221–6.
6. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism. *Eur Heart J* 2019;40(42):3453–5.
7. Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of pulmonary embolism: an update. *J Am Coll Cardiol* 2016;67(8):976–90.
8. Jiménez D, de Miguel-Díez J, Guijarro R, et al. Trends in the nanagement and outcomes of acute pulmonary Eembolism: analysis from the RIETE Registry. *J Am Coll Cardiol* 2016;67(2):162–70.
9. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J* 2019;54(3):1901647.
10. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res* 2016;118(9):1340–7.
11. Goldhaber SZ. Assessing the prognosis of acute pulmonary embolism: tricks of the trade. *Chest* 2008;133(2):334–6.
12. Jiménez D, Uresandi F, Otero R, et al. Troponin-based risk stratification of patients with acute nonmassive pulmonary embolism: systematic review and metaanalysis. *Chest* 2009;136(4):974–82.
13. 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 (18):2276–315.
14. Jiménez D, Díaz G, Molina J, et al. Troponin I and risk stratification of patients with acute nonmassive pulmonary embolism. *Eur Respir J* 2008;31(4):847–53.
15. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: the prep study, a prospective multicenter cohort study. *Am J Respir Crit Care Med* 2010;181(2):168–73.
16. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation* 2008;117(13):1717–31.
17. Kucher N, Wallmann D, Carone A, Windecker S, Meier B, Hess OM. Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism. *Eur Heart J* 2003;24 (18):1651–6.
18. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41(4):543–603.
19. Keller K, Coldewey M, Dippold W, Beule J, Balzer JO. Simplified CRB-65 for risk stratification and predicting prognosis in acute pulmonary embolism. *Phlebologie* 2015;44:192–9.

20. Keller K, Schmitt VH, Sagoschen I, Munzel T, Espinola-Klein C, Hobohm L. CRB-65 for risk stratification and prediction of prognosis in pulmonary embolism. *J Clin Med* 2023;12(4):1264.
21. Uresandi F, Otero R, Cayuela A, et al. [A clinical prediction rule for identifying short-term risk of adverse events in patients with pulmonary thromboembolism]. *Arch Bronconeumol* 2007;43(11):617–22 [[in Spanish].
22. Aujesky D, Roy PM, Le Manach CP, et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. *Eur Heart J* 2006;27(4):476–81.
23. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172(8):1041–6.
24. Ozsu S, Abul Y, Orem A, et al. Predictive value of troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism. *Multidiscip Respir Med* 2013;8(1):34.
25. Moores L, Aujesky D, Jimenez D, et al. Pulmonary Embolism Severity Index and troponin testing for the selection of low-risk patients with acute symptomatic pulmonary embolism. *J Thromb Haemost* 2010;8(3):517–22.
26. Lankeit M, Gomez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. *Chest* 2012;141(4):916–22.
27. Hariharan P, Takayesu JK, Kabrhel C. Association between the Pulmonary Embolism Severity Index (PESI) and short-term clinical deterioration. *Thromb Haemost* 2011;105(4):706–11.
28. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. *Thromb Haemost* 2008;100(5):943–8.
29. Zhou XY, Ben SQ, Chen HL, Ni SS. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. *Respir Res* 2012;13(1):111.
30. 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(5):373–83.
31. Reinöhl J, Kaier K, Reinecke H, et al. Effect of availability of transcatheter aortic-valve replacement on clinical practice. *N Engl J Med* 2015;373(25):2438–47.
32. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. A critical review of available methods. *J Clin Epidemiol* 2003;56(3):221–9.
33. Guralnik JM. Assessing the impact of comorbidity in the older population. *Ann Epidemiol* 1996;6(5):376–80.
34. Jareno Esteban JJ, de Miguel Díez J, Fernández Bermejo LA. Pulmonary embolism and comorbidity. *Open Respir Arch* 2022;4(3):100188.
35. Ng AC, Chow V, Yong AS, Chung T, Kritharides L. Prognostic impact of the Charlson comorbidity index on mortality following acute pulmonary embolism. *Respiration* 2013;85(5):408–16.
36. Polo Friz H, Orenti A, Gelfi E, et al. Predictors of medium- and long-term mortality in elderly patients with acute pulmonary embolism. *Heliyon* 2020;6(9):e04857.
37. Fernández Bermejo LA, Gutiérrez Ortega C, Jareño Esteban JJ. Prognostic value of the Charlson index in mortality in patients with pulmonary embolism associated with cancer versus non-tumour pulmonary embolism. *Med Clin (Barc)* 2022;158(5):201–5.
38. Golpe R, Pérez-de-Llano LA, Castro-Añón O. Prognostic value of the Charlson comorbidity index in pulmonary embolism. *Respiration* 2013;85(5):438.
39. de Miguel-Díez J, Albaladejo-Vicente R, Lopez-de-Andres A, et al. Changing trends in hospital admissions for pulmonary embolism in Spain from 2001 to 2018. *J Clin Med* 2020;9(10):3221.
40. de Miguel-Díez J, Jiménez-García R, Jiménez D, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. *Eur Respir J* 2014;44(4):942–50.
41. Polo Friz H, Corno V, Orenti A, et al. Comorbidity assessment as predictor of short and long-term mortality in elderly patients with hemodynamically stable acute pulmonary embolism. *J Thromb Thrombolysis* 2017;44(3):316–23.
42. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;107(23 suppl 1):I9–I16.
43. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35(43) [3033-3069, 3069a-3069k.
44. Schwartz T, Hingorani A, Ascher E, et al. Pulmonary embolism without deep venous thrombosis. *Annals of vascular surgery* 2012;26(7):973–6.
45. Sorensen HT, Horvath-Puho E, Lash TL, et al. Heart disease may be a risk factor for pulmonary embolism without peripheral deep venous thrombosis. *Circulation* 2011;124(13):1435–41.
46. Keller K, Prochaska JH, Coldewey M, et al. History of deep vein thrombosis is a discriminator for concomitant atrial fibrillation in pulmonary embolism. *Thromb Res* 2015;136(5):899–906.
47. Keller K, Hobohm L, Münzel T, Lankeit M, Konstantinides S, Ostad MA. Impact of systemic atherosclerosis on clinical characteristics and short-term outcomes in patients with deep venous thrombosis or thrombophlebitis. *Am J Med Sci* 2022;363(3):232–41.
48. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med* 2011;171(9):831–7.