Aus dem Centrum für Thrombose und Hämostase (CTH)
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Behandlung und Nachsorge der akuten Lungenembolie in vulnerablen Patientenpopulationen

Inauguraldissertation
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Vorgelegt von

Ioannis Farmakis, MSc
aus Thessaloniki, Griechenland

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Wissenschaftlicher Vorstand: Univ.-Prof. Dr. Hansjörg Schild

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Abkürzungsverzeichnis

ACG: adjusted clinical groups

CBT: catheter-based thrombectomy

CDC: Center for Disease Control and Prevention

CDT: catheter-directed therapy

CDT: catheter-directed thrombolysis

CI: confidence interval

DVT: deep vein thrombosis

ECMO: extracorporeal membrane oxygenation

HCUP: Healthcare Cost & Utilization Project

ICD-10: International Classification of Diseases, 10th Edition

IQR: interquartile range

IVC: inferior vena cava

LE: Lungenembolie

LOS: length of stay

NIS: Nationwide Inpatient Sample

OR: odds ratio

PE: pulmonary embolism

SE: surgical embolectomy

ST: systemic thrombolysis

VTE: venous thromboembolism

VTE: venöse Thromboembolie

US: United States

WHO: World Health Organization

Einleitung / Ziel der Dissertation

Die Lungenembolie (LE) ist die dritthäufigste Todesursache bei Herz-Kreislauf-Erkrankungen und stellt weltweit eine große Belastung für nationale Gesundheitssysteme und die Gesellschaft dar (1). In Europa und den USA erreichten die LE-bedingten Sterblichkeitsraten während des letzten Jahrzehnts ein Plateau (2, 3). Besonders vulnerable Patientenpopulationen wie Schwangere, ältere und/oder „gebrechliche“ *(frail)* Menschen sowie nicht zuletzt Patient:innen aus benachteiligten sozialen Verhältnissen, sind oft unterrepräsentiert oder sogar von großen klinischen Studien ausgeschlossen.

Folgende Aspekte der LE-Behandlung und –Nachsorge müssen daher näher untersucht werden:

- Das Risiko einer venösen Thromboembolie (VTE) ist während der Schwangerschaft bis zu 6-mal höher als in der nicht schwangeren weiblichen Bevölkerung im gebärfähigen Alter. Allerdings wird die Optimierung der Behandlungsstrategien von Schwangeren mit LE dadurch erschwert, dass Schwangerschaft ein häufiges Ausschlusskriterium in randomisierten kontrollierten Studien ist. Die verfügbare Evidenz zur Prävention und Behandlung von akuter LE während der Schwangerschaft ist spärlich und die aktuellen Leitlinien basieren auf Expertenkonsens, wobei die Evidenz hauptsächlich aus Beobachtungsdaten stammt (4). Die Beschreibung der Trends bei der LE-bedingten Müttersterblichkeit ist von besonderer Bedeutung, um das Ausmaß dieses Problems besser darzustellen, potenzielle Lücken in der gegenwärtigen klinischen Bewertung und Praxis zu erkennen und das vorhandene begrenzte Wissen zu erweitern.
- Obwohl die Sterblichkeitsraten in den letzten zwei Jahrzehnten bei älteren Menschen zurückgegangen sind, bleibt das Alter bei Patienten mit LE ein signifikanter Risikofaktor für eine frühe Sterblichkeit (5). Unter den Reperfusionsbehandlungs-optionen gilt insbesondere die systemische Thrombolyse als die Therapie der Wahl bei Patient:innen mit hämodynamischer Beeinträchtigung oder Dekompensationsrisiko. Allerdings wird einerseits oft ein Alter >75 Jahre als relative Kontraindikation für eine systemische Thrombolyse genannt und darüber hinaus haben gebrechliche Patient:innen in fortgeschrittenem Alter ein hohes Operationsrisiko. Kathetergestützte Therapien (KT) haben sich kürzlich als Alternativen für die Behandlung von LE mit hohem und mittlerem hohem Risiko herausgestellt, obwohl derzeit Daten aus randomisierten kontrollierten Studien zur Wirksamkeit und Sicherheit von KT hinsichtlich „harter“ klinischer Endpunkte - insbesondere bei älteren Patienten – noch fehlen (6).

- Es bestehen Unterschiede in den Inzidenzraten und der Sterblichkeit an akuter LE zwischen ethnischen Gruppen sowie Gruppen mit unterschiedlichem sozioökonomischem Status. Allerdings ist die vorliegende Evidenz bezüglich der Zusammenhänge zwischen einer Vielzahl sozialer Gesundheitsfaktoren und LE unzureichend erforscht. (7, 8).

Ziel der vorliegenden kumulativen Dissertation war:

1) die Assoziation mehrerer sozialer Faktoren einschließlich des sozioökonomischen Status, der ethnischen Zugehörigkeit, des Versicherungsstatus und des Wohnortes zu bewerten und diese mit dem klinischen Verlauf im Krankenhaus und der Prognose einer akuten LE zu korrelieren
2) die LE-bedingte Muttersterblichkeitsraten in den USA in den letzten zwei Jahrzehnten unter Verwendung landesweiter Statistiken zur Personenstandsregistrierung auszuwerten
3) die gegenwärtige Häufigkeit der Verwendung von Reperfusionstherapien für die Behandlung älterer und gebrechlicher Patient:innen mit LE im Krankenhaus zu ermitteln und speziell ihre Zusammenhang mit dem Auftreten klinischer Ereignisse zu untersuchen.

Publikation #1: Muttersterblichkeit im Zusammenhang mit Lungenembolie in den Vereinigten Staaten, 2003-2020

Zitieren:

Farmakis IT, Barco S, Hobohm L, Braekkan SK, Connors JM, Giannakoulas G, Hunt BJ, Keller K, Mavromanoli AC, Trinchero A, Konstantinides SV, Valerio L. Maternal mortality related to pulmonary embolism in the United States, 2003-2020. Am J Obstet Gynecol MFM. 2023 Jan;5(1):100754. doi: 10.1016/j.ajogmf.2022.100754. Epub 2022 Sep 23. PMID: 36155111.

Verfügbar in:

Maternal mortality related to pulmonary embolism in the United States, 2003–2020 - ScienceDirect

Abstract

Background: Pulmonary embolism is a leading cause of maternal morbidity and mortality in Western countries. In the United States, pulmonary embolism-related mortality rates have plateaued in the general population after an initial decrease the past 20 years.

Objective: To describe the changes in pulmonary embolism -related maternal mortality rates in the United States over the past two decades.

Study Design: In this epidemiological study of public vital registration data (death certificates encompassing underlying and contributing causes of death) from the Centers for Disease Control and Prevention Mortality Multiple Cause of Death database (2003-2020) we identified all maternal deaths with a pulmonary embolism code listed in any position of the death certificates. We investigated the changes in annual crude pulmonary embolism -related maternal mortality rates for the years 2003 to 2020, considering the effect of the introduction of the pregnancy checkbox in death certificates on the pulmonary embolism -related maternal mortality rates.

Results: Overall, 735 pulmonary embolism -related maternal deaths out of 12,871 total maternal deaths (5.7%) were recorded between 2003 and 2020; the overall pulmonary embolism -related maternal mortality rate was 1.02 (95% confidence interval 0.95-1.10) per 100,000 live births. The pulmonary embolism -related maternal mortality rates increased from 0.93 in 2003 to 1.96 in 2020; however, when accounting for the implementation of the pregnancy checkbox in the death certificates, the trends in pulmonary embolism -related maternal mortality were largely unchanged from 2003 to 2020. The crude pulmonary embolism -related maternal mortality rates differed across maternal age groups (overall 0.61, 1.09, and 3.83 maternal deaths per 100,000 live births for ≤24, 25-39, and ≥40 years old, respectively) and racial/ethnicity groups (2.89, 0.47, 0.77, and 0.63 maternal deaths per 100,000 live births for black non-Hispanics, other non-Hispanics, white non-Hispanics, and Hispanics, respectively).

Conclusion: Maternal mortality rates due to pulmonary embolism did not decrease during the period 2003-2020, as opposed to mortality rates from pulmonary embolism in the general population. More research is required to assess whether improvement in venous thromboembolism prevention and pulmonary embolism diagnosis and management strategies might reduce death due to pulmonary embolism in this vulnerable population.

Keywords: maternal mortality; pulmonary embolism; pregnancy; epidemiology; CDC multiple causes of death; venous thrombosis

Introduction

Acute venous thromboembolism (VTE), and particularly its potentially fatal manifestation pulmonary embolism (PE), is a leading cause of maternal morbidity and mortality (9). The risk of VTE during pregnancy is up to 6 times higher than in the non-pregnant female population at reproductive age, with an absolute risk ranging between 2.7 and 12.2 per 10,000 deliveries per year compared to 2 per 10,000 persons per year in non-pregnant women (10). Estimates regarding maternal PE-related death and its temporal trends are sparse and inconsistent, even in high-income countries (10, 11). Reliable information on the occurrence of acute diseases and their associated mortality in vulnerable patient groups, such as in pregnant women, is essential for prospective risk stratification and optimization of management to prevent or treat hemodynamic deterioration during acute PE events (11, 12). Therefore, describing the trends in PE-related maternal mortality is of particular importance to better depict the magnitude of this problem, recognize potential gaps in the contemporary clinical evaluation and practice, as well as expand the existing limited knowledge.

Over the past 20 years, the overall PE-related mortality rate decreased in Europe, whereas it plateaued in the United States (US) after the previous decades-long decline (13, 14). In this epidemiological analysis, we sought to evaluate PE-related maternal mortality rates in the US over the past two decades using nationwide vital registration statistics.

Materials and Methods

We accessed the Mortality Multiple Cause of Death database (years 2003-2020) provided by the US Centers for Disease Control and Prevention (CDC) (15). The database provides information on the causes of death of all decedent US residents, as indicated on their death certificates. The database includes demographic (including age, sex, race and ethnicity), as well as geographical (i.e., place of death) and diagnostic data (i.e., indicating whether an autopsy was performed or not). Up to 20 causes of death are available for each death record, as reported by physicians (“entity axis” field). Of them, the condition that directly led to death is defined as the underlying cause of death, all other conditions as contributing causes of death. A standardized process of translation of codes, elimination of repetitions, and automatic reassignment converts the causes of death as entered by the physician in the death certificate (“entity axis” in the CDC terminology, as each condition of “entity” is preserved as entered) into a sequence of causes free of contradictions and medically plausible (“record axis” in the CDC terminology, as the sequence and codes are adapted by considering all other conditions

in the whole record) (16). As in previous studies, we used the record axis for this analysis (14). Disease classification and ordering details can be found on the CDC website (cdc.gov).

We used the World Health Organization (WHO) definition of maternal death: “the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes” (17). Accordingly, we primarily identified maternal deaths using the International Classification of Disease, 10th Revision (ICD-10) codes A34, O00-O95, and O98-O99 as underlying cause of death (the full ICD-10 definitions are provided in Supplementary Table 1). We excluded late maternal deaths (death of a woman occurring more than 42 days but less than one year after termination of pregnancy) defined by ICD-10 codes O96 and O97. We used the “WHO application of ICD-10 deaths during pregnancy, childbirth and the puerperium” to categorize underlying causes of death in mutually exclusive, totally inclusive groups (**Supplementary Table A1**) (17).

Beginning from 2003, a “pregnancy checkbox” has been introduced gradually in US death certificates to reduce the number of maternal deaths missed due to imprecise reporting: its use has been associated with more accurate identification of maternal deaths (18). This checkbox item specifies whether the decedent was currently in a pregnancy or had a pregnancy in the past year and, in such case, enforced the appropriate use of maternal ICD-10 O-codes. However, the checkbox was not implemented nationwide at the same time, but progressively across States from 2003 until 2017, when it was finally adopted in the whole United States. This staggered implementation hinders the evaluation of true temporal maternal mortality trends in this period, since more maternal deaths were captured in each State after the local introduction of the checkbox, thus correcting the maternal mortality rates upwards (19). Indeed, prior reports documented that, when the checkbox was implemented, less clearly defined ICD-10 codes, such as O26.8 (“Other specified pregnancy related conditions”) and O99 (“Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium”) were used more frequently (19). Therefore, we additionally performed a sensitivity analysis of the temporal trends in PE-related maternal mortality rates, excluding deaths that reported either O26.8 or O99 as an underlying cause of death, which has been shown to mitigate the effect of the pregnancy checkbox implementation and reflects the possible underestimation of maternal mortality rates in the absence of the checkbox (19, 20). To prevent misclassification of causes of death as maternal deaths due to errors in the use of the pregnancy checkbox and a subsequent inflation of maternal mortality rates for older women, we excluded deaths of women at aged 55 years or older (21).

We defined deaths related to PE as deaths with ICD-10 codes in any place of the death certificate that were specific for PE or DVT, including I26.x and O88.2 (PE), as well as I80.x, I82.2, I82.4, I82.9, O22.3, and O87.1 (DVT) in line with previous research.(3, 13, 22) The ICD-10 codes used to define the different causes of death are presented in **Supplementary Table A1**.

In order to calculate race/ethnicity-specific as well as age-specific mortality rates, we used the annual total birth counts for the period 2003-2020 (overall and by maternal race/ethnicity) and the maternal age groups provided by the National Vital Statistics System of the National Center for Health Statistics (23). Both birth and mortality data were categorized across four racial/ethnicity groups: non-Hispanic black, non-Hispanic other (including American Indian, Alaska Native, Asian and Native Hawaiian or Other Pacific Islander), non-Hispanic white, and Hispanic. Age was categorized in three groups: ≤24 years, 25-39 years, and ≥40 years.

The present study used de-identified data for public use and did not require approval by an institutional review board. Two investigators (ITF, LV) independently performed data extraction and validation, as well as the statistical analysis. This report abides by the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) standards (24).

Statistical analysis

We investigated the association of mortality related to PE (PE in any place in the death certificate) with mortality related to other causes (in any place in the death certificate) with relative risk regression using a log-link binomial generalized linear model adjusting for age. We calculated crude PE-related maternal mortality rates by dividing the number of PE-related deaths by the total births in any given year (deaths per 100,000 live births). We did not provide age-standardized estimates of PE-related maternal mortality rates because we did not anticipate major differences in the distribution of pregnancies during the 2003-2020 period across the age groups. We estimated the proportionate mortality of PE-related maternal mortality, defined as the proportion of PE-related maternal deaths out of all maternal deaths. Locally estimated scatterplot smoothing with least squares fitting to generate smoothed lines with 95% confidence intervals (CI) were used to depict the trends in crude mortality rates and proportionate mortality over the study period. Differences in contingency tables were explored with the use of the Pearson's Chi-squared test or Fisher's exact test as appropriate. All analyses were stratified by racial/ethnic and age groups. Statistical analysis was performed using R (version 4.1.2).

Results

Overall, 12,871 maternal deaths were recorded in the US from 2003 to 2020 with increasing numbers over time: 496 deaths in 2003 and 863 deaths in 2020 (**Table 1**). This corresponds to an increase in reported all-cause maternal mortality from 12.1 maternal deaths per 100,000 live births in 2003 to 23.9 maternal deaths per 100,000 live births in 2020. This increase followed the introduction of the pregnancy checkbox.

Table 1. Characteristics and causes of maternal deaths 2003-2020 in the presence versus absence of pulmonary embolism (PE).

Characteristic	**Overall** N = 12,871[1]	**Maternal deaths with PE** N = 735[1]	**Maternal deaths without PE** N = 12,136[1]	**p-value**
Age group				<0.001
≤24	2,290 (18)	134 (18)	2,156 (18)	
25-39	7,727 (60)	520 (71)	7,207 (59)	
≥40	2,854 (22)	81 (11)	2,773 (23)	
Race				<0.001
Black	4,380 (34)	303 (41)	4,077 (34)	

Characteristic	**Overall** N = 12,871[1]	**Maternal deaths with PE** N = 735[1]	**Maternal deaths without PE** N = 12,136[1]	**p-value**
Hispanic	2,061 (16)	107 (15)	1,954 (16)	
Other	733 (5.7)	28 (3.8)	705 (5.8)	
White	5,697 (44)	297 (40)	5,400 (44)	
Autopsy performed	5,931 (46)	451 (61)	5,480 (45)	<0.001
Marital status				0.3
Divorced	1,203 (9.3)	55 (7.5)	1,148 (9.5)	
Married	5,797 (45)	342 (47)	5,455 (45)	
Single	5,593 (43)	326 (44)	5,267 (43)	
Unknown	127 (1.0)	6 (0.8)	121 (1.0)	
Widowed	151 (1.2)	6 (0.8)	145 (1.2)	

Characteristic	Overall N = 12,871[1]	Maternal deaths with PE N = 735[1]	Maternal deaths without PE N = 12,136[1]	p-value
Place of death				
Decedent's home	1,768 (14)	66 (9.0)	1,702 (14)	
Hospice facility	178 (1.4)	2 (0.3)	176 (1.5)	
Hospital, Clinic or Medical Center - Dead on Arrival	157 (1.2)	15 (2.0)	142 (1.2)	
Hospital, clinic or Medical Center - Inpatient	7,829 (61)	371 (50)	7,458 (61)	
Hospital, Clinic or Medical Center - Outpatient or admitted to Emergency Room	2,420 (19)	268 (36)	2,152 (18)	
Nursing home/long term care	133 (1.0)	0 (0)	133 (1.1)	
Other	315 (2.4)	11 (1.5)	304 (2.5)	
Unknown	71 (0.6)	2 (0.3)	69 (0.6)	
Other causes of death				

Characteristic	**Overall** N = 12,871[1]	**Maternal deaths with PE** N = 735[1]	**Maternal deaths without PE** N = 12,136[1]	**p-value**
Cardiovascular diseases	569 (4.4)	46 (6.3)	523 (4.3)	0.013
Respiratory diseases	364 (2.8)	10 (1.4)	354 (2.9)	0.013
Cancer	163 (1.3)	4 (0.5)	159 (1.3)	0.071
Bleeding	159 (1.2)	8 (1.1)	151 (1.2)	0.7
Autoimmune disease	40 (0.3)	1 (0.1)	39 (0.3)	0.7
Obesity	127 (1.0)	18 (2.4)	109 (0.9)	0.2
COVID-19	103 (0.8)	3 (0.4)	100 (0.8)	<0.001
Causes of death related to pregnancy, childbirth and the puerperium				
Pregnancy with abortive outcome	512 (4.0)	5 (0.7)	507 (4.2)	
Hypertensive disorders in pregnancy, childbirth and the puerperium	938 (7.3)	7 (1.0)	931 (7.7)	

Characteristic	Overall N = 12,871[1]	Maternal deaths with PE N = 735[1]	Maternal deaths without PE N = 12,136[1]	p-value
Obstetric hemorrhage	744 (5.8)	19 (2.6)	725 (6.0)	
Pregnancy-related infection	281 (2.2)	1 (0.1)	280 (2.3)	
Other obstetric complications*	2,586 (20)	535 (73)	2,051 (17)	
Unanticipated complications of management	34 (0.3)	2 (0.3)	32 (0.3)	
Non-obstetric complications	4,312 (34)	68 (9.3)	4,244 (35)	
Unknown/undetermined	460 (3.6)	2 (0.3)	458 (3.8)	
Contributory cause	3,004 (23)	96 (13)	2,908 (24)	

[1] n (%), *includes the O88.2 ICD code

Focusing on the deaths due to PE, 735 PE-related maternal deaths were recorded between 2003 and 2020, corresponding to 5.7% of all maternal deaths recorded in the same period; this figure peaked at 8.2% in 2020. After age adjustment, PE-related maternal deaths were more likely to be associated with non-Hispanic black race and with concomitant

cardiovascular causes of death. In contrast, they were less likely to occur in patients with a concomitant respiratory disease (**Figure 1**).

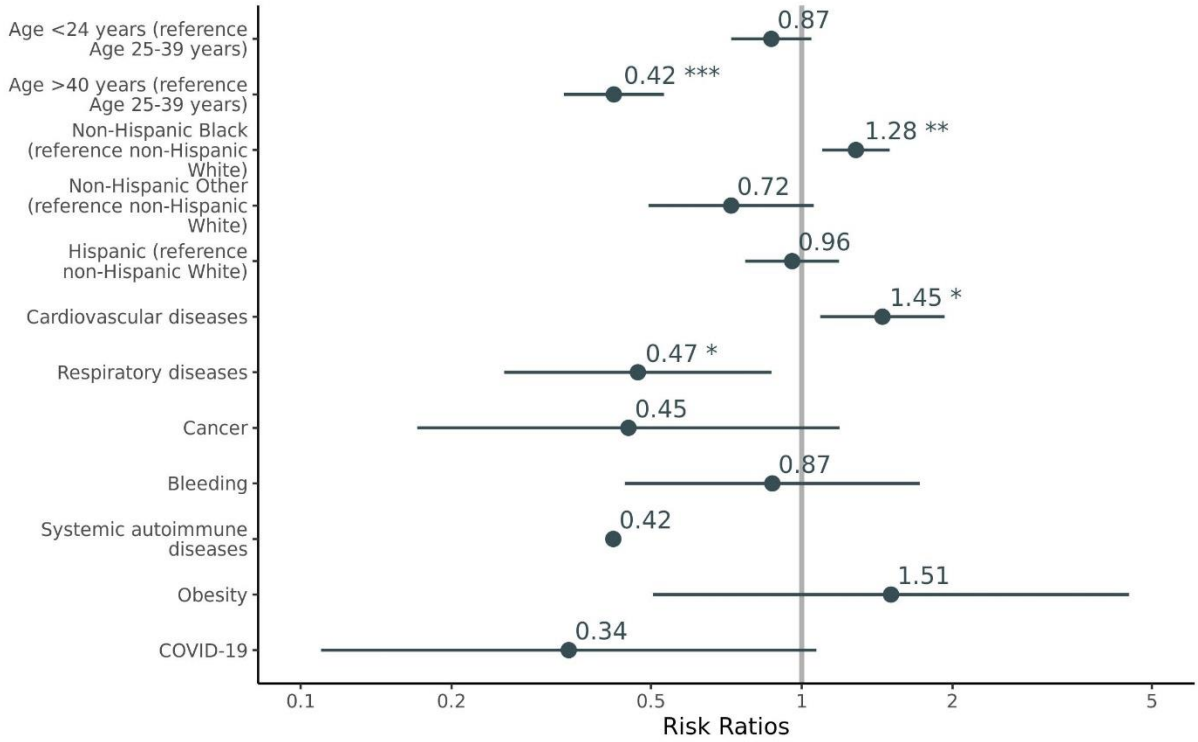


Figure 1. Title: Forest plot of the association of covariates with the maternal deaths related to PE. Legend: The figure depicts the association of age, race/Hispanic origin and other causes of death to the maternal deaths related to PE. All risk ratios have been adjusted for age. PE: pulmonary embolism.

The overall maternal mortality rate related to PE between 2003 and 2020 was 1.02 (95% CI 0.95-1.10) per 100,000 live births. The trend in PE-related maternal mortality rates remained stable between 2003 and 2015, and increased abruptly thereafter peaking at 1.96 (95% CI 1.7-2.2) maternal deaths per 100,000 live births in 2020 and is depicted in **Figure 2A**. The trend in proportionate PE-related maternal mortality is displayed in **Figure 3A** and shows that the proportion of PE-related death out of all maternal deaths increased in the later years of the period, as the pregnancy checkbox was implemented nationwide.

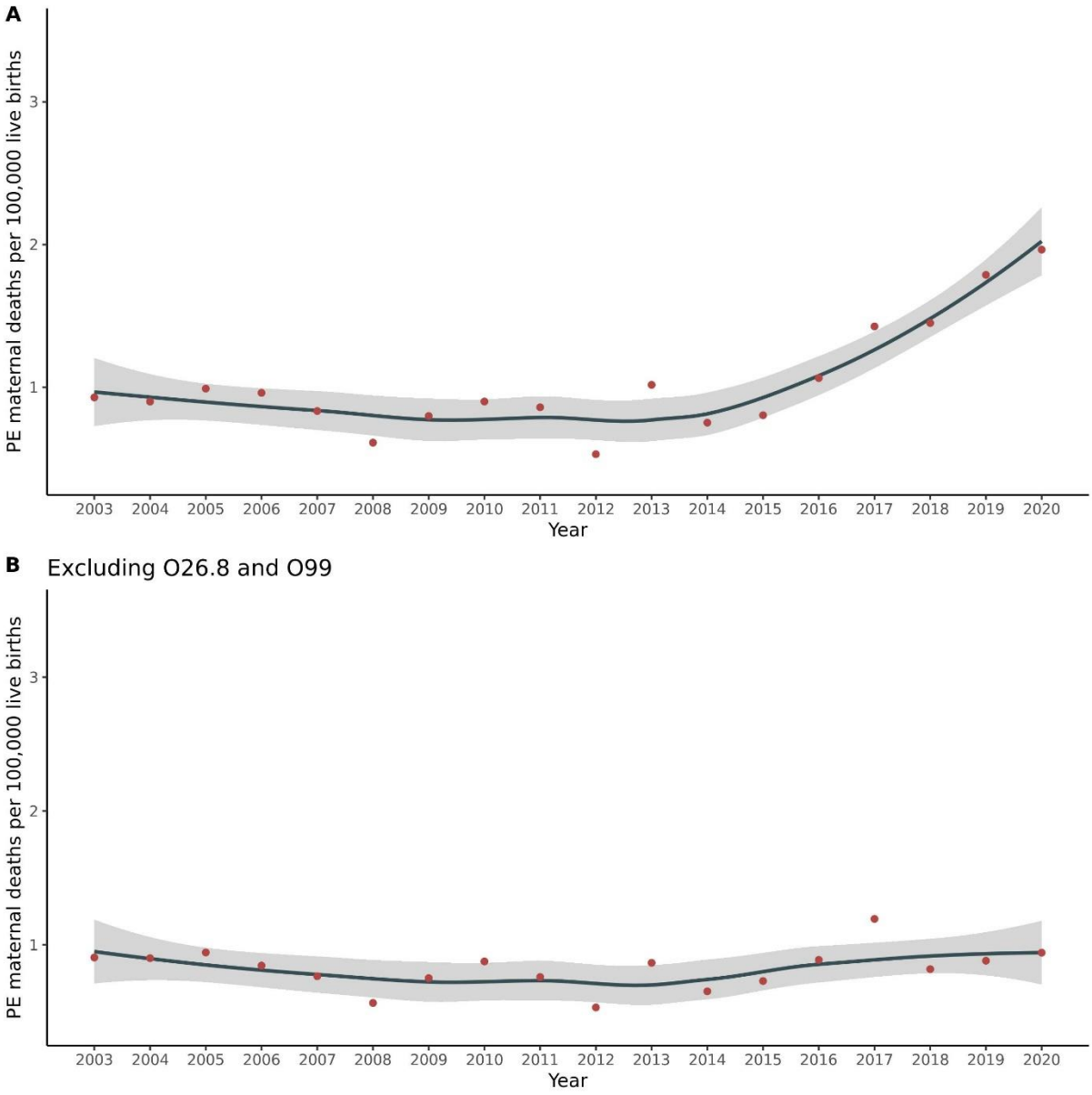


Figure 2. Title: Trends in maternal mortality rates related to pulmonary embolism during the period from 2003 to 2020. Legend: The figure depicts the rates in the overall population (A), and in the sensitivity analysis excluding O26.8 ("Other specified pregnancy related conditions") and O99 ("Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium") ICD-10 codes as underlying causes of death, which mitigates the effect of the pregnancy checkbox implementation (B). The points in red represent the observed crude rates at each year, while the solid line is the result of statistical smoothing along with 95% confidence interval (shaded surface). PE: pulmonary embolism.

The use of O26.8 or O99 ICD-10 codes as underlying cause of death in PE-related maternal deaths increased abruptly after 2015 (**Supplementary Figure A2**), following the progressive introduction of the pregnancy checkbox. In the sensitivity analysis accounting for the implementation of the pregnancy checkbox, after the exclusion of deaths with O26.8 and O99 ICD-10 codes as underlying cause of death, the trends in PE-related maternal mortality remained stable from 2003 to 2020 (**Figure 2B**). On the other hand, in the sensitivity analysis, the rise in proportionate mortality due to PE in later years is not evident, possibly indicating the effect of the pregnancy checkbox in revealing a higher burden of PE among maternal deaths (**Figure 3B**). Comparing the PE-related maternal deaths in the two periods – the first years of the pregnancy checkbox implementation (2003-2005) versus the period after its universal use across states (2018-2020) – we observed that PE was reported more frequently in the death certificates in the group aged 25-39 years, although autopsy was performed less frequently (**Table 2**). Report of cardiovascular diseases (24% vs 0%), respiratory diseases (5.2% vs 0%) and bleeding (3.6% vs 0%) as cause of deaths anywhere in death certificates was more frequent in later than in earlier years of the period considered.

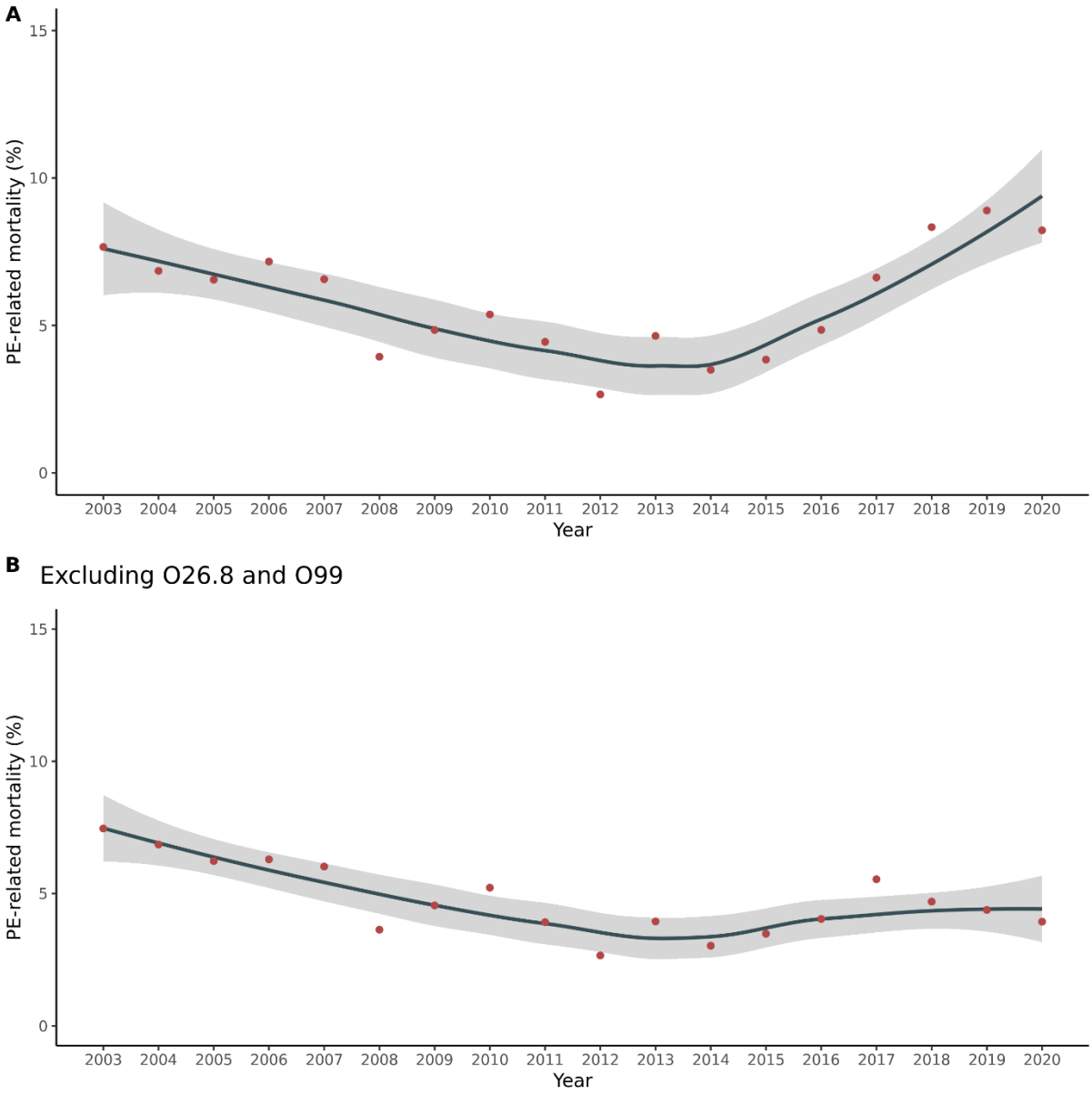


Figure 3. Title: Trends in pulmonary embolism related proportionate maternal mortality during the 2003-2020 period. Legend: The figure depicts the proportionate mortality due to PE among all maternal deaths in the overall population (A), and in the sensitivity analysis excluding O26.8 ("Other specified pregnancy related conditions") and O99 ("Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium") ICD-10 codes as underlying causes of death, which mitigates the effect of the pregnancy checkbox implementation and shows the possible underestimation of maternal deaths in the absence of the checkbox (B). The points in red represent the observed proportionate mortality at each year, while the line is the result of statistical smoothing along with 95% confidence interval (shaded surface).

The crude PE-related maternal mortality rates differed across maternal age groups (overall 0.61, 1.09, and 3.83 maternal deaths per 100,000 live births for ≤24, 25-39, and ≥40 years old, respectively). A steeper increase over time was observed in the age group 25-39 years than in the age group ≤24 years (**Figure 4A**), which was not evident in the sensitivity analysis (**Figure 4C**). In contrast, the ≥40 years old age group showed fluctuating trends across the time period in both analyses. The crude PE-related maternal mortality rate was 2.89 deaths per 100,000 live births in black non-Hispanics, 0.47 in other non-Hispanics, 0.77 in white non-Hispanics, and 0.63 in Hispanic origin. Trends in maternal PE mortality across ethnicities showed a steeper increase among black non-Hispanics than in the other groups (**Figure 4B** and **Figure 4D)**.

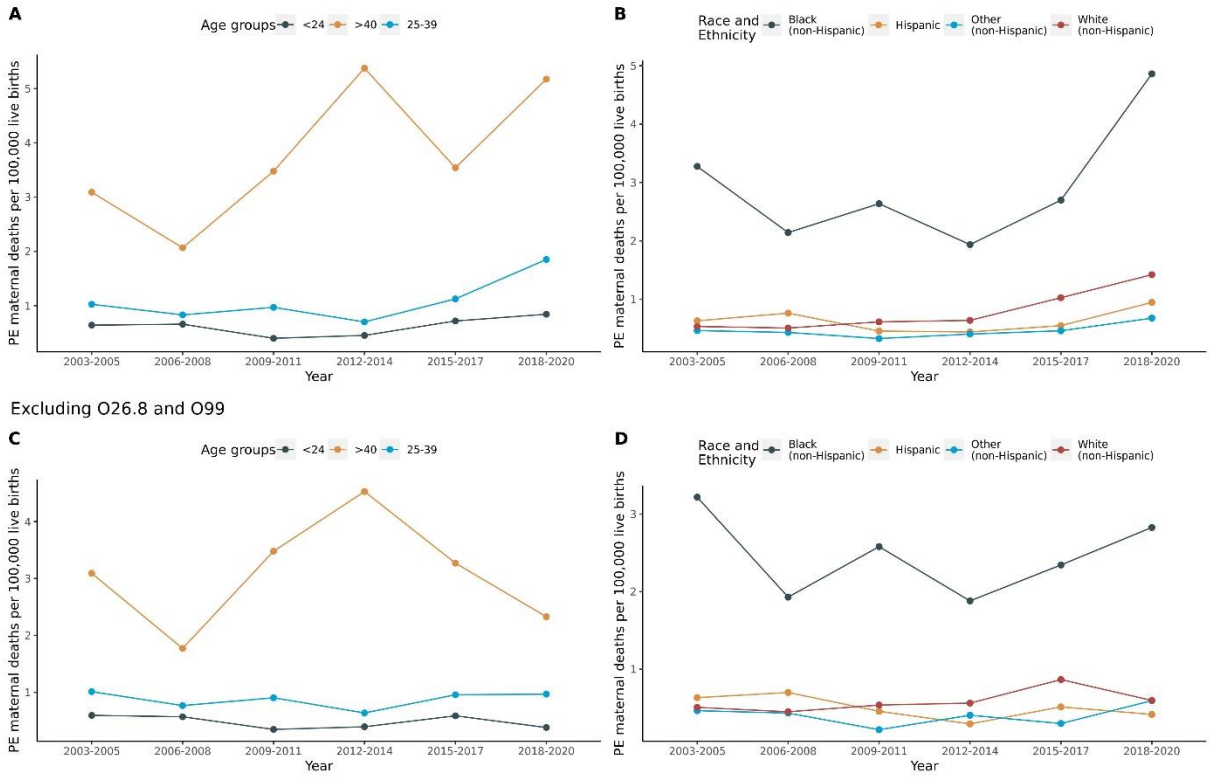


Figure 4. Title: Trends in maternal mortality rates related to pulmonary embolism during the period from 2003 to 2020 in different subgroups. Legend: According to age groups (A) and race/Hispanic origin (B). Sensitivity analysis excluding O26.8 and O99 as underlying causes of death, according to age groups (C) and race/Hispanic origin (D). Crude rates are depicted without statistical smoothing. PE: pulmonary embolism.

Discussion

Principal findings and Results

In this epidemiological analysis, the increased specificity of reporting of maternal mortality associated with PE over time in the US database results in an observed increase in maternal mortality rates related to PE from 0.93 per 100,000 live births in the year 2003 to 1.96 per 100,000 live births in 2020 in the US. This is in general accordance with the increase in all-cause maternal mortality rates during the same period as recorded in the literature (25). However, the increase suggested by death certificates may not represent a true temporal increase in factual PE-related maternal mortality, as it may primarily depend on the way maternal death surveillance was performed and maternal deaths were recorded in death certificates (19). Beginning in 2003, the “pregnancy checkbox” was adopted in the death certificates with the goal of reducing the number of missed maternal deaths (18). The implementation of the checkbox was gradual: by 2018, after all states had adopted it, increased awareness and reduced under-coding were reported. Consequently, the overall maternal mortality rates reported in the US have been increasing since 2003. However, this increase has been observed to have been driven by the potentially inappropriate use of the codes O26.8 and O99 (20). In line with these observations, our sensitivity analysis conducted by excluding these codes confirmed that maternal mortality rates remained rather stable in the period considered.

Clinical and Research Implications

Our findings suggest that PE remains a significant driver of maternal mortality, contributing to 8.2% of all maternal deaths in the year 2020. In an analysis of German nationwide inpatient data, the PE-related maternal mortality rate was estimated at 0.8 per 100,000 live births (11). Although the German study used only inpatient data, out-of-hospital deaths are unlikely to be the sole reason of the low reported rate, since the present analysis indicates that ~90% of PE-associated maternal deaths in the US occurred in the hospital. Therefore, the considerable difference between the US and the German mortality rate suggests that a similar underreporting of maternal deaths may occur in other Western countries as in the US before the implementation of the pregnancy checkbox. Since the universal implementation of the pregnancy checkbox in 2018, the PE-related maternal mortality rate in the US almost doubled. Accordingly, and while taking into account that the temporal trends in maternal mortality were stable in our analysis, we may consider the true PE-related maternal mortality rates to be best represented by the years 2018-2020 (nationwide implementation of the checkbox), when they approached 2 deaths per 100,000

live births. We have previously published mortality data from the general population in US and Canada denoting stable or decreasing PE-related mortality trends (14). Given that PE is a preventable cause of death, and that pregnancy and especially the early postpartum period is a known significant risk factor for PE, we would expect that PE-related mortality rates would be decreasing in this vulnerable population. However, we did not observe such a decrease.

In concordance with our findings, a retrospective analysis of the US Nationwide Inpatient Sample (NIS) by Elgendy et al. indicated that the rates of acute PE per 100,000 pregnancy-related hospitalizations did not change significantly from 2007 to 2015 (18.01 in 2007 vs 19.36 in 2015) (26). However, cardiovascular risk factors, such as obesity (27), new-onset hypertension (28), and smoking remain considerable in younger women, which could also contribute to explain the higher prevalence of cardiovascular causes of death in the later period (29). Thromboprophylaxis could be another potential driver of the trends observed (30). Data from MBRRACE in the United Kingdom indicate that maternal deaths from VTE have decreased after the introduction of thromboprophylaxis guidelines, suggesting an increased use of thromboprophylaxis; trends of thromboprophylaxis use among pregnant women are lacking in the US.

Taken together, these factors could partly explain the unchanged rates of hospitalizations as reported by Elgendy et al., but also the stable mortality rates of our study. The risk for PE during a pregnancy-associated hospitalization increased particularly in women aged >40 years, similar to our study. The risk was also greater in pregnant women of black race, as in the present analysis, possibly reflecting social factors and healthcare inequalities (14, 31). A trend analysis using NIS data from 2000 to 2018 indicated that the PE rates averagely increased 4.9% per year for cesarean delivery hospitalizations and 8.7% per year for vaginal delivery hospitalizations (32). A similar trend was not observed in our analysis.

Strengths and Limitations

A limitation of our analysis is that there was no knowledge of whether the pregnancy checkbox was used (or even existed) in each individual death certificate, and therefore we were not able to analyze separately deaths without the use of the pregnancy checkbox to identify more accurate temporal trends in the report of PE-related maternal mortality. However, we believe that the sensitivity analysis excluding the clearly defined codes O26.8 and O99 provides an insight into the true temporal trends of PE-related maternal mortality, as per previous analyses (20). We cannot exclude that some PE deaths were misclassified as maternal deaths due to the misuse of the pregnancy checkbox, but we partially addressed this limitation by excluding from the analysis women 55 years or older at the time of death. Lastly,

the CDC Mortality Multiple Cause of Death database provides 4-digit ICD-10 codes as causes of death; this prevented us from differentiating between mortality rates occurring during pregnancy, delivery or puerperium, which would have required the more detailed 7-digit ICD-10 codes. Also, we had no reliable information on the prevalence of risk factors such as obesity, smoking, and hypertension, which are not provided in death certificates.

Conclusions

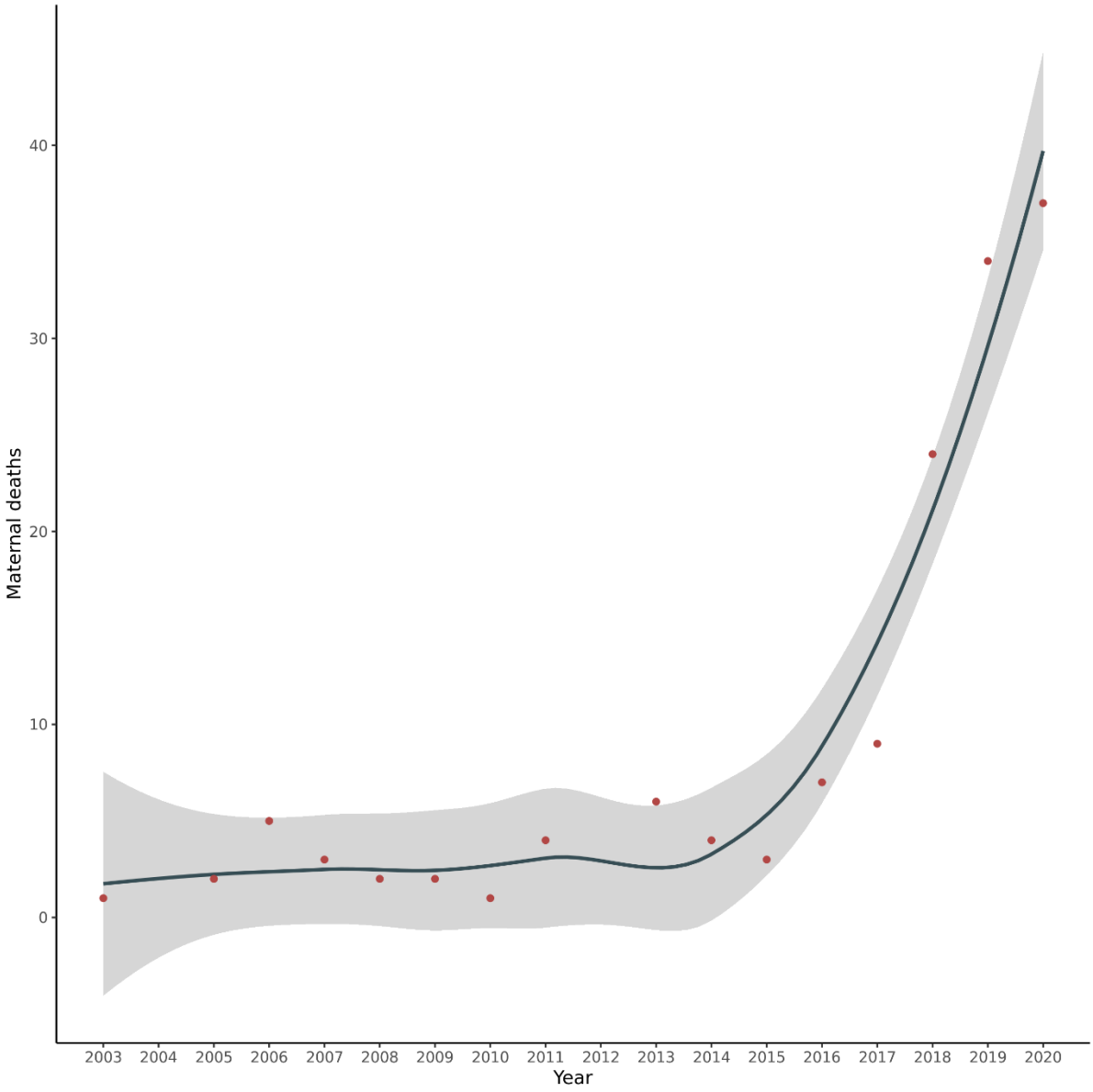
In conclusion, this analysis found that the PE-related maternal mortality rate was 2 deaths per 100,000 live births in 2020 and PE accounted for 6% of all maternal deaths in the entire period. Maternal mortality rates related to PE remained stable during the period 2003-2020. The risk for PE-related maternal mortality was highest in women aged >40 years and women of black race. More research is required to assess whether public health strategies to promote awareness improvements in VTE prevention, or advances in the diagnosis and management of PE would reduce the risk of death from PE in this vulnerable population.

Anhang zur Publikation #1: Muttersterblichkeit im Zusammenhang mit Lungenembolie in den Vereinigten Staaten, 2003-2020

Supplementary Table A1. International Classification of Diseases 10th Revision (ICD-10) codes for the classification of causes of deaths among all maternal deaths.

Cause of death	ICD-10 Codes
Pulmonary embolism	I26.0, I26.9, O88.2
Deep vein thrombosis	I80.x, I82.2, I82.4, I82.9, O22.3, O87.1
Cancer	C. codes, D0.x, D3[7-9].x, D4[0-5].x, Z85.x
Respiratory diseases	J. codes
Cardiovascular diseases	I1[0-5].x, I2[0-5].x, I27.x, I3[1-3].x, I4x.x, I50.x, I6[3-7].x, I7x.x
Hemorrhage	R04.x, R58.x, D62.x,D68.3, D69.9, K62.5, K66.1, K2[5-8].x, K92.0, K92.1, K92.2, H11.3, H21.0, H31.3, H35.6, H43.1, H45.0, I6[0-2].x, I31.2, J94.2, M25.0, N02.x, N93.9, N95.0, R31.x, S06.x, S27.1, T79.2
Obesity	E66, O99.2
COVID-19	U07.1
Systemic autoimmune diseases	M06.9, M30.x, M31.x, M32.x, M33.x, M34.x, M35.x, M36.x, I73.0, D86.9, D59.1, D59.0, D69.2, G70, D89.9
WHO application of ICD-10 deaths during pregnancy, childbirth and the puerperium"	
Pregnancy with abortive outcome	O00.[01289], O01.[019], O02.[0189], O03.x, O04.x, O05.x, O06.x, O07.x
Hypertensive disorders in pregnancy, childbirth and the puerperium	O11.x, O12.[012], O13.x, O14.[0129], O15.[0129], O16.x
Obstetric Hemorrhage	O20.[089], O43.2, O44.1, O45.[089], O46.[089], O67.[089], O71.[01347], O72.[0123]
Pregnancy related infections	O23.[0123459], O75.3, O41.1, O85.x, O86.[012348], O91.[012], A34

Other obstetric complications	O21.[12], O22.[3589], O24.4, O26.[69], O44.0, O71.[25689], O73.[01], O75.4, O75.8, O75.9, O87.[139], O88.[01238], O90.[01234589]
Unanticipated complications of management	O29.[01235689], O74.[012346789], O89.[01235689]
Non-obstetric complications	O10.[012349], O24.[01239], ^O98.x, O99.x
Unknown/Undetermined	O95.x
Contributory causes	O08.x, O21.[089], O22[0124], O25, O26.[1234578], O28.x, O29.4, O30.[01289], O31.[0128], O32.x, O33.x, O34.x, O35.x, O36.x, O40.x, O41.x, O42.x, O47.x, O48, O60.x, O61, O62.[0123489], O63.x, O64.[01234589], O65.[01234589], O66.[01234589], O68.[012389], O69.[01234589], O70.x, O74.5, O75.[012567]



Supplementary Figure A1. Trends in the use of O26.8 and O99 ICD-10 codes as underlying cause of death in maternal deaths related to pulmonary embolism during the period from 2003 to 2020. The points in red represent the observed absolute death count at each year, while the solid line is the result of statistical smoothing along with 95% confidence interval (shaded surface).

Publikation #2: Eine landesweite Analyse von Reperfusionstherapien bei Lungenembolien bei älteren Patienten und bei Gebrechlichkeit

Zitieren:

Farmakis IT, Barco S, Giannakoulas G, Keller K, Valerio L, Tichelbäcker T, Partovi S, Ahrens I, Konstantinides SV, Hobohm L. A nationwide analysis of reperfusion therapies for pulmonary embolism in older patients with frailty. EuroIntervention. 2023 Sep 28:EIJ-D-23-00399. doi: 10.4244/EIJ-D-23-00399. Epub ahead of print. PMID: 37767997.

Verfügbar in:

A nationwide analysis of reperfusion therapies for pulmonary embolism in older patients with frailty - EuroIntervention (pcronline.com)

Abstract

Background: Reperfusion therapy is challenging in the elderly. Catheter-directed therapies are an alternative therapy for higher risk pulmonary embolism (PE) if systemic thrombolysis (ST) is contraindicated or has failed. Their safety has not been evaluated in specific vulnerable populations.

Aims: To assess the safety of reperfusion therapies in elderly and frail patients in the real-world.

Methods: In the US Nationwide Inpatient Sample from 2016 through 2020, we identified hospitalizations of patients ≥ 65 years with PE, and defined a frailty subgroup using the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnosis indicator. We investigated reperfusion therapies (ST, catheter-directed thrombolysis [CDT], catheter-based thrombectomy [CBT], surgical embolectomy [SE]) and associated safety outcomes (overall and major bleedings).

Results: Among 980,245 hospitalizations of patients ≥65 years with PE (28.0% frail), reperfusion therapies were used in 4.9% (17.6% among high-risk PE). ST remained stable, while catheter-directed therapy increased from 1.7% in 2016 to 3.2% in 2020. Among all hospitalizations with reperfusion, CDT was, compared to ST, associated with reduced major bleedings (5.8% vs 12.2%, OR 0.58, 95%CI 0.49-0.70), also among frail patients. CBT was, compared to SE, associated with reduced major bleedings (11% vs 22.4%, OR 0.63, 95%CI 0.43-0.91), but not among frail patients. These differences were particularly significant in patients with non-high-risk PE. Differences persisted for overall bleedings as well.

Conclusion: Catheter-directed therapies may be a safer alternative to classical reperfusion therapies for elderly and frail patients with PE requiring reperfusion treatment.

Keywords: pulmonary embolism; elderly; frailty; reperfusion; thrombolysis; catheter-directed therapies

Introduction

Acute pulmonary embolism (PE) is a frequent cardiovascular disease with an exponential rise in incidence with age (33, 34). Although the annual PE-related mortality rates have decreased over the past two decades, especially among the elderly, PE is still a main contributor to overall mortality in the elderly (35, 36). Reperfusion therapies, primarily systemic (intravenous) thrombolysis (ST) or surgical embolectomy (SE), have traditionally been the treatment of choice in patients with hemodynamic instability or risk of imminent decompensation (1, 37). However, age >75 is often mentioned as a relative contraindication for ST since the rate of major extracranial bleeding reached 11.1% in aged patients in the Pulmonary Embolism Thrombolysis (PEITHO) trial (38). On the other hand, patients with advanced age and frailty often have a high surgical risk, and SE may not be an ideal alternative (39, 40). Therefore, these patients are in need of alternative reperfusion strategies.

Catheter-directed therapies, including catheter-directed thrombolysis (CDT) and catheter-based thrombectomy (CBT) can swiftly restore the right ventricular function in terms of hemodynamic and radiological parameters in high- and intermediate-high risk PE patients, and are suggested in those in whom thrombolysis has failed or is contraindicated (37). Standard or ultrasound-assisted CDT consists of local infusion of lower dose thrombolytics directly into the pulmonary arteries. CBT may refer either to thrombus fragmentation with the use of rotational pigtail catheters or thrombus aspiration by applying suction with the use of large bore catheters. Pharmacomechanical catheter-directed techniques have also been used. A recent meta-analysis evaluated the safety profile of these endovascular therapy approaches reporting a major bleeding rate of 6.7% and 1.4% for high-risk and intermediate-risk PE, respectively (41). However, this evidence is derived mainly from smaller single-arm studies, whereas major controlled randomized trials investigating the efficacy and safety of CDT are still ongoing (42). Moreover, frail older patients are usually underrepresented in randomized trials by fulfilling exclusion criteria.

In the present study, we aimed to assess the contemporary use of reperfusion therapies for the management of elderly and frail hospitalized patients with acute PE and specifically investigate the safety with regard to bleeding of different reperfusion treatment approaches in a large nationwide sample.

Methods

The Nationwide Inpatients Sample (NIS), provided by the Agency for Healthcare Research and Quality, is the largest publicly accessible, all-payer, de-identified, inpatient healthcare

database in the US and is developed for the Healthcare Cost and Utilization Project (HCUP). The database represents roughly 97% of the US population and it contains a 20% stratified sample of discharges from US hospitals that take part in the HCUP, excluding rehabilitation and long-term acute care facilities. For this analysis, we used data from the NIS during the period 2016 through 2020. The database includes only de-identified data and this analysis was exempt of institutional review board approval or informed consent. Additional information on the NIS is provided in the HCUP NIS Database Documentation website (www.hcup-us.ahrq.gov).

Study population and data definition

The International Classification of Diseases, 10th version (ICD-10-CM for diagnoses and ICD-10-PCS for procedures) is used to code the diagnoses and procedures in the NIS database. The database contains up to 40 diagnoses and 25 procedures for each hospital discharge record. For the purpose of the present study, all hospitalizations of elderly (≥65 years) patients were selected with a discharge diagnosis code of acute PE (primary and secondary diagnosis). Frail patients were defined applying the Johns Hopkins Adjusted Clinical Groups (ACG) frailty-defining diagnosis indicator (43, 44, 45). This indicator consists of a total of ten frailty-defining unweighted diagnoses: malnutrition, dementia, severe vision impairment, decubitus ulcer, urinary incontinence, weight loss, poverty, barriers to access to care, difficulty in walking, and falls; at least one of 10 diagnoses (in conjunction with age more than 65 years old) was required to define frailty. Hospitalizations with an additional diagnosis of shock, vasopressor use, cardiac arrest, or need for cardiopulmonary resuscitation were classified as high-risk acute PE.

The reperfusion therapeutic strategies during hospitalization were classified as ST, CDT, CBT, and SE. If two or more reperfusion therapies were used during the same hospitalization, we considered in our descriptive analysis the reperfusion therapy performed first, whereas those cases were excluded in the inferential analysis. Safety outcomes and complications during the index PE hospitalization included primarily overall bleeding rates and major bleeding rates (defined as presence of intracranial bleeding, hemopericardium, hemoperitoneum, hemarthrosis, also with or without transfusion). We also assessed in-hospital mortality, length of stay, shock, and acute renal failure.

Supplementary Table S1 lists the ICD-10-CM and ICD-10-PCS codes used to define the aforementioned variables, as well as comorbidities.

Statistical analysis

Since the percentages of missing data were below 3% for all variables, we assumed that they were missing at random and conducted a complete case analysis. For categorical data, descriptive statistics comprised counts and percentages, and for continuous variables, medians and interquartile range (IQR). Logistic regression was used to calculate odds ratios of overall bleeding, major bleeding, and all-cause in-hospital mortality, and make comparisons of: (i) ST versus CDT, and (ii) CBT versus SE. Comparisons were made among patients who received only one reperfusion therapy, excluding those who received multiple therapies. The regression models were adjusted for age, sex, presence of high-risk PE, and comorbidities (arterial hypertension, diabetes, obesity, congestive heart failure, chronic pulmonary disease, and cancer). We performed a subgroup analysis according to frailty status. All analyses were conducted by application of discharge-level weights provided in the HCUP database and by taking into account the NIS stratification and hospital clustering. A two-sided p-value <0.05 was set as the level of statistical significance. The statistical analysis was conducted in R (R Project for Statistical Computing, version 4.1.3.).

Results

Out of a total of 1,942,505 patients hospitalized with PE diagnosis between 2016 and 2020, 980,245 (50.5%) were ≥ 65 years of age and were included in the present analysis. In these elderly patients, median age was 75 (IQR 70-82) years, while 54% were women (**Table 1**). Among those, 274,175 (28.0%) hospitalized patients were considered frail, based on the Johns Hopkins ACG frailty-defining indicator as explained in the Methods, and served for the predefined subgroup analysis.

Table 1. Baseline characteristics of pulmonary embolism hospitalizations among patients aged ≥ 65 years according to frailty status.

Characteristic	**Overall**, N = 980,245[1]	**Non-frail**, N = 706,070[1]	**Frail**, N = 274,175[1]
Age (years)	75 (70, 82)	74 (69, 81)	79 (72, 86)
Women	527,935 (54)	370,825 (53)	157,110 (57)
Race			
White	728,660 (77)	533,450 (78)	195,210 (73)
Black	133,585 (14)	89,985 (13)	43,600 (16)
Hispanic	51,790 (5.4)	36,070 (5.3)	15,720 (5.9)

Asian/Pacific Islander	13,000 (1.4)	8,585 (1.3)	4,415 (1.7)
Native American	3,200 (0.3)	2,315 (0.3)	885 (0.3)
Other	20,815 (2.2)	14,305 (2.1)	6,510 (2.4)
Deep vein thrombosis	347,255 (35)	252,975 (36)	94,280 (34)
Diabetes mellitus	279,535 (29)	203,870 (29)	75,665 (28)
Myocardial infarction	124,065 (13)	89,435 (13)	34,630 (13)
Congestive heart failure	273,895 (28)	191,575 (27)	82,320 (30)
Chronic pulmonary disease	301,865 (31)	219,830 (31)	82,035 (30)
Renal disease	202,230 (21)	143,595 (20)	58,635 (21)
Cancer	347,235 (35)	252,675 (36)	94,560 (34)
Cerebrovascular disease	78,555 (8.0)	47,530 (6.7)	31,025 (11)
Dementia	116,840 (12)	0 (0)	116,840 (43)
Hypertension	725,275 (74)	526,870 (75)	198,405 (72)
Obesity	175,470 (18)	144,500 (20)	30,970 (11)
Renal impairment	140,310 (14)	100,080 (14)	40,230 (15)
High-risk PE	63,840 (6.5)	43,800 (6.2)	20,040 (7.3)

[1] Median (IQR); n/N (%). PE: pulmonary embolism

In this study population of patients ≥ 65 years, reperfusion therapies were used in 4.0% of PE hospitalizations in 2016 with an increase up to 5.6% in 2020 (**Figure 1**); interestingly in high-risk PE, reperfusion use rates remained largely unchanged with 16.9% in 2016 and 16.5% in 2020. Reperfusion rates by age group and high-risk PE are presented in **Supplementary Figure S1**. ST was the most used reperfusion therapy (2.5% overall, 12.3% for high-risk PE), followed by catheter directed thrombolysis (1.8% overall, 3.1% for high-risk PE), CBT (0.7% overall, 2.5% for high-risk PE), and SE (0.1% overall, 0.9% for high-risk PE). Overall, use of CDT increased from 1.7% in 2016 to 3.2% in 2020, and both CDT and CBT showed an increasing trend throughout the study period (**Figure 1**). Use of reperfusion therapies was more frequent in non-frail patients (5.6%, compared to 3.1% in those with frailty), and this was also true among patients with high-risk PE (non-frail, 19.9%; frail, 12.6%).

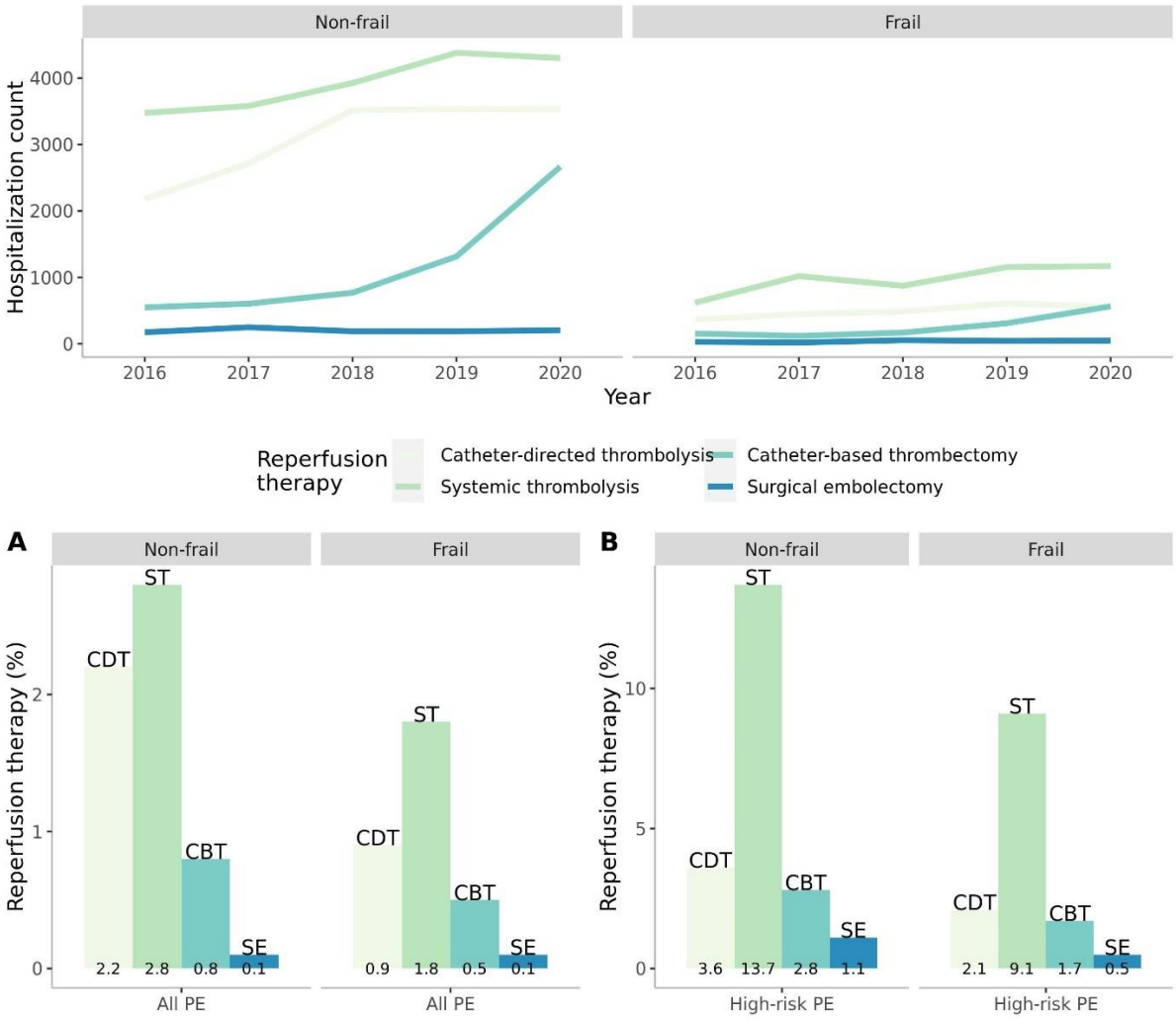


Figure 1. Counts of hospitalizations of elderly patients with PE requiring reperfusion therapies across the period 2016-2020 in the Nationwide Inpatient Sample, with (upper panel right) and without frailty (upper panel left). Rates of reperfusion therapies in all patients with PE (lower panel, A) and patients with high-risk PE (lower panel, B) according to frailty status. PE: pulmonary embolism; No: no reperfusion treatment; CBT: catheter-based thrombectomy; CDT: catheter-directed thrombolysis; SE: surgical embolectomy; ST: systemic thrombolysis.

Bleeding complications were documented in 15.6% of elderly patients; of those, major bleeding in 7.6% and intracranial hemorrhage in 1.0%. Since transfusions may also be procedural-related, by not taking them into account, major bleeding rates were i) 2% among patients not receiving any reperfusion treatment, ii) comparable for CDT and CBT at 2% and 3%, respectively, and iii) observed higher at 4% and 7% for ST and SE, respectively. Intracranial hemorrhage, which is the most feared complication of lytic treatment, was low at 1% in all groups, except for the group of ST, where it reached 3%. Bleeding events stratified

by type of reperfusion treatment are shown in **Figure 2**. The in-hospital case fatality rate was 8.4% in the entire study population, while among patients with high-risk PE it was as high as 55.3%. Patients without frailty had 7.4% in-hospital mortality (56.3% in high-risk PE), while those with frailty had considerably higher overall in-hospital mortality of 11.2%. In-hospital outcomes and complications in elderly patients who received at least one reperfusion therapy are presented in **Figure 2** and, according to frailty status, in **Table 2**.

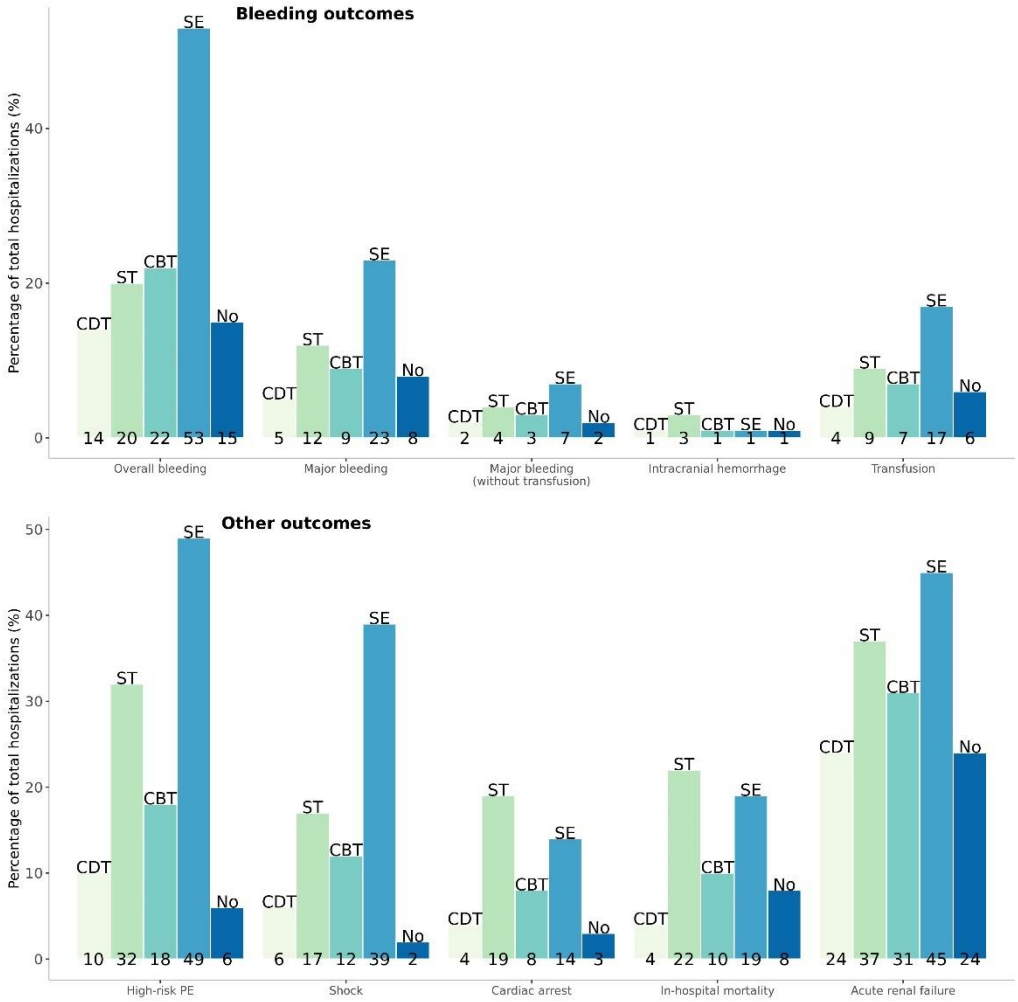


Figure 2. Rates of bleeding outcomes (top panel), including overall bleedings, major bleedings, transfusions, intracranial bleedings, and other outcomes (lower panel) across reperfusion treatments (systemic thrombolysis [ST], catheter-directed thrombolysis [CDT], catheter-based thrombectomy [CBT], and surgical embolectomy [SE]). No: no reperfusion treatment; CBT: catheter-based thrombectomy; CDT: catheter-directed thrombolysis; SE: surgical embolectomy; ST: systemic thrombolysis.

Table 2. Severity of pulmonary embolism, therapeutic procedures, complications, and outcomes of the study patients stratified by frailty status and type of reperfusion therapy.

Characteristic	Non-frail					Frail				
	No reperfusion, N = 666,295[1]	**Catheter-based thrombectomy**, N = 4,200[1]	**Catheter-directed thrombolysis**, N = 13,965[1]	**Surgical embolectomy**, N = 870[1]	**Systemic thrombolysis**, N = 18,535[1]	**No reperfusion**, N = 265,795[1]	**Catheter-based thrombectomy**, N = 975[1]	**Catheter-directed thrombolysis**, N = 2,155[1]	**Surgical embolectomy**, N = 175[1]	**Systemic thrombolysis**, N = 4,640[1]
High-risk PE	35,085 (5.3)	740 (18)	1,260 (9.0)	420 (48)	5,720 (31)	17,520 (6.6)	210 (22)	300 (14)	90 (51)	1,760 (38)
VA-ECMO	415 (<0.1)	60 (1.4)	30 (0.2)	80 (9.2)	105 (0.6)	65 (<0.1)	NR	NR	25 (14)	15 (0.3)
Inferior vena cava filter	42,880 (6.4)	930 (22)	2,365 (17)	315 (36)	2,955 (16)	21,700 (8.2)	275 (28)	470 (22)	60 (34)	810 (17)
Bleeding	94,775 (14)	890 (21)	1,825 (13)	460 (53)	3,460 (19)	48,695 (18)	260 (27)	355 (16)	90 (51)	1,195 (26)
Major bleeding	44,635 (6.7)	365 (8.7)	685 (4.9)	200 (23)	2,035 (11)	25,395 (9.6)	120 (12)	150 (7.0)	45 (26)	755 (16)
Major bleeding (without transfusion)	11,280 (1.7)	110 (2.6)	285 (2.0)	65 (7.5)	770 (4.2)	5,230 (2.0)	20 (2.1)	35 (1.6)	NR	235 (5.1)

Intracranial hemorrhage	6,035 (0.9)	50 (1.2)	130 (0.9)	10 (1.1)	485 (2.6)	3,150 (1.2)	NR	20 (0.9)	0 (0)	125 (2.7)
Transfusion	35,130 (5.3)	270 (6.4)	460 (3.3)	140 (16)	1,435 (7.7)	21,020 (7.9)	110 (11)	120 (5.6)	40 (23)	555 (12)
Acute renal failure	147,525 (22)	1,240 (30)	3,240 (23)	370 (43)	6,510 (35)	72,490 (27)	360 (37)	690 (32)	100 (57)	2,000 (43)
Shock	14,225 (2.1)	475 (11)	840 (6.0)	330 (38)	3,015 (16)	6,585 (2.5)	125 (13)	180 (8.4)	75 (43)	875 (19)
Cardiac arrest	18,985 (2.8)	370 (8.8)	495 (3.5)	125 (14)	3,525 (19)	8,530 (3.2)	55 (5.6)	125 (5.8)	25 (14)	940 (20)
In-hospital mortality	46,505 (7.0)	415 (9.9)	580 (4.2)	165 (19)	4,040 (22)	29,285 (11)	105 (11)	145 (6.7)	35 (20)	1,115 (24)
Length of stay	4.0 (2.0, 7.0)	5.0 (3.0, 8.0)	4.0 (3.0, 7.0)	9.0 (6.0, 16.5)	5.0 (3.0, 8.0)	6 (3, 10)	7 (4, 11)	6 (4, 10)	13 (7, 18)	7 (4, 12)

*Patients receiving more than one reperfusion therapy were excluded. [1] n/N (%); Median (IQR). NR: not reported, due to data privacy as per HCUP AHRQ regulations; PE: pulmonary embolism; VA-ECMO: veno-arterial extracorporeal membrane oxygenation

Catheter-directed thrombolysis versus systemic thrombolysis

Among patients ≥ 65 years who received thrombolysis CDT was associated with less major bleeding compared to systemic (intravenous) thrombolytic treatment (5.8% vs 12.2%; OR, 0.58; 95% CI, 0.49-0.70), also among the subgroup of frail patients (8.6% vs 16.2%, OR, 0.60; 95% CI, 0.41-0.88) (**Figure 3A**). Overall bleedings were also significantly less frequent in the patients treated with CDT group compared to those receiving ST (14.4% vs 20.4%; OR 0.79; 95% CI, 0.70-0.90); this difference was observed also in the subgroup of frail patients (18.2%

vs 25.8%; OR 0.72; 95% CI, 0.54-0.94) (**Figure 3A**). Patients receiving CDT had lower rates of in-hospital mortality compared to patients receiving ST (5.0% vs 22.3%; OR, 0.33; 95% CI, 0.28-0.40), also in the subgroup of frail patients (6.7% vs 23.9%; OR, 0.33; 95% CI, 0.26-0.40) (**Supplementary Figure S1**).

Catheter-based thrombectomy versus surgical embolectomy

Among all hospitalizations of elderly patients who received either SE or CBT, CBT was significantly associated with reduced major bleeding (11.0% vs 22.4%; OR 0.63; 95% CI, 0.43-0.91), without statistical significance among the subgroup of frail patients (14.8% vs 22.5%; OR 0.73; 95% CI, 0.28-1.93) (**Figure 3B**). Overall bleedings were also significantly fewer in the CBT group compared to SE (23.3% vs 50.4%; OR 0.40; 95% CI, 0.30-0.53); a tendency in the same direction was also observed among frail patients (28.4% vs 45.0%; OR 0.55; 95% CI, 0.26-1.14) (**Figure 3B**). In regards to in-hospital mortality, patients receiving CBT showed a trend towards lower rates compared to patients receiving SE (11.1% vs 21.1%; OR 0.85; 95% CI, 0.54-1.35), and among frail patients (10.6% vs 20.0%; OR 0.52; 95% CI, 0.20-1.32) (**Supplementary Figure S2**).

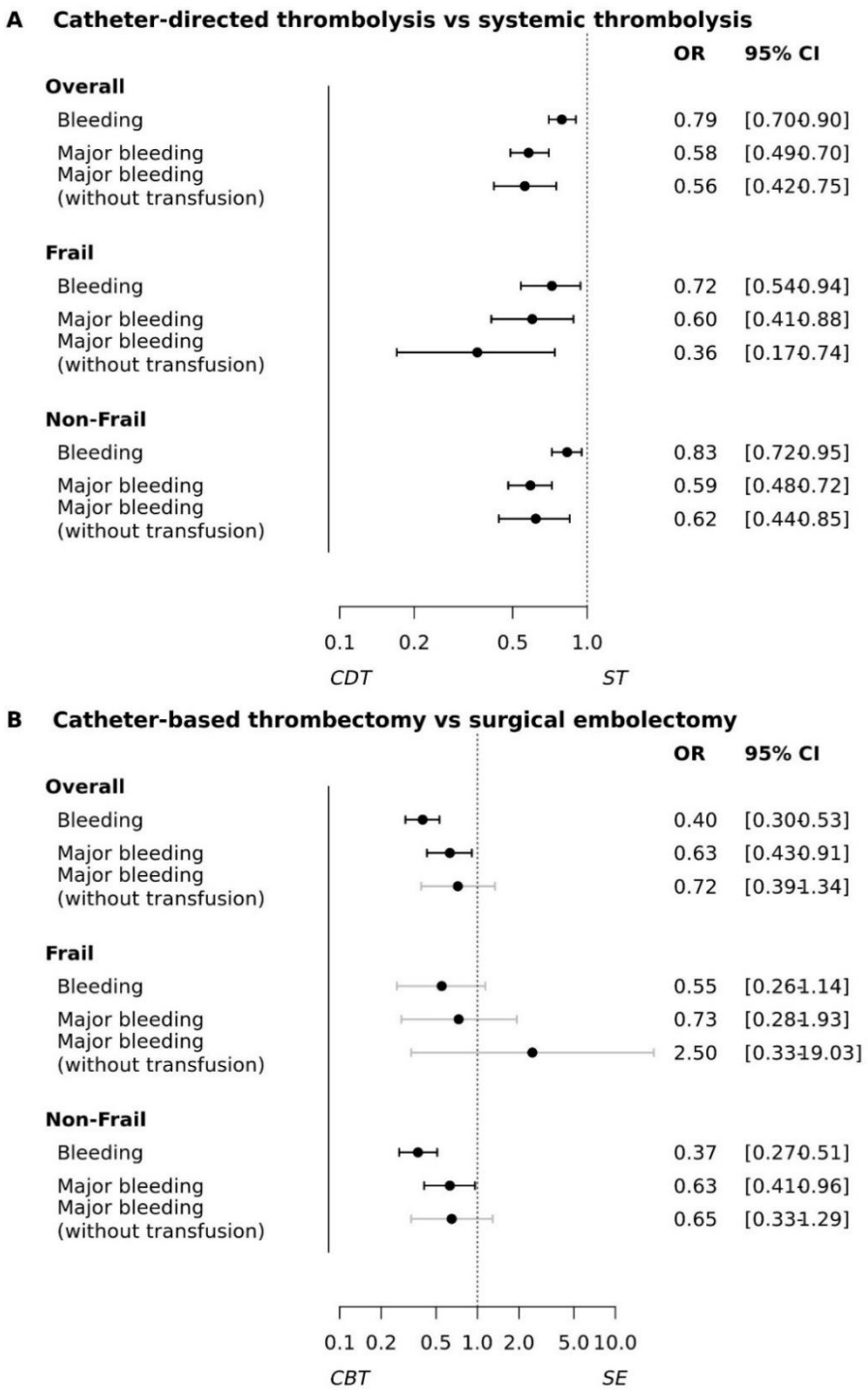


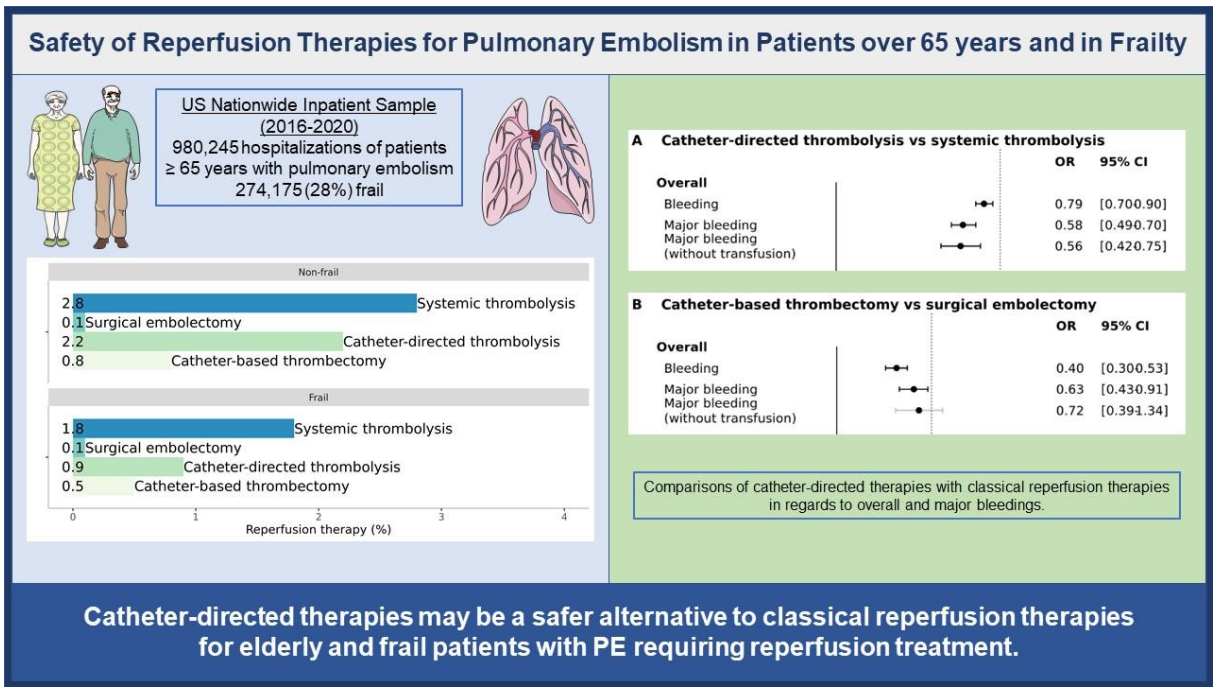
Figure 3. Multivariable logistic regression for overall and major bleeding (with or without transfusion) for catheter-directed thrombolysis vs systemic thrombolysis (A) and catheter-based thrombectomy vs surgical embolectomy (B) in elderly patients with PE according to frailty status. The model was adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, obesity, congestive heart failure, chronic pulmonary disease, and cancer) and high-risk PE. PE: pulmonary embolism

High-risk patients

Among the subgroup of high-risk PE, CDT compared to ST was not associated with reduced incidence of overall or major bleedings, while CBT compared to SE was significantly associated with reduced overall bleedings (OR 0.33, 95% CI 0.21-0.53), but not major bleedings (**Supplementary Figure S3**). The additional analyses based on high- or non-high-risk status can also be seen in **Supplementary Figure S3**.

Discussion

Investigating the NIS of the years 2016 to 2020 the main findings can be summarized as follows (**Central Illustration**): 1) among elderly patients with a diagnosis of PE, the use of reperfusion therapies was increasing in the investigated time period and reached almost 6% in 2020; 2) reperfusion therapies were low among high-risk PE patients and were used only in approximately 2 out of 10 patients with high-risk PE and this was even further decreased in the high-risk PE frail patient subgroup with only 12% undergoing reperfusion therapeutic strategies; 3) CDT and especially CBT use showed continuously increased usage throughout the entire study period; 4) CDT showed lower rates of overall and major bleedings compared to ST and CBT showed lower rates of overall and major bleedings compared to SE.



Central Illustration

Previous analyses have focused on the use of “classical” reperfusion therapies, namely ST and SE. In a German nationwide analysis of the years 2005-2020, the rate in the use of such therapies was low (< 5% and < 0.1%, respectively) in the elderly (> 60 years) population (36). In addition, based on the US NIS data of the years 1999-2008, 23.3% of patients with unstable (high-risk) primary PE hospitalization and age > 60 years received thrombolytic treatment (46). This percentage is comparable to the one based on our analysis of the years 2016-2020 (23.2%) for the use of ST in high-risk primary PE hospitalizations. Similar conclusions apply to the usage rates of SE (47).

More recently, CDT has been increasingly used in the treatment of high-risk as well as intermediate-high risk PE (48) and is also recommended with a class IIa indication in current European guidelines in cases where thrombolysis is contraindicated or has failed (1, 37). Concerning CDT, the ULTIMA and CANARY trials, and also other single-arm trials, have shown hemodynamic amelioration in patients receiving those treatments, however, the mean age of included patients was below 65 years and little efficacy or safety data was mentioned for this particular population (49, 50, 51, 52, 53). In a retrospective analysis of 18 elderly patients receiving CDT only one patients had a bleeding event following the procedure (6), while in a systematic review of ultrasound-assisted CDT, of 611 patients > 60 years the rate of intracranial hemorrhage was 1.1% and of major bleeding 4.9% (54). These results were confirmed in our study, which showed a low rate of intracranial hemorrhage or major bleeding using administrative data of 16,120 elderly patients receiving CDT. In addition, we showed that the rates of overall bleedings, major bleedings, and intracranial hemorrhage were comparable in the CDT group and the group of elderly patients not receiving any reperfusion therapy, suggesting a potential sign of safety for this population, irrespective also of the presence of frailty. However, this safety signal warrants thorough investigation in randomized trials before any concrete recommendation for its use can be given (42).

Fewer data exists on the use of CBT in the elderly population. The FLASH registry recently published results on the use of the FlowTriever aspiration of thromboemboli system and reported a major bleeding rate of 1.4% within 48 hours in a population of PE patients with a mean age of 61 years (55). In the EXTRACT-PE trial using the Indigo aspiration system, rate of major bleeding within 48 hours was also 1.7% among patients with mean age of 59.8 years (56). These results refer to single-arm studies and small inclusion of elderly, and especially frail patients, where the probability of bleeding outcomes is expected to be higher. In our analysis of elderly patients, rates of major bleeding among CBT procedures were higher reaching 9% (12% in patients with frailty) and 3% if we exclude the transfusions, which may be procedural-related; however, the rate of major bleeding in patients receiving no reperfusion was also high at 8% and 2%, with and without transfusions respectively. Compared to SE,

CBT may be associated with reduced bleedings and in-hospital mortality, especially among patients without hemodynamic decompensation. Definite answers on the safety of this relatively novel reperfusion approach for PE, hopefully also among elderly patients, could be provided by currently enrolling randomized controlled trials (ClinicalTrials.gov NCT05684796, NCT05612854, NCT05111613).

Limitations

This study evaluated administrative data and is subject to the limitations of this source of evidence making the results hypothesis-generating. The classification of comorbidities, events and the use of advanced therapies was defined according to ICD-10 codes; therefore, misclassification in a few cases cannot be excluded. Especially for major bleedings, a concrete definition through the use of ICD-10 codes does not exist. As such, we used ICD-10 codes that topographically define major bleeding (e.g., intracranial, intraperitoneal, etc.), as well as ICD-10 codes for transfusion; therefore, we chose bleeding events that are per se defined as major. Furthermore, it is not certain whether the factors defining high-risk were present before or after the PE. Even though adjustment for several clinical factors was performed confounding by indication could influence the results of the analysis (thus patients who did not receive reperfusion treatment might have been the sickest, those at highest bleeding risk, or perhaps those with bleeding already).

Conclusion

In elderly and frail patients with pulmonary embolism, the current use of classic reperfusion treatments (ST or SE) is low, even among high-risk PE hospitalizations, indicating an increasing fear of physicians for bleeding and perioperative complications. The use of CDT has increased and emerges as a promising safe alternative against classical reperfusion therapies for this vulnerable patient population.

Anhang zur Publikation #2: Eine landesweite Analyse von Reperfusionstherapien bei Lungenembolien bei älteren Patienten und bei Gebrechlichkeit

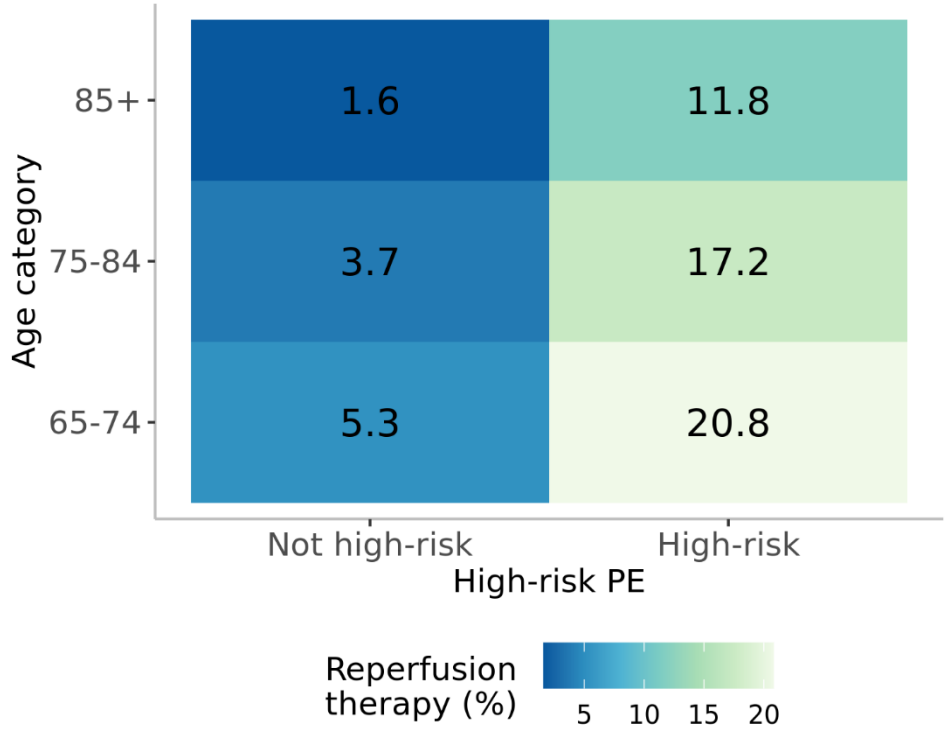
Supplementary Table S1. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS) diagnosis codes.

Diagnosis	**ICD-10-CM**
Pulmonary embolism	I26.01, I26.02, I26.09, I26.90, I26.92, I26.93, I26.94, I26.99
Deep vein thrombosis	I82.220, I82.210, I82.290, I82.401, I82.492, I82.442, I82.432, I82.493, I82.411, I82.421, I82.412, I82.402, I82.4Z2, I82.441, I82.443, I82.413, I82.431, I82.422, I82.4Z1, I82.491, I82.4Z3, I82.403, I82.409, I82.4Y2, I82.4Y3, I82.433, I82.423, I82.4Y1, I82.499, I82.419, I82.439, I82.449, I82.4Z9, I82.429, I82.90
Shock	R57.0, R57.9
Respiratory failure	J96, R09.2
Cardiac arrest	I46.2, I46.8, I46.9
Bleeding	R04.x, R58.x, D62.x, D68.3, D69.9, K62.5, K66.1, K2 [5-8].x, K92.0, K92.1, K92.2, H11.3, H21.0, H31.3, H35.6, H43.1, H45.0, I6[0-2].x, I31.2, J94.2, M25.0, N02.x, N93.9, N95.0, R31, S06.x, S27.1, T79.2
Major bleeding	I60, I61, I62, I31.2, I23.0, J94.2, K66.1, M25
Intracranial hemorrhage	I60, I61, I62
Acute renal failure	N179, N170, N178, N171, N172
Malnutrition	E41, E43
Dementia	F0150, F0151, F0280, F0281, F0390, F0391, G309, G301, G308, G300, G311
Severe visual impairment	H54[018]
Decubitus ulcer	L89
Urinary incontinence	N31, N36.4, N39.4, R15[19]
Weight loss	R627, Z681, R64, R633, R634, R636

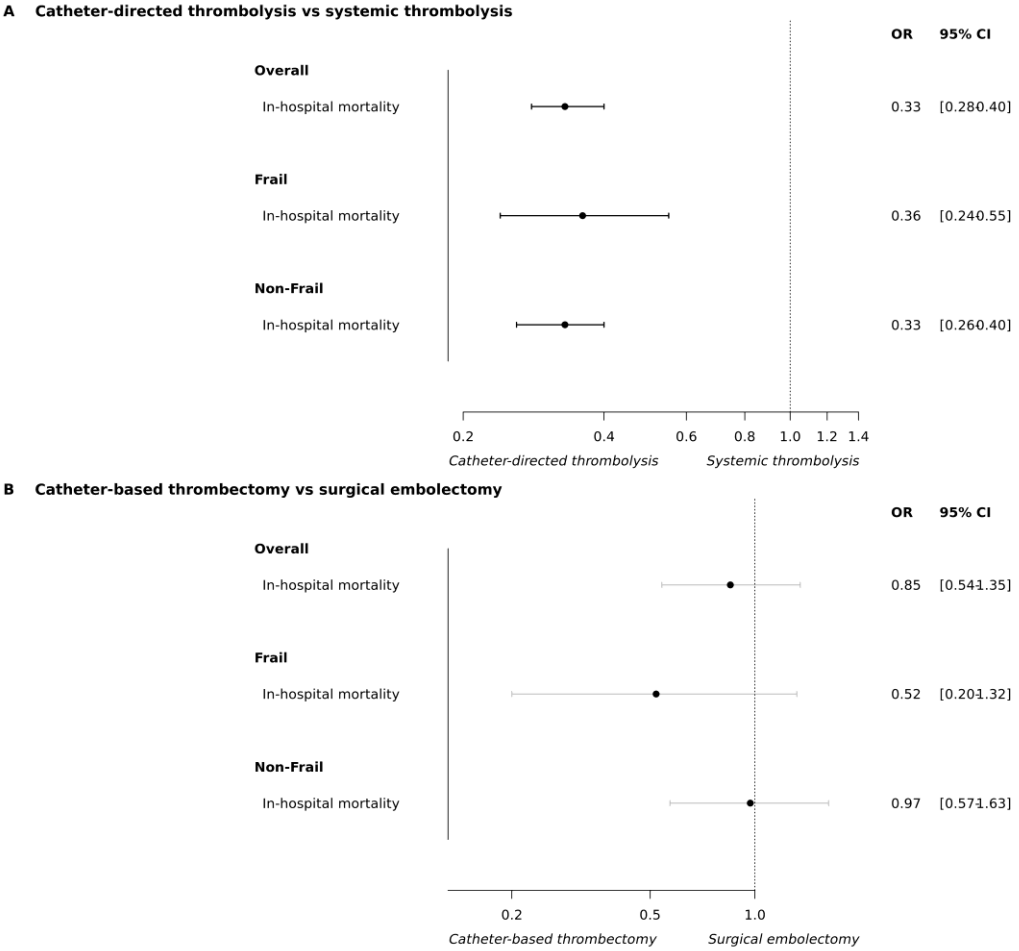
Social support needs	Z59, Z74, Z75, Y93
Difficulty in walking	R26, R27, Z993
Falls	W010XXA, W010XXD, W0110XA, W01198A, W01190A, W0110XD, W01198D, W01118A, W04XXXA, W04XXXD, W04XXXS, W05XXXA, W05XXXD, W05XXXS, W06XXXA, W06XXXD, W06XXXS, W07XXXA, W07XXXD, W07XXXS, W08XXXA, W08XXXD, W08XXXS, W108XXA, W109XXA, W108XXD, W109XXD, W100XXA, W101XXA, W101XXD, W108XXS, W102XXA, W1781XA, W1789XA, W1800XA, W1801XA, W1802XA, W1809XA, W1811XA, W1812XA, W1831XA, W1839XA, W1840XA, W1841XA, W1842XA, W1849XA, W19XXXA
Myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x,
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Obesity	E66, Z68.3, Z68.4
Diabetes mellitus	E10.x, E11.x, E13.x
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Cancer	C.x, D0.x, D3[7-9].x, D4[0-5].x, Z85.x
Procedure	**ICD-10-PCS**
Vasopressor use	3E033XZ, 3E043XZ
Ventilator support	5A1935Z, 5A1945Z, 5A1955Z
Cardiopulmonary resuscitation	5A12012
Systemic thrombolysis	3E03317, 3E04317, 3E05317

Catheter-directed thrombolysis	3E06317, 02FP3Z0, 02FQ3Z0, 02FR3Z0
Catheter-based thrombectomy	02CP3ZZ, 02CQ3ZZ, 02CR3ZZ, 02FP3ZZ, 02FQ3ZZ, 02FR3ZZ
Surgical embolectomy	02CP0ZZ, 02CP4ZZ, 02CQ0ZZ, 02CQ4ZZ, 02CR0ZZ, 02CR4ZZ
Extracorporeal membrane oxygenation	5A1522G, 5A15223
Transfusion	30233N0, 30233N1, 30233P0, 30233P1, 30233H0, 30233H1,30243N0, 30243N1, 30243P0, 30243P1, 30243H0, 30243H1
Renal replacement therapy	5A1D60Z, 5A1D00Z, 5A1D70Z, 5A1D90Z, 5A1D80Z

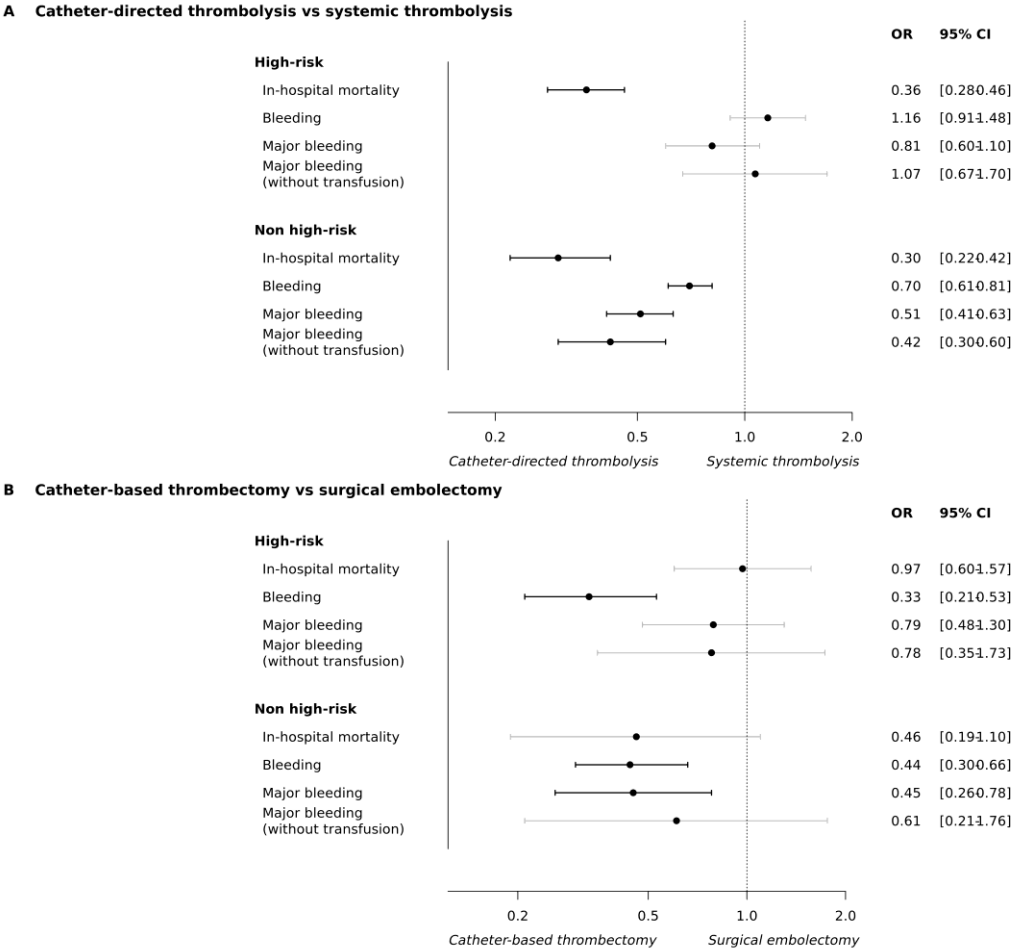
Supplementary Figure S1. Reperfusion rates by age group and high-risk pulmonary embolism.



Supplementary Figure S2. Multivariable regression model for in-hospital mortality.



Supplementary Figure S3. Multivariable regression model for clinical outcomes among high-risk PE.



Publikation #3: Soziale Faktoren der Behandlung und des Ergebnisses einer Lungenembolie

Zitieren:

Farmakis IT, Valerio L, Giannakoulas G, Hobohm L, Cushman M, Piazza G, Konstantinides SV, Barco S. Social determinants of health in pulmonary embolism management and outcome in hospitals: Insights from the United States nationwide inpatient sample. Res Pract Thromb Haemost. 2023 Apr 6;7(3):100147. doi: 10.1016/j.rpth.2023.100147. PMID: 37181280; PMCID: PMC10173008.

Verfügbar in:

Social determinants of health in pulmonary embolism management and outcome in hospitals: Insights from the United States nationwide inpatient sample - ScienceDirect

Abstract

Background: The role of social determinants on the treatment and course of acute pulmonary embolism (PE) is understudied.

Purpose: To investigate the association between social determinants of health with the in-hospital management and early clinical outcomes following acute PE.

Methods: We identified hospitalizations of adults with acute PE discharge diagnosis from the Nationwide Inpatient Sample (NIS) (years 2016-2018). Multivariable regression was used to investigate the association between race/ethnicity, type of expected primary payer, and income with use of advanced PE therapies (thrombolysis, catheter directed treatment, surgical embolectomy, extracorporeal membrane oxygenation), length of stay (LOS), hospitalization charges, and in-hospital death.

Results: A total of 1,124,204 hospitalizations with a PE diagnosis were estimated from the 2016-2018 NIS, corresponding to a hospitalization rate of 14.9/10,000 adult persons-year. The use of advanced therapies was lower in Black and Asian/Pacific Islander (vs. White patients; $OR_{adjusted}$ 0.87, 95%CI 0.81-0.92 and $OR_{adjusted}$ 0.76, 95%CI 0.59-0.98) and in Medicare- or Medicaid-insured (vs. privately-insured; $OR_{adjusted}$ 0.73, 95%CI 0.69-0.77 and 0.68, 95%CI 0.63-0.74), although they had the greatest LOS and hospitalization charges. In-hospital mortality was higher in the lowest income quartile (vs. highest quartile; $OR_{adjusted}$ 1.09, 95%CI 1.02-1.17). Among high-risk PE, patients of other than White race had the highest in-hospital mortality.

Conclusion: We observed inequalities in advanced therapies use for acute PE and higher in-hospital mortality in non-White persons. Low socioeconomic status was also associated with lesser use of advanced treatment modalities and greater in-hospital mortality. Future studies should further explore and consider the long-term impact of social inequities in PE management.

Keywords: pulmonary embolism; social determinants of health; inequality; disparity

Introduction

Social determinants of health encompass “the circumstances in which people are born, grow, live, work, and age, and the systems put in place to deal with illness” (57) and include economic status, race and ethnicity, culture and language, residential environment, social support and inclusion, and access to healthcare. In cardiovascular diseases, tremendous progress has been achieved in reducing mortality over the past several decades. However, the burden of disease remains vast and in absolute numbers cardiovascular disease is the leading cause of death in the United States (US) (58). Many disadvantaged population groups are disproportionately burdened with high cardiovascular risk and outcomes, which may, in turn, further contribute to racial and socioeconomic inequalities (59),(60).

Pulmonary embolism (PE) is the third most common cause of cardiovascular disease mortality, accounting for a major burden of disease in low-, middle-, and high-income countries (36, 61). In the US, PE-related mortality rates plateaued during the last decade, while increasing among young and middle-aged adults (14, 62). There are disparities in the incidence rates and mortality of acute PE across racial and ethnic groups (7, 14). In contrast, higher socioeconomic status is associated with lower venous thromboembolism (VTE) risk (8). However, evidence on associations of the broad range of social determinants of health with PE and its management is sparse and not well characterized.

The aim of this investigation was to assess the associations of several social determinants of health, including socioeconomic status, race and ethnicity, insurance status, and place of residence, with in-hospital management and outcomes of acute PE.

Methods

We used data from the Nationwide Inpatient Sample (NIS) in 2016, 2017, and 2018, provided by the Agency for Healthcare Research and Quality. The NIS database is developed for the Healthcare Cost and Utilization Project (HCUP) and is the largest publicly available all-payer inpatient healthcare database in the United States (US). This data represents ~97% of the US population and contains a 20% stratified sample of discharges from US hospitals that participate in the HCUP, excluding rehabilitation and long-term acute care hospitals. The database contains only de-identified data, and no institutional review board approval was required for this analysis. Additional information on the NIS is available at the HCUP NIS Database Documentation website (www.hcup-us.ahrq.gov).

Study population and data definition

The NIS datasets include up to 40 diagnoses and 25 procedures for each discharge record, which are coded according to the International Classification of Diseases, 10th revision (ICD-10-CM for diagnoses and ICD-10-PCS for procedures). We identified all hospitalizations of adult (≥18 years) patients with a discharge diagnosis of PE as defined by the ICD-10-CM I26.0 and I26.9. We defined high-risk acute PE as hospitalizations with an additional diagnosis of shock (ICD-10-CM R57.0, R57.9), ventilator support (ICD-10-CM Z99.11), cardiac arrest (ICD-10-CM I46.8, I46.9), need for cardiopulmonary resuscitation (ICD-10-PCS 5A12012), or vasopressor use (ICD-10-PCS 3E033XZ, 3E043XZ). We defined a primary PE diagnosis as a first-listed diagnosis code for acute PE (ICD-10-CM I26.0, I26.9) or as a second-listed after a diagnosis code for deep vein thrombosis (ICD-10-CM I82.2, I82.4, I82.9).

The use of advanced therapy during the hospitalization for PE was defined as the use of at least one of the following: systemic thrombolysis, catheter-directed treatment (CDT, including catheter directed thrombolysis and percutaneous thrombectomy), surgical embolectomy, and extracorporeal membrane oxygenation (ECMO). The use of inferior vena cava (IVC) filters was studied separately. We defined the following complications during index PE hospitalization: any bleeding, non-traumatic intracranial hemorrhage (ICD-10-CM I62.), or any adverse effect of thrombolytic drugs (T45.615A) or anticoagulants (T45.515A). The ICD-10 codes used for the definition of the aforementioned variables, and patient comorbidities are presented in **Supplementary Table 1**.

The following social determinants of health were considered: race and ethnicity (non-Hispanic White, and non-White including Black, Hispanic, Asian or Pacific Islander, Native American, or other race), type of primary payer (Medicare, Medicaid, private insurance, or other form), and household income (defined as median household income of residents in the patient's zip code in each respective year and expressed in quartiles. Place of residence was defined as urban, suburban and rural (63). Hospitals were categorized according to location and teaching status (rural, urban teaching, urban non-teaching) and bedsize capacity (small, medium, and large).

Outcomes

We focused on use of any advanced therapy for acute PE, in-hospital mortality, length of stay, and total charges during the hospital stay.

Statistical analysis

Proportions of missing data were below 3% for all variables and we assumed that the missing data were missing at random; hence, we performed a complete case analysis. Categorical

variables were described as counts and percentages, while continuous variables were described with medians and interquartile range (IQR). We used the US Census Bureau population counts for adults ≥18 years to estimate crude hospitalization and mortality rates for PE by racial group or ethnicity, and we estimated 95% confidence intervals (CI) using the Wilson score interval with continuity correction. Logistic regression was used to calculate odds ratios of use of advanced therapies and all-cause in-hospital mortality based on age, sex, race and ethnicity, type of health insurance, and income. We used linear regression with the same independent variables to examine their association with length of stay and total charges during hospital stay. We compared all results for those with normal or high-risk PE. All models were additionally adjusted for variables considered likely to affect the outcome measures, including high-risk PE, primary versus secondary diagnosis of PE, place of residence, hospital location/teaching status, hospital bed size, and history of hypertension, diabetes mellitus, myocardial infarction, cerebrovascular disease, congestive heart failure, renal disease, chronic pulmonary disease, cancer, and dementia. We applied the discharge-level weights provided on the HCUP database to produce national estimates for all analyses. We used clustered covariance estimation to compute clustered confidence intervals to take into account the stratification and hospitals defining the clusters. A two-sided p-value <0.05 indicated statistical significance. We used R (R Project for Statistical Computing, version 3.6.3.) for the statistical analysis.

Results

We estimated a total of 1,124,204 hospitalizations with a PE diagnosis in 2016-2018, of which 615,570 (54.8%) had PE as the primary cause of hospitalization and 66,570 (5.9%) had high-risk PE. The majority of hospitalizations occurred in private, not-for-profit, urban, teaching, large size hospitals. Hospitalized patients had a median age of 65 (IQR 52-75) years, 51% were women, and 29% of non-White race. The primary payer was Medicare in 52%, private or other insurance in 34%, and Medicaid in 14%; 29% resided in zip codes with household income in the lowest quartile. The baseline characteristics of the overall population, and those with high-risk PE are presented in **Table 1**.

Table 1. Baseline characteristics of pulmonary embolism hospitalizations.

Characteristic	**Overall**, N = 1,124,204*	**Not high-risk PE**, N = 1,057,634*	**High-risk PE**, N = 66,570*
Age	64 (52, 75)	64 (52, 75)	65 (54, 75)
Female	578,030 (51%)	546,210 (52%)	31,820 (48%)
Race/Ethnicity			
White	771,780 (71%)	730,175 (72%)	41,605 (65%)
Black	195,045 (18%)	181,290 (18%)	13,755 (22%)
Hispanic	72,420 (6.7%)	67,530 (6.6%)	4,890 (7.7%)
Asian/Pacific Islander	13,985 (1.3%)	12,650 (1.2%)	1,335 (2.1%)
Native American	4,880 (0.4%)	4,605 (0.5%)	275 (0.4%)
Other	26,520 (2.4%)	24,585 (2.4%)	1,935 (3.0%)
Place of residence			
Urban	589,320 (53%)	552,040 (52%)	37,280 (56%)
Suburban	228,755 (20%)	215,785 (20%)	12,970 (20%)
Rural	301,505 (27%)	285,540 (27%)	15,965 (24%)
Health insurance			

Characteristic	**Overall**, N = 1,124,204*	**Not high-risk PE**, N = 1,057,634*	**High-risk PE**, N = 66,570*
Private Insurance	300,840 (27%)	285,775 (27%)	15,065 (23%)
Medicare	588,305 (52%)	551,645 (52%)	36,660 (55%)
Medicaid	156,240 (14%)	146,115 (14%)	10,125 (15%)
Other	77,100 (6.9%)	72,535 (6.9%)	4,565 (6.9%)
Household income			
Income Q1	323,775 (29%)	303,110 (29%)	20,665 (32%)
Income Q2	293,340 (27%)	276,740 (27%)	16,600 (25%)
Income Q3	266,735 (24%)	251,610 (24%)	15,125 (23%)
Income Q4	220,260 (20%)	207,360 (20%)	12,900 (20%)
Hospital bed size			
Large size	589,855 (52%)	549,455 (52%)	40,400 (61%)
Medium size	321,235 (29%)	303,625 (29%)	17,610 (26%)
Small size	213,115 (19%)	204,555 (19%)	8,560 (13%)
Hospital location/teaching status			
Urban teaching	775,780 (69%)	723,840 (68%)	51,940 (78%)

Characteristic	**Overall**, N = 1,124,204*	**Not high-risk PE**, N = 1,057,634*	**High-risk PE**, N = 66,570*
Urban non-teaching	251,680 (22%)	239,905 (23%)	11,775 (18%)
Rural	96,745 (8.6%)	93,890 (8.9%)	2,855 (4.3%)
Hospital ownership			
Private, not-for-profit	855,565 (76%)	805,460 (76%)	50,105 (75%)
Public	128,585 (11%)	119,900 (11%)	8,685 (13%)
Private, investor-owned	140,055 (12%)	132,275 (13%)	7,780 (12%)
Weekend admission	258,855 (23%)	242,520 (23%)	16,335 (25%)
Comorbidities			
Hypertension	677,605 (60%)	637,305 (60%)	40,300 (61%)
Diabetes mellitus	272,960 (24%)	253,015 (24%)	19,945 (30%)
Myocardial infarction	103,130 (9.2%)	90,685 (8.6%)	12,445 (19%)
Cerebrovascular disease	70,345 (6.3%)	62,340 (5.9%)	8,005 (12%)
Congestive heart failure	238,495 (21%)	211,500 (20%)	26,995 (41%)
Renal disease	161,970 (14%)	146,805 (14%)	15,165 (23%)

Characteristic	**Overall**, N = 1,124,204*	**Not high-risk PE**, N = 1,057,634*	**High-risk PE**, N = 66,570*
Chronic pulmonary disease	308,960 (27%)	291,325 (28%)	17,635 (26%)
Cancer	319,755 (28%)	302,970 (29%)	16,785 (25%)
Dementia	69,390 (6.2%)	65,595 (6.2%)	3,795 (5.7%)

The overall hospitalization rate for acute PE was 14.9 per 10,000 adult person-years (95% CI 14.8-14.9). The hospitalization rate was lower in Asian or Pacific Islander (3.0 per 10,000 adult person-years, 95% CI 2.9-3.1), Native American (5.6 per 10,000 adult person-years, 95% CI 5.4-5.7), Hispanic (6.0 per 10,000 adult person-years, 95% CI 5.9-6.1), and White patients (13.1 per 10,000 adult person-years, 95% CI 13.1-13.2) vs. Black patients (20.1 per 10,000 adult person-years, 95% CI 20.0-20.2). Patients of races other than White were more likely to be younger, to belong in the lowest income category (except Asian), to be covered with Medicaid insurance, and to live in urban areas (except Native American) (**Figure 1**).

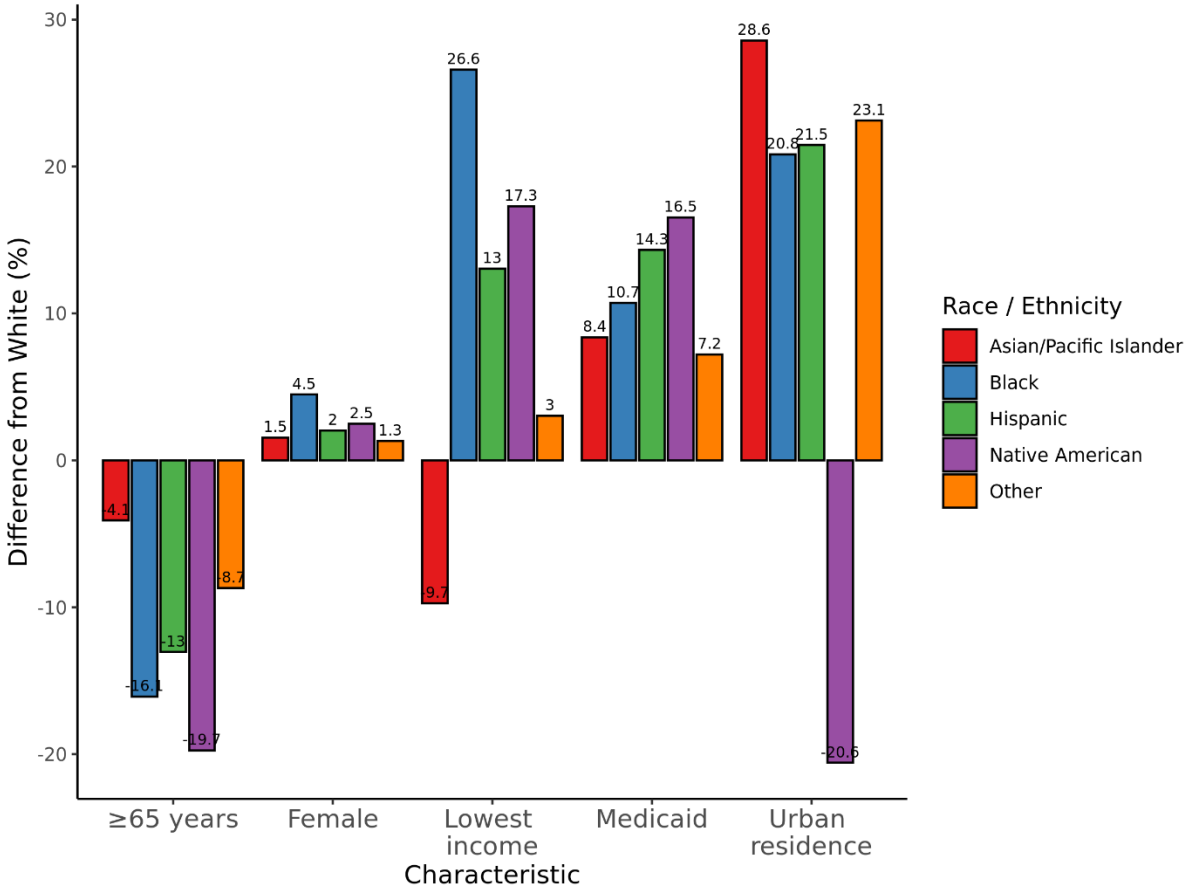


Figure 1. Differences in the prevalence of baseline characteristics among patients of non-White ethnicity/race (Asian/Pacific Islander, Black, Hispanic, Native American, Other) and White race.

A detailed report of baseline characteristics of patients according to race is presented in **Supplementary Table 2**. All races other than White (except for Native Americans) compared with White race were associated with greater odds of presenting with high-risk PE than less severe PE. High-risk PE events were more prevalent in urban teaching hospitals of large size (**Supplementary Figure 1**).

Use of advanced therapies

The use of advanced therapies was reported in 5.5% of all hospitalizations for acute PE (**Table 2**) and in 19% of hospitalizations for high-risk PE.

Table 2. Outcomes in hospitalized patients with acute pulmonary embolism.

Characteristic	**Overall**, N = 1,124,204*	**Not high-risk PE**, N = 1,057,634*	**High-risk PE**, N = 66,570*	**p-value**†
In-hospital mortality	72,305 (6.4%)	39,105 (3.7%)	33,200 (50%)	<0.001
Length of stay, days	4 (2, 8)	4 (2, 8)	8 (3, 17)	<0.001
Total charges, US$	40,469 (21,366, 84,828)	38,345 (20,722, 77,740)	124,160 (58,797, 266,107)	<0.001
Use of any advanced therapy	61,320 (5.5%)	48,375 (4.6%)	12,945 (19%)	<0.001
Bleeding	165,425 (15%)	144,150 (14%)	21,275 (32%)	<0.001
Adverse effect of thrombolysis	890 (<0.1%)	610 (<0.1%)	280 (0.4%)	<0.001
Intracranial hemorrhage (non-traumatic)	3,880 (0.3%)	3,175 (0.3%)	705 (1.1%)	<0.001
Adverse effect of anticoagulants	13,660 (1.2%)	12,545 (1.2%)	1,115 (1.7%)	<0.001

* n/N (%); Median (IQR)

† chi-squared test adjusted by a design effect estimate; Wilcoxon rank-sum test for complex survey samples, ECMO: extracorporeal membrane oxygenation, PE: pulmonary embolism

The use of the different types of advanced therapies is presented in **Figure 2**. Advanced therapies were used less frequently in older patients, female patients, and Black and Asian/Pacific Islander patients; similarly, it was less frequent in patients with Medicare or Medicaid insurance (vs. private insurance).

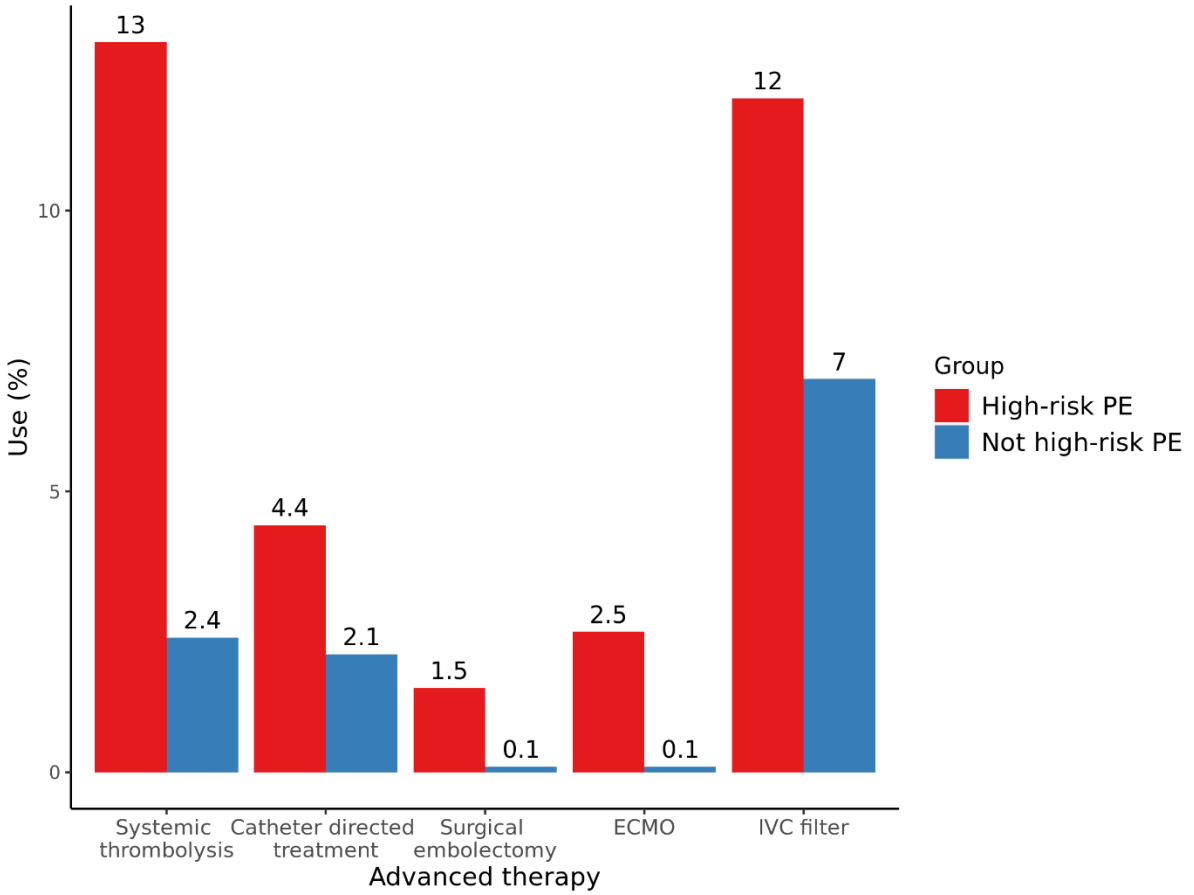


Figure 2. Use of advanced therapies according to the presence of high-risk PE.

ECMO: extracorporeal membrane oxygenation, IVC: inferior vena cava, PE: pulmonary embolism

Risk estimates and reference strata are presented in **Figure 3**. Among high-risk PE patients, the use of any advanced therapy was greater in women, less likely in Asian/Pacific Islander race, in patients with Medicaid insurance, and in patients in the lowest quartile of income; **Figure 3**.

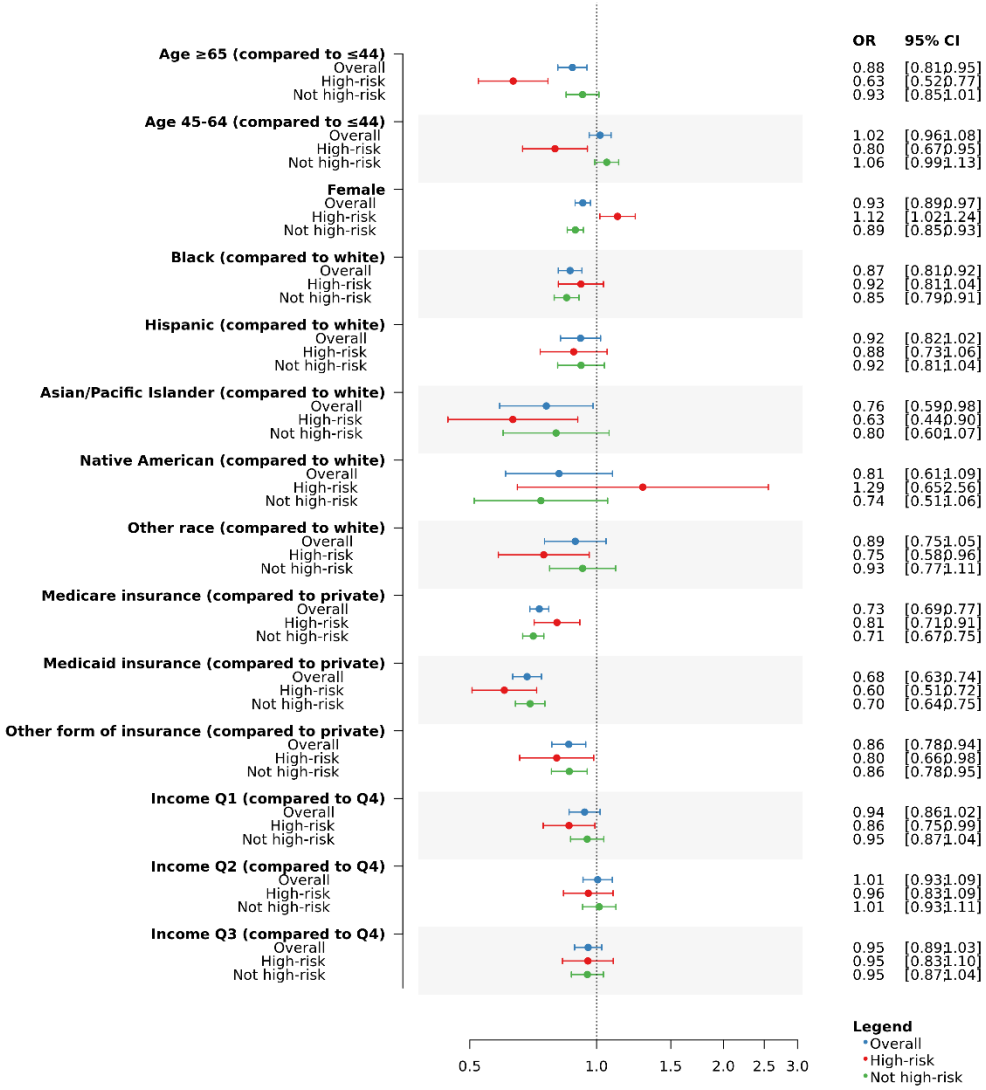


Figure 3. Multivariable logistic regression for the use of advanced therapies in hospitalized patients, overall and in the subgroup of patients with high-risk and no high-risk acute pulmonary embolism.

The model is adjusted for high-risk PE, primary PE hospitalization, place of residence, hospital location/teaching status, hospital bed size, hypertension, diabetes mellitus, myocardial infarction, cerebrovascular disease, congestive heart failure, renal disease, chronic pulmonary disease, cancer, and dementia. The x-axis is plotted on a natural logarithmic scale.

PE: pulmonary embolism

All types of advanced therapy were used less often among patients with Medicaid (**Supplementary Figures 2-6**): this also regarded high-risk PE patients (**Supplementary Figure 2-6**).

In-hospital case fatality rate and mortality

The overall in-hospital case fatality rate was 6.4% (72,305 deaths recorded among 1,124,204 hospitalizations): corresponding to a crude mortality rate of 0.96 (95% CI 0.95-0.97) deaths per 10,000 adult person-years. Older age, as well as Asian/Pacific Islander race compared with White, and the lowest quartile of income in the zip code (vs. highest quartile) was significantly associated with increased in-hospital mortality in the overall population, while Medicaid insurance (vs. private insurance) showed a strong trend towards increased mortality (**Figure 4**). For high-risk patients, the case fatality rate was 50% (33,200 out of 66,570 hospitalizations). In this group, factors related to increased in-hospital mortality included older age and all races other than White (except for Native Americans) compared to White race (**Figure 4**).

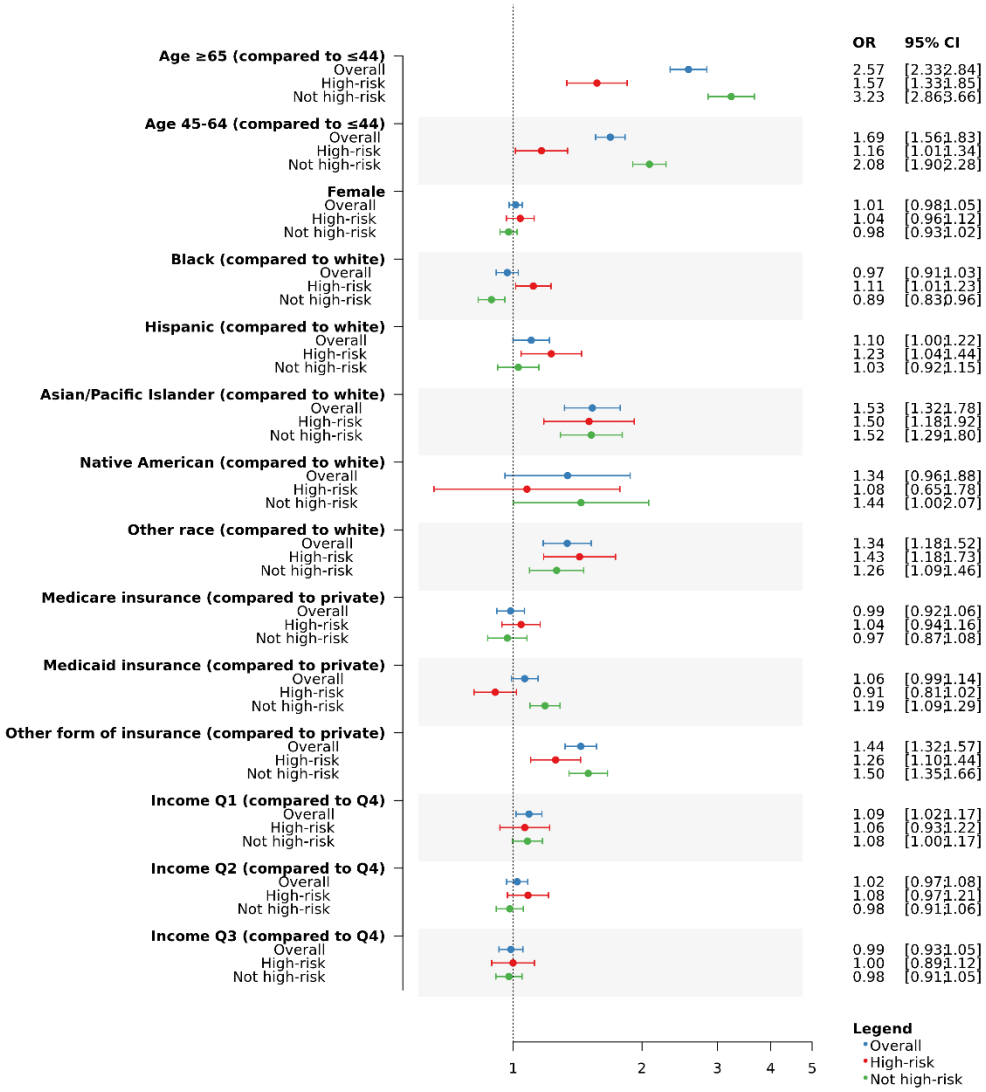


Figure 4. Multivariable logistic regression for in-hospital mortality, overall and in the subgroup of patients with high-risk and no high-risk acute pulmonary embolism.

The model is adjusted for high-risk PE, primary PE hospitalization, use of any advanced therapy, place of residence, hospital location/teaching status, hospital bed size, hypertension, diabetes mellitus, myocardial infarction, cerebrovascular disease, congestive heart failure, renal disease, chronic pulmonary disease, cancer, and dementia. The x-axis is plotted on a natural logarithmic scale. PE: pulmonary embolism

Length of stay and total charges

Overall, the median length of stay in the hospital was 4 days (IQR 2-8 days). Among patients discharged alive, the length of stay was significantly longer in Asian/Pacific Islander patients

(vs. White patients) and patients with Medicare or Medicaid insurance (vs. private insurance), as well as patients in the lowest income quartile in their zip code. Shorter stay was recorded among women and in older patients (**Table 3**).

Table 3. Multivariable linear regression models for factors associated with length of stay and total charges in hospitalized acute pulmonary embolism.

	Length of stay	**Total charges**
Predictors	*Estimates (days)*	*Estimates (US $)*
Age ≤44	*Reference*	*Reference*
Age 45-64	-0.69	-5,291
	(-0.90; -0.48)	(-7,954; -2,629)
Age ≥ 65	-1.12	-13,863
	(-1.43; -0.81)	(-18,352; -9,374)
Male	*Reference*	*Reference*
Female	-0.29	-8,046
	(-0.38; -0.19)	(-10,188; -5,904)
White	*Reference*	*Reference*
Black	0.05	-3,852
	(-0.08; 0.18)	(-8,112; 407)
Hispanic	0.17	21,395
	(-0.07; 0.43)	(14,612; 28,179)
Asian/Pacific Islander	0.62	26,773
	(0.12; 1.13)	(16,403; 37,143)

Native American	0.37 (-0.44; 1.21)	-2,220 (-14,916; 10,476)
Other race	0.75 (0.11; 1.39)	20,120 (6,678; 33,562)
Private Insurance	*Reference*	*Reference*
Medicare	0.56 (0.43; 0.70)	2,875 (224; 5,526)
Medicaid	1.92 (1.62; 2.23)	12,608 (9,095; 16,121)
Other insurance	1.39 (1.17; 1.62)	5,119 (1,347; 8,891)
Higher household income quartile (Q4)	*Reference*	*Reference*
Lowest household income quartile (Q1)	0.23 (0.07; 0.40)	-4,185 (-11,639; 3,269)
Household income quartile Q2	0.05 (-0.08; 0.19)	-4,023 (-10,379; 2,331)
Household income quartile Q3	-0.00 (-0.12; 0.11)	-4,461 (-9,642; 720)

The model is adjusted for all variables listed in the table plus high-risk PE, primary diagnosis of PE in the hospitalization, use of any advanced therapy, place of residence, hospital location/teaching status, hospital bed size, hypertension, diabetes mellitus, myocardial infarction, cerebrovascular disease, congestive heart failure, renal disease, chronic pulmonary disease, cancer, and dementia. 95% confidence interval in brackets.

PE: pulmonary embolism

Overall, the median total charges in the hospital amounted to $40,469 (IQR $21,366-84,828). Among patients discharged alive, the total charges were significantly greater in Hispanic and Asian/Pacific Islander patients (vs. White patients), and patients with Medicare or Medicaid insurance (vs. private insurance), whereas they were lower in older and female patients (**Table 3**).

Discussion

In this retrospective study of the NIS of years 2016-2018, we observed several disparities in the in-hospital management and outcomes of patients with PE that were associated with social factors. Patients of each race or ethnicity other than White (including Black, Hispanic, and Asian/Pacific Islander patients) were more likely to suffer from high-risk PE, indicating increasing PE severity; yet, the use of advanced therapies was lower for such patients in the overall population and in high-risk PE. Among those with high-risk PE, in-hospital mortality appeared greater in all races other than White compared to White patients. Insurance coverage by Medicaid has eligibility criteria that indicate lower socioeconomic status and was strongly associated with lower likelihood to receive treatment with advanced therapies. In addition, belonging to the lowest quartile of income according to the zip code was significantly associated with higher in-hospital mortality.

There is increasing recent research on the association of other than White race with worse clinical outcomes in VTE, and PE in particular. Epidemiological data from the US show that mortality rates related to PE were consistently higher among the Black population during the last 20 years, with an almost 2-fold difference compared with White people (14). The higher hospitalization rates in Black patients than White patients we observed in this national US sample is in line with findings of a previous study based on administrative, visit-level data from the state of Illinois (64). In addition, the hospitalization rates for Asian/Pacific Islander and Hispanic patients were lower than those of White patients; this finding is in line with known racial differences in VTE incidence, but may also reflect barriers to healthcare access (65). In another US study of 10,329 hospitalizations, Phillips et al. showed that Black persons had greater odds for higher PE severity, while also being less likely to receive a catheter-directed or surgical intervention; however, in-hospital mortality rates did not differ (31). These findings are in accordance with our findings of lower use of advanced therapies and no apparent difference in in-hospital mortality rates among Black and White patients in the overall population. However, the effect estimate for mortality in high-risk PE was higher for non-White

(Black, Hispanic, and Asian/Pacific Islander) patients and especially high for Asian/Pacific Islander patients, even though the factors that influence the association to increased mortality are not clear. Douce et al. showed in a national sample that outpatient treatment for DVT was half as frequent in Black compared to White participants, which could be due to social determinants in access to this care (66). Although there are biologic differences pertaining to VTE among discrete races, such as greater levels in various hemostatic and endothelial markers (including factor VIII, von Willebrand factor, plasmin antiplasmin, and D-dimer) in Black patients (67), it is possible that factors accompanying policies reflecting structural racism explain part of our findings, including residential and school segregation. Supporting this, in a study of patients with myocardial infarction (all with the same health insurance) no significant difference in mortality was observed among Black compared to White patients from well-resourced neighborhoods, however, Black Americans from disadvantaged neighborhoods had higher mortality compared with White Americans (68). Altogether, our findings suggest racial and ethnic disparities in the management of acute PE and in the access to advanced treatment modalities. These findings are in line with previous data that report persistent differences between racial/ethnic groups in health care access, utilization, and affordability measures (69). However, whether the results may be also driven by provider discretion cannot be excluded.

There is limited previous data on the influence of socioeconomic disadvantage on short- and long-term outcomes of PE. A recent study among older adults hospitalized for PE in the US showed that the socioeconomically disadvantaged patients received advanced therapy less often, and while they did not have greater in-hospital mortality, they had greater 1-year mortality and 30-day readmission rates (70). In our study, patients with Medicaid insurance were less likely to undergo advanced therapies, even after adjusting for variables including the bed size or the location/teaching status of the hospital. Furthermore, there was a significant association between belonging to the lowest household income (based on zip codes) and increased in-hospital mortality, but also a non-significant trend between Medicaid insurance coverage and increased in-hospital mortality. In addition, we observed a much greater length of stay and cost of hospitalization for Medicaid patients; this suggests a hypothesis that reducing economic disparities may decrease the overall costs for the healthcare system.

These findings are not unique to PE. Also, in the setting of myocardial infarction demographics, race, and socioeconomic disparities have been linked to reduced access to invasive procedures and worse clinical outcomes (71, 72). However, the results of our study may raise awareness at a time when major clinical trials of catheter-directed therapies are currently being designed and conducted for the management of acute PE and which are likely

to increase their — already increasing (48) — use in a much wider scale. Our findings indicate that delivery of clinically appropriate care to more disadvantaged populations may be disproportionately poor; while we used retrospective data that cannot be used to infer causality, our analysis suggests that it cannot be excluded that this disproportion may translate into clinical outcomes. The associations of the different factors (Race, insurance coverage, income) with less advanced therapy use and worse fatality were independent of each other, suggesting these factors act synergistically, i.e., the more factors an individual has the more likely they are to show worse outcome.

Limitations

This study evaluated administrative data and is subject to the limitations of this source of evidence. The study is observational so no causal inferences are possible; the interpretation of the results is hypothesis generating. We were not able to investigate more nuanced social determinants of health, such as the neighborhood area deprivation index, which has been linked to worse health outcomes in other cardiopulmonary diseases (73). The patient's environment and the local availability of healthcare resources plays a major role in the management of acute diseases including PE, since not all management algorithms can be extrapolated in all settings (74). Other factors, such as disease tolerance and psychosocial factors may also delay the care of an acute disease and affect clinical outcome and could vary by race or socioeconomic status (75). In addition, socioeconomic status comprises more parameters than household income, such as individual education and occupation, which we were not able to capture and may influence clinical outcomes. We used median income in each patient's zip code, which might misclassify their individual household income, leading to underestimation of associations. The interrelatedness of the studied social determinants of health is complex and we cannot, based on these data, evaluate with certainty which of the parameters has greater impact on access to the cure and clinical outcomes. This is particularly the case, if one considers that several other determinants of health, notably education quality and level, and demographic variables were not available for analysis. However, we hypothesize that they each act independently. The classification of comorbidities and the use of advanced therapies was defined according to ICD-10 codes; therefore, misclassification is likely. We were also not able to classify patients with PE into typical risk stratification groups, such as low and intermediate risk, except for the high-risk subgroup. That said, we cannot be sure that the factors defining high-risk were present before or after the PE. Lastly, although advanced therapy use, and especially catheter directed treatment, has not been proven to date to improve outcomes in patients without high-risk PE and they are not generally fully indicated by current guidelines, we cannot ascertain their contributing prognostic role and only regard the use of it as a quality of care indicator (1, 76).

Conclusion

This investigation highlights disparities in the in-hospital management of PE according to several social determinants of health. Race/ethnicity other than White and low socioeconomic status measures were associated with lesser use of advanced treatment modalities, such as thrombolysis or catheter-directed interventions. Race/ethnicity other than White was not clearly associated with greater in-hospital mortality except in those with high-risk PE. Low socioeconomic status was associated with higher in-hospital mortality rates. Future studies should investigate if there is a causal relationship between socioeconomic status and in-hospital outcomes, further investigate the long-term impact of social inequities, make an effort to recruit broadly across race/ethnicity and socioeconomic status, and explore ways to mitigate the burden imposed by PE and its complications in minority populations.

Anhang zur Publikation #3: Soziale Faktoren der Behandlung und des Ergebnisses einer Lungenembolie

Supplementary Table 1. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS) diagnosis codes.

Diagnosis	**ICD-10-CM**
Pulmonary embolism	I26.01, I26.02, I26.09, I26.90, I26.92, I26.93, I26.94, I26.99
Deep vein thrombosis	I82.220, I82.210, I82.290, I82.401, I82.492, I82.442, I82.432, I82.493, I82.411, I82.421, I82.412, I82.402, I82.4Z2, I82.441, I82.443, I82.413, I82.431, I82.422, I82.4Z1, I82.491, I82.4Z3, I82.403, I82.409, I82.4Y2, I82.4Y3, I82.433, I82.423, I82.4Y1, I82.499, I82.419, I82.439, I82.449, I82.4Z9, I82.429, I82.90
Shock	R57.0, R57.9
Ventilator support	Z99.11
Cardiac arrest	I46.8, I46.9
Cardiopulmonary resuscitation	5A12012
Vasopressor use	3E033XZ, 3E043XZ
Bleeding	R04.x, R58.x, D62.x, D68.3, D69.9, K62.5, K66.1, K2[5-8].x, K92.0, K92.1, K92.2, H11.3, H21.0, H31.3, H35.6, H43.1, H45.0, I6[0-2].x, I31.2, J94.2, M25.0, N02.x, N93.9, N95.0, R31, S06.x, S27.1, T79.2
Intracranial hemorrhage	I62.9, I62.00, I62.01, I62.03, I62.02, I62.1
Adverse effects of thrombolytic drugs	T45.615A
Adverse effects of anticoagulants	T45.515A
Myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x,
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x,

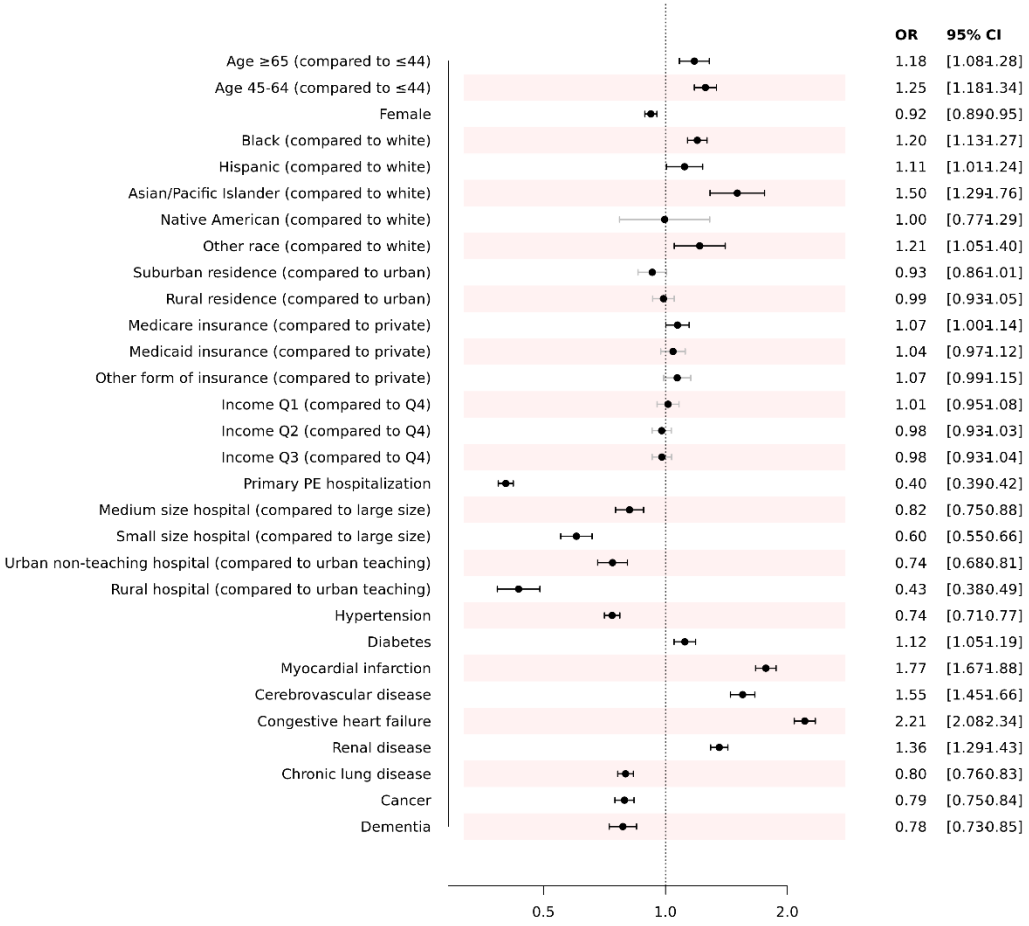
	J68.4, J70.1, J70.3
Diabetes mellitus	E10.x, E11.x, E13.x
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Cancer	C.x, D0.x, D3[7-9].x, D4[0-5].x, Z85.x
Procedure	**ICD-10-PCS**
Systemic thrombolysis	3E03317, 3E04317, 3E05317
Catheter directed treatment	3E06317, 02CP3ZZ, 02CQ3ZZ, 02CR3ZZ, 02FP3Z0, 02FP3ZZ, 02FQ3Z0, 02FQ3ZZ, 02FR3Z0, 02FR3ZZ
Surgical embolectomy	02CP0ZZ, 02CP4ZZ, 02CQ0ZZ, 02CQ4ZZ, 02CR0ZZ, 02CR4ZZ
Extracorporeal membrane oxygenation	5A1522F, 5A1522G, 5A1522H, 5A15223
Inferior vena cava filter	06H03DZ

Supplementary Table 2. Baseline characteristics of pulmonary embolism hospitalizations according to race.

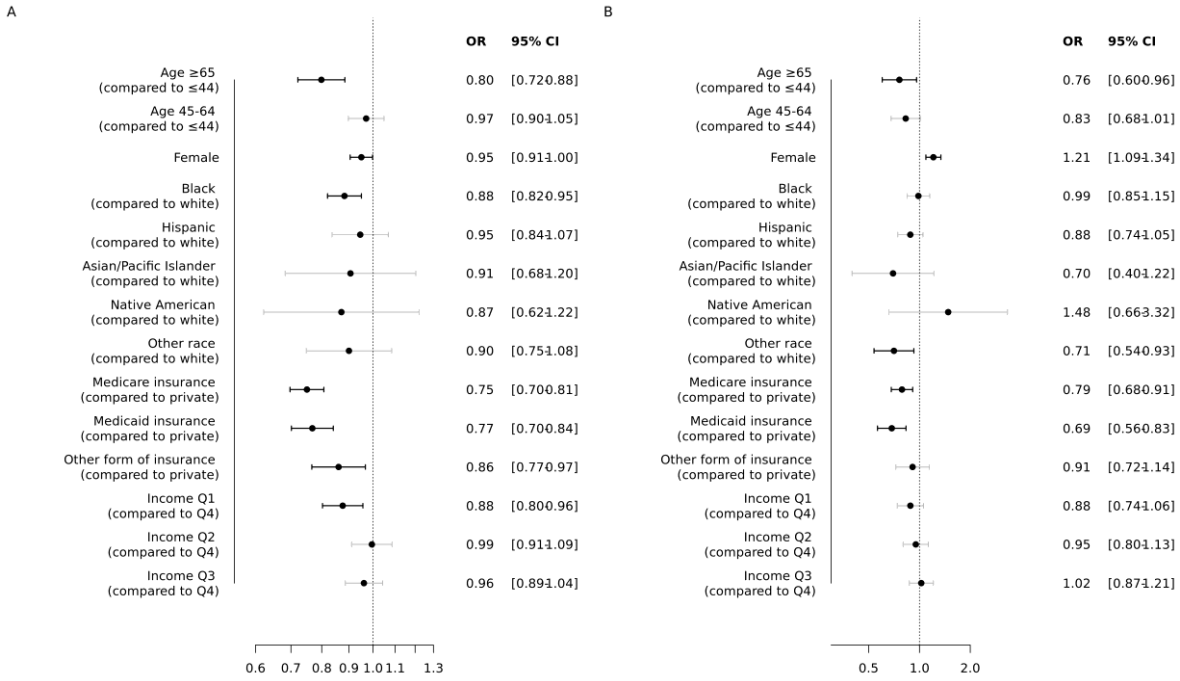
Characteristic	White, N = 771,780	Black, N = 195,045	Hispanic, N = 72,420	Asian/Pacific Islander, N = 13,985	Native American, N = 4,880	Other, N = 26,520	p-value
Age	66 (54, 77)	59 (46, 71)	60 (46, 72)	64 (50, 75)	57 (42, 69)	62 (48, 73)	<0.001
Female	389,555 (50%)	107,190 (55%)	38,025 (53%)	7,275 (52%)	2,585 (53%)	13,735 (52%)	
Place of residence							<0.001
Urban	363,655 (47%)	132,525 (68%)	49,670 (69%)	10,585 (76%)	1,295 (27%)	18,630 (71%)	
Suburban	167,595 (22%)	31,890 (16%)	13,340 (19%)	2,225 (16%)	900 (18%)	3,220 (12%)	
Rural	238,195 (31%)	29,630 (15%)	8,745 (12%)	1,060 (7.6%)	2,685 (55%)	4,320 (17%)	
Health insurance							<0.001
Private Insurance	210,975 (27%)	47,395 (24%)	16,965 (23%)	4,395 (31%)	930 (19%)	7,590 (29%)	
Medicare	431,735 (56%)	87,535 (45%)	29,655 (41%)	6,040 (43%)	2,090 (43%)	11,465 (43%)	

Characteristic	White, N = 771,780	Black, N = 195,045	Hispanic, N = 72,420	Asian/Pacific Islander, N = 13,985	Native American, N = 4,880	Other, N = 26,520	p-value
Medicaid	82,755 (11%)	41,815 (21%)	18,140 (25%)	2,670 (19%)	1,330 (28%)	4,755 (18%)	
Other	45,250 (5.9%)	17,990 (9.2%)	7,590 (10%)	875 (6.3%)	470 (9.8%)	2,700 (10%)	
Household income							<0.001
Income Q1 (lowest)	180,485 (24%)	97,490 (51%)	26,385 (37%)	1,910 (14%)	1,985 (43%)	7,005 (27%)	
Income Q2	212,515 (28%)	41,370 (22%)	17,930 (25%)	2,470 (18%)	1,180 (26%)	6,030 (23%)	
Income Q3	197,920 (26%)	31,965 (17%)	15,780 (22%)	3,435 (25%)	885 (19%)	5,805 (23%)	
Income Q4 (highest)	167,780 (22%)	20,870 (11%)	10,765 (15%)	5,935 (43%)	575 (12%)	6,930 (27%)	
Weekend admission	176,180 (23%)	46,230 (24%)	16,950 (23%)	3,265 (23%)	1,125 (23%)	5,975 (23%)	

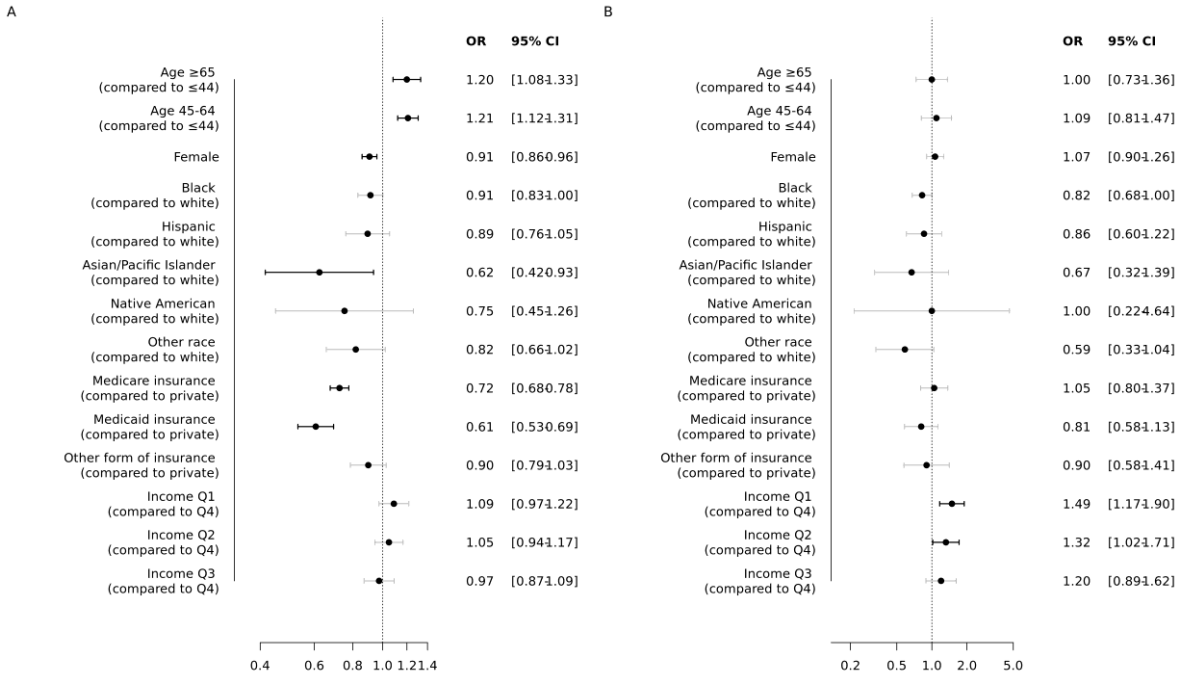
Supplementary Figure 1. Multivariable regression model for factors associated with high-risk pulmonary embolism hospitalization.



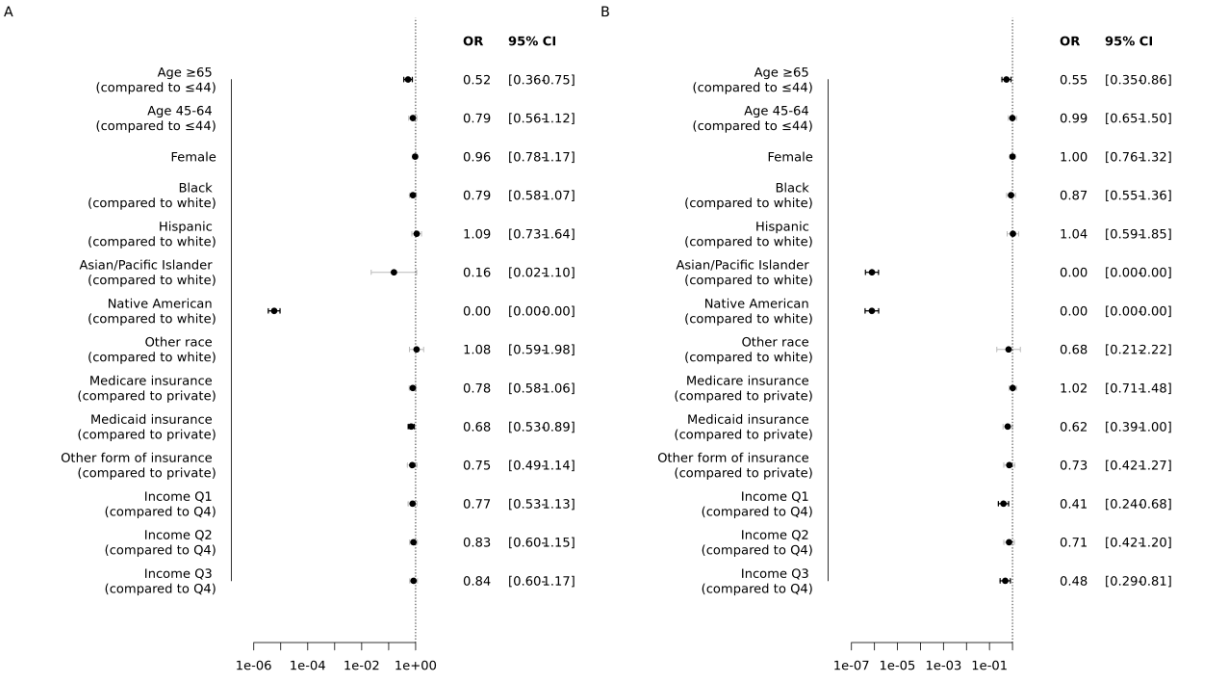
Supplementary Figure 2. Multivariable regression models for the use of systemic thrombolysis, overall (A) and in the subgroup of patients with high-risk acute pulmonary embolism (B)



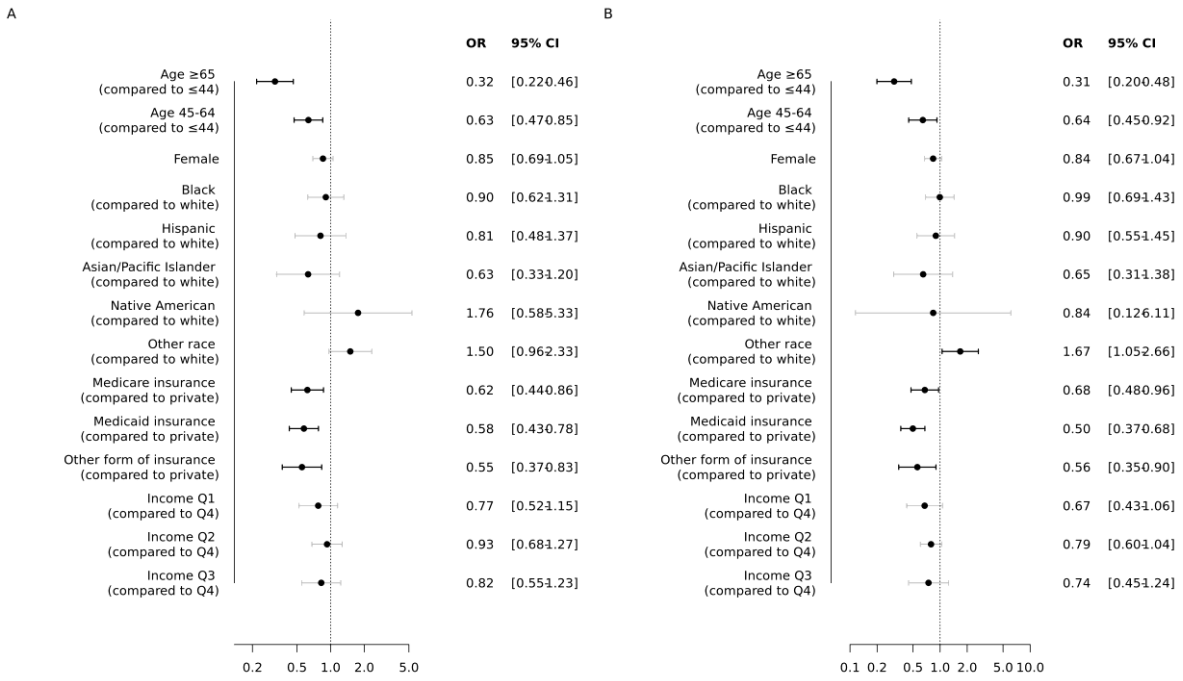
Supplementary Figure 3. Multivariable regression models for the use of catheter directed treatment, overall (A) and in the subgroup of patients with high-risk acute pulmonary embolism (B)



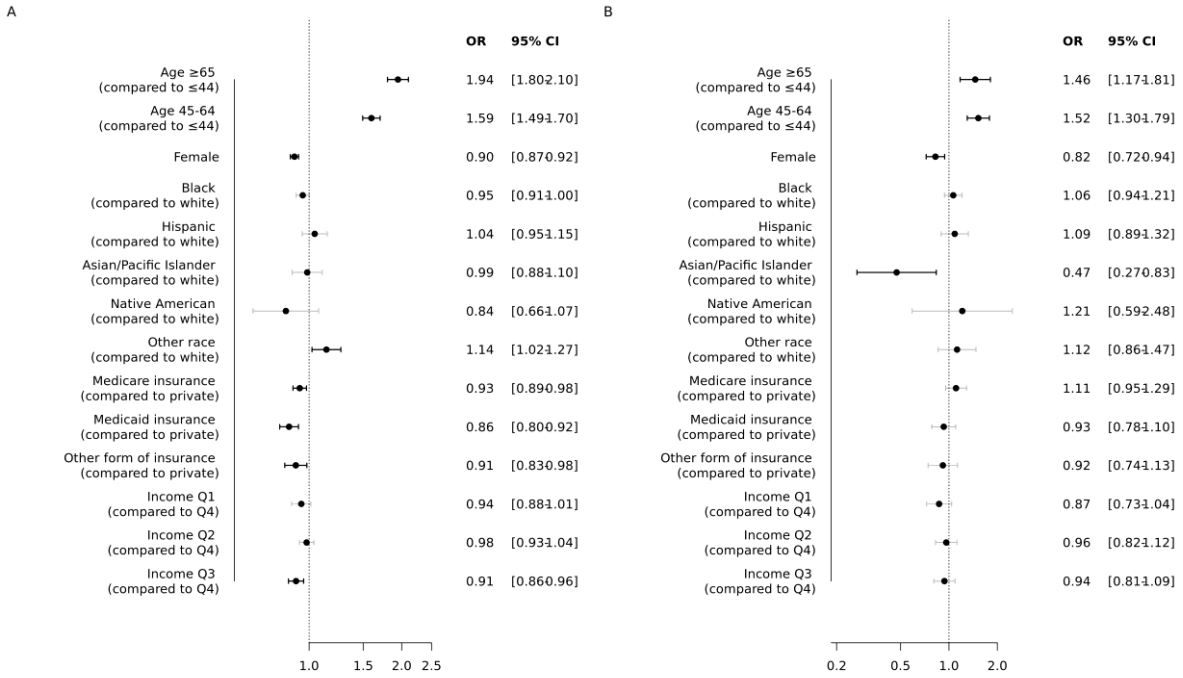
Supplementary Figure 4. Multivariable regression models for the use of surgical embolectomy, overall (A) and in the subgroup of patients with high-risk acute pulmonary embolism (B)



Supplementary Figure 5. Multivariable regression models for the use of extracorporeal membrane oxygenation, overall (A) and in the subgroup of patients with high-risk acute pulmonary embolism (B)



Supplementary Figure 6. Multivariable regression models for the use of inferior vena cava filter, overall (A) and in the subgroup of patients with high-risk acute pulmonary embolism (B)



Diskussion

Die Lungenembolie (LE) ist die schwerste Form der venösen Thromboembolie (VTE) und nach Herzinfarkt und Schlaganfall die dritthäufigste Ursache für kardiovaskuläre Todesfälle (77). In den letzten Jahren wurden große Fortschritte bei der Behandlung dieser akuten Erkrankung erzielt, wodurch die Sterblichkeitsrate gesunken und die Prognose verbessert werden konnte (2, 78). Insbesondere wurden die Risikostratifizierungskriterien und die entsprechenden Managementalgorithmen umfassend angepasst, was zu einer Verbesserung der kurz- und langfristigen Prognose geführt hat. Dies verdeutlicht den Nutzen der evidenzbasierten Medizin auch im Bereich der LE.

Es ist jedoch ein häufiges Problem und eine Einschränkung der meisten bisherigen klinischen Studien, dass gefährdete („vulnerable“) oder benachteiligte Bevölkerungsgruppen ausgeschlossen werden. Diese begrenzte Inklusivität klinischer Studien ist in der kardiovaskulären Medizin üblich und verhindert die Verallgemeinerung der Ergebnisse. Die großen klinischen Studien zu direkten oralen Antikoagulantien (DOACs) zur Sekundärprävention von VTE, die insgesamt mehr als 20 000 Patienten umfassten, sind ein klassisches Beispiel für dieses Phänomen (79, 80, 81, 82). So lag das Durchschnittsalter der eingeschlossenen Bevölkerung in all diesen Studien unter 60 Jahren. Dies steht im Widerspruch zur Epidemiologie der VTE, worin das Alter nachweislich ein bedeutender unabhängiger Risikofaktor für die Entwicklung einer VTE ist. Darüber hinaus ist auch die fehlende ethnische Vielfalt ein Problem bei diesen Studien. Die Phase-III-Studie RE-COVER zu Dabigartan schloss zu 95 % die weiße Bevölkerung ein (79), während die Phase-III-Studie HOKUSAI VTE zu Edoxaban zu 70 % die kaukasische Bevölkerung einschloss (82). Die entsprechenden Gruppenanteile für die Phase-III-Studie EINSTEIN-PE zu Rivaroxaban und die Phase-III-Studie AMPLIFY zu Apixaban sind in den Veröffentlichungen nicht angegeben (80, 81). Es ist auch zu erwarten, dass die an der Durchführung solcher Studien beteiligten Zentren zumeist akademisch und in städtischen Gebieten angesiedelt waren, so dass Patient:innen in ländlichen Gebieten oder in Gebieten mit eingeschränktem Zugang zur Maximalversorgung eher ausgeschlossen wurden (83). Ein häufiges Ausschlusskriterium für diese Studien ist schließlich die Schwangerschaft, was jedoch gerechtfertigt ist, da die Sicherheit sowohl der Vitamin K-Antagonisten als auch der direkten oralen Antikoagulanzien in der Schwangerschaft fraglich oder nicht gegeben ist.

Die begrenzte Inklusivität klinischer Studien zur LE führt zu dem Paradox, dass für Bevölkerungsgruppen, die besonders LE-gefährdet sind, wie z. B. Patienten schwarzer Hautfarbe, mit niedrigem sozioökonomischem Status, ältere und gebrechliche Patienten oder schwangere Frauen, keine wertvollen klinischen Daten für das Management dieser Erkrankung vorliegen. Die Behandlung der akuten LE befindet sich derzeit an einem

entscheidenden Wendepunkt. Neue kathetergestützte Therapien bieten eine Alternative für die Reperfusionsbehandlung von Patient:innen mit schwerer LE, die bis vor kurzem nur mit systemischer Thrombolyse oder chirurgischer Embolektomie behandelt werden konnten. Diese Therapien sind zwar für die Behandlung der akuten LE zugelassen, werden aber in den aktuellen Leitlinien nur bedingt als Alternative zur systemischen Thrombolyse empfohlen, und zwar nur für Patient:innen der höchsten Risikokategorie, d. h. für jene mit hämodynamischer Instabilität (84). Derzeit werden klinische Studien durchgeführt, die ausreichend aussagekräftig sein werden, um die Wirksamkeit und Sicherheit der kathetergestützten Therapien bei der Behandlung der akuten LE nachzuweisen (42, 85). Es ist wahrscheinlich, dass es nach der Veröffentlichung dieser Studien zu einer erweiterten Indikation für die Reperfusionsbehandlung bei einem weitaus größeren Anteil von Patient:innen mit akuter LE kommen kann.

Daher ist es von entscheidender Bedeutung, Daten für das aktuelle Management und die Prognose der LE für diese besonders gefährdeten oder unterrepräsentierten Bevölkerungsgruppen bereitzustellen. Die Ergebnisse der vorliegenden Dissertation sollten die Lücken in der Literatur schließen, indem sie auf drei verschiedene, aber hoch relevante Patientengruppen fokussierten: 1) schwangere Patientinnen 2) Patienten im höheren Alter und mit Gebrechlichkeit und 3) Patient:innen mit sozialen Benachteiligungen,.

Das Ziel der ersten Veröffentlichung dieser kumulativen Dissertation war, einen tieferen Einblick in die Epidemiologie der Schwangerschafts-assoziierten LE zu gewinnen. In den letzten 20 Jahren zeigen epidemiologische Daten für die Gesamtbevölkerung, dass die LE-bedingte Sterblichkeitsrate in Europa und in den USA rückläufig ist, wobei in letzter Zeit ein Plateau erreicht wurde (13, 14). Die in dieser Arbeit vorgestellten Ergebnisse zeigen, dass die Müttersterblichkeitsrate in den letzten 20 Jahren weitgehend unverändert geblieben ist (19). Somit besteht eine Abweichung vom Trend der LE-bedingten Akutletalität in der Allgemeinbevölkerung, welche rückläufig ist. Wir würden erwarten, dass die LE-bedingten Sterblichkeitsraten in dieser gefährdeten Bevölkerungsgruppe ebenfalls zurückgehen, da LE eine vermeidbare Todesursache ist und die Schwangerschaft sowie die frühe postpartale Phase ein bekanntermaßen signifikanter Risikofaktor für LE ist. Wir konnten jedoch keinen solchen Rückgang feststellen. Dieses Ergebnis wird durch eine retrospektive Analyse von Elgendy et al. unterstützt, aus der hervorgeht, dass sich die Raten der akuten LE pro 100.000 schwangerschaftsbedingte Krankenhausaufenthalte zwischen 2007 und 2015 nicht wesentlich verändert haben (26).

Zur Erklärung dieser Ergebnisse können mehrere Faktoren herangezogen werden, die von großer Bedeutung sind, da die LE nach wie vor eine wichtige Ursache für die Müttersterblichkeit ist und im Jahr 2020 zu 8,2 % aller Todesfälle bei Müttern beigetragen hat:

1. Unabhängig von der Behandlung der mütterlichen PE sind kardiovaskuläre Risikofaktoren, wie Adipositas (27), Bluthochdruck (28), und Rauchen bei jüngeren Frauen nach wie vor häufig und können zu einer großen Zahl von potenziell schwereren Fällen von PE während und nach der Schwangerschaft führen. Diese Unterschiede könnten auch die höhere Prävalenz kardiovaskulärer Todesursachen in späteren Phasen des Lebens erklären (29).
2. Die Thromboseprophylaxe könnte eine weitere mögliche Ursache für die beobachteten Trends sein (30). Die Daten aus MBRRACE-UK („Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK“) im Vereinigten Königreich deuten zwar darauf hin, dass die Zahl der Todesfälle durch VTE bei Müttern nach der Einführung von Thromboseprophylaxe-Leitlinien zurückgegangen ist, doch sind diese Daten uneinheitlich und betreffen nur einen kleinen Prozentsatz der schwangeren Frauen, d. h. diejenigen mit einem früheren VTE-Ereignis oder einer Häufung von Risikofaktoren.
3. Es gibt nur sehr wenig Daten zu der Akutbehandlung der PE bei schwangeren oder stillenden Frauen, da sie von randomisierten kontrollierten Studien weitgehend ausgeschlossen sind. Eine Hochrisiko-LE in der Schwangerschaft kann ein verheerendes Ereignis sein, das mit einer Sterblichkeitsrate von bis zu 37 % einhergeht (4). Die Schwangerschaft gilt als relative Kontraindikation für den Einsatz der systemischen Thrombolyse, da die peripartale Phase und die frühe postpartale Phase (der Zeitraum, in dem die meisten LE-Fälle auftreten) mit einem hohen Blutungsrisiko verbunden sind. Daher wird die Thrombolyse nur spärlich eingesetzt und als letzte Möglichkeit betrachtet. Neuere kathetergestützte Therapien sind in der Schwangerschaft nicht untersucht worden, und in der Literatur wurden bisher nur wenige Fälle veröffentlicht (86, 87, 88). Dennoch bleibt die Antikoagulation die Hauptstütze der Behandlung in der Schwangerschaft (84). Niedermolekulares Heparin passiert die Plazenta nicht und wird nicht mit den teratogenen Wirkungen in Verbindung gebracht, die bei Vitamin-K-Antagonisten vor allem im ersten Trimenon beobachtet wurden; daher können sie sicher verabreicht werden (30). Dennoch gibt es auch in diesem Bereich einen Mangel an spezifischen randomisierten Daten, und die Dosierungsstrategien in der schwangeren Bevölkerung folgen denen der allgemeinen Bevölkerung (89). Direkte orale Antikoagulanzien sind in der Schwangerschaft kontraindiziert, da auch hier keine ausreichenden Sicherheitsdaten für diese gefährdete Bevölkerungsgruppe vorliegen (90, 91).

Zusammengenommen könnten all diese Faktoren die in dieser Arbeit berichteten stagnierenden Sterblichkeitsraten teilweise erklären. Das Risiko war auch bei schwangeren Frauen schwarzer Hautfarbe höher, was möglicherweise soziale Faktoren und Ungleichheiten

im Gesundheitswesen widerspiegelt, wie in der dritten Veröffentlichung aus der vorliegenden Dissertation hervorgehoben wird (14, 31). Obwohl es in jüngster Zeit durch die Validierung von Diagnosealgorithmen für PE bei schwangeren Frauen insgesamt zu einer Verbesserung der LE-Erkennung in dieser Situation gekommen ist (92), wird dieses Paradigma in Studien zur Behandlung von Patienten mit schwerer LE nicht berücksichtigt. Die Planung und Durchführung solcher Studien sind eine besondere Herausforderung, wenn man die Besonderheiten dieser Bevölkerungsgruppe und die begrenzte Zahl der Fälle berücksichtigt. Wie die Ergebnisse der vorliegenden Arbeit jedoch zeigen, trägt die Sterblichkeit im Zusammenhang mit der PE nach wie vor erheblich zur Gesamtmüttersterblichkeit (und der fötalen Sterblichkeit) bei, die nicht dem in der übrigen Bevölkerung beobachteten rückläufigen Trend folgt. Weitere wertvolle Erkenntnisse diesbezüglich könnten in Zukunft aus großen multizentrischen internationalen Registern gewonnen werden.

In der zweiten Veröffentlichung dieser kumulativen Arbeit wurde ein besonderes Augenmerk auf die Patient:innen gelegt, bei denen sowohl die Prävalenz von LE als auch die Inzidenz von Komplikationen ihrer Therapie höher sind, nämlich ältere und gebrechliche Menschen. In der Literatur fanden sich in den letzten 20 Jahren Daten zum Einsatz "klassischer" Reperfusionstherapien, nämlich der systemischen Thrombolyse und der chirurgischen Embolektomie. So wurde in einer deutschlandweiten Analyse die systemische Thrombolyse bei <5 % und die chirurgische Embolektomie bei <0,1 % der älteren Bevölkerung mit PE (definiert als über 60 Jahre) eingesetzt (36). In früheren US-Analysen waren die Ergebnisse ähnlich (46, 47). Ein fortgeschrittenes Alter über 75 Jahre wird häufig als relative Kontraindikation gegen eine systemische Thrombolyse genannt. Diese Kontraindikation ergibt sich vor allem aus dem überhöhten Risiko für schwere extrakranielle Blutungen, das in der PEITHO-Studie bei älteren Patient:innenen eine Rate von 11,1 % erreichte (38). Andererseits besteht bei älteren und gebrechlichen Patienten auch ein hohes chirurgisches Risiko, was die Entscheidung zu einer chirurgischen Embolektomie, insbesondere in instabilen Hochrisikosituationen, erheblich erschwert (39, 40). Für diese Patient:innen sind daher alternative Reperfusionsstrategien erforderlich.

In der Dissertation wurde gezeigt, dass die Reperfusionstherapien bei älteren Menschen nur in etwa 20 % der Fälle mit Hochrisiko-LE eingesetzt wurden. Dieser Anteil war in der Untergruppe der gebrechlichen Hochrisiko-LE-Patient:innen sogar noch geringer: Nur 12 % unterzogen sich einer Reperfusionstherapie. Kathetergestützte Therapien bieten eine neue, vermutlich sicherere Alternative für die Behandlung der akuten mittelschweren und hochriskanten LE. Dabei handelt es sich um perkutane Behandlungsoptionen, die hauptsächlich von interventionellen Kardiologen oder Radiologen durchgeführt werden (93). Obwohl es viele verschiedene intravaskuläre Systeme gibt, können diese Therapien prinzipiell in zwei verschiedene Kategorien eingeteilt werden: kathetergestützte pharmakomechanische

Thrombolyse und kathetergestützte rein mechanische Thrombektomie (93, 94). Der Einsatz der kathetergestützten Thrombolyse und insbesondere der kathetergestützten Thrombektomie nahm während des gesamten Studienzeitraums kontinuierlich zu - ein wesentliches Merkmal, das ihre zentrale zukünftige Rolle unterstreicht.

Die kathetergestützte Thrombolyse wird zunehmend zur Behandlung von LE mit hohem und intermediär-hohem Risiko eingesetzt (48). Sie wird auch in den aktuellen europäischen Leitlinien in Fällen empfohlen, in denen eine Thrombolyse kontraindiziert ist oder versagt hat (1, 37). Publiziert sind zwei kleine randomisierte kontrollierte Studien, die ULTIMA- und die CANARY-Studie, die bei Patienten, die diese Behandlungen erhielten, eine Verbesserung der Hämodynamik im Vergleich zur alleinigen Antikoagulation zeigten (49, 50). Mehrere andere einarmige Studien haben unterstützende Daten für die Wirksamkeit und Sicherheit der kathetergestützten Thrombolyse geliefert (41, 51, 52, 94). Der Anteil älterer Teilnehmer:innen in diese Studien war jedoch sehr begrenzt, und das Durchschnittsalter der eingeschlossenen Patienten lag unter 65 Jahren. Für diese spezielle Bevölkerungsgruppe wurden nur wenige Daten zur Wirksamkeit oder Sicherheit veröffentlicht. In einer retrospektiven Analyse von 18 älteren Patienten, die eine kathetergestützte Thrombolyse erhielten, kam es nur bei einem Patienten zu einem Blutungsereignis nach dem Verfahren (6) und in einer anderen retrospektiven Analyse von 19 Patienten, die eine ultraschallgestützte kathetergestützte Thrombolyse erhielten, gab es keine Todesfälle oder Blutungskomplikationen im Krankenhaus (95). In einer systematischen Analyse der ultraschallassistierten kathetergestützten Thrombolyse lag die Rate der intrakraniellen Blutungen bei über 60-Jährigen bei 1,1 % und die der schweren Blutungen bei 4,9 % (54). Diese Ergebnisse wurden durch die Ergebnisse der vorliegenden Studie bestätigt, in der eine niedrige Rate an intrakraniellen Blutungen oder größeren Blutungen festgestellt wurde. Darüber hinaus waren die Raten von Gesamtblutungen, größeren Blutungen und intrakraniellen Blutungen in der Gruppe mit kathetergestützter Thrombolyse vergleichbar mit den Raten in der Gruppe der älteren Patienten, die keine Reperfusionstherapie erhielten. Dieses Ergebnis deutet auf ein gutes Sicherheitsprofil der aktuell verwendeten Katheter-Thrombolysesysteme und -verfahren in dieser Hochrisikopopulation hin, insbesondere unter Berücksichtigung der Tatsache, dass Alter ein Risikofaktor für Blutungen ist, und zwar unabhängig vom Vorliegen einer Gebrechlichkeit. Dieses Sicherheitssignal muss allerdings in randomisierten kontrollierten Studien geprüft werden, bevor eine konkrete Empfehlung für den Einsatz der kathetergestützten Thrombolyse in der älteren Bevölkerung gegeben werden kann (42).

Über den Einsatz der kathetergestützten mechanischen Thrombektomie oder mechanischen Aspiration liegen bei älteren Menschen weniger Daten vor. Vor kurzem wurden die Ergebnisse des FLASH-Registers veröffentlicht, eines multizentrischen, von der Industrie gesponserten Registers für die Verwendung des FlowTriever-Systems zur Aspiration von

Thromboembolien. In diesem Register wurde eine Rate schwerer Blutungen von 1,4 % innerhalb von 48 Stunden in einer Population von LE-Patienten mit einem Durchschnittsalter von 61 Jahren festgestellt (55). In der EXTRACT-PE-Studie, die sich auf die Verwendung des Indigo-Absaugsystems konzentrierte, war die Rate schwerer Blutungen innerhalb von 48 Stunden mit 1,7 % bei Patienten mit einem Durchschnittsalter von 59,8 Jahren ebenfalls vergleichbar (56). In einer Meta-Analyse einarmiger Studien zu mechanischen Aspirationssystemen mit einem Patienten-Durchschnittsalter von 58 Jahren lag die Rate schwerer Blutungen bei 4% (96). Wie bei den Studien zur kathetergestützten Thrombolyse ist die Extrapolation der Ergebnisse aus Studien zur kathetergestützten Thrombektomie auf die ältere Bevölkerung sehr schwierig, da sie nur zu einem kleinen Teil ältere und insbesondere gebrechliche mit hohem Blutungsrisiko einschlossen. In der Analyse dieser Arbeit lag die Rate schwerer Blutungen bei der kathetergestützten Thrombektomie mit 9 % (12 % bei Patienten mit Gebrechlichkeit) deutlich höher. Auch die Rate schwerer Blutungen bei Patienten, die keine Reperfusion erhielten, war mit 8 % hoch. Im Vergleich zur chirurgischen Embolektomie kann die kathetergestützte Thrombektomie jedoch mit einer geringeren Anzahl von Blutungen und einer geringeren Sterblichkeit im Krankenhaus verbunden sein, insbesondere bei Patienten ohne hämodynamische Dekompensation. Derzeit laufende randomisierte kontrollierte Studien könnten endgültige Antworten auf die Frage nach der Sicherheit dieser relativ neuen Reperfusionsmethoden bei LE liefern, hoffentlich auch bei älteren Patienten (ClinicalTrials.gov NCT05684796, NCT05612854, NCT05111613) (85).

In der dritten Veröffentlichung dieser kumulativen Arbeit wurden mehrere Ungleichheiten bei der Behandlung und den Ereignissen bei Patient:innen mit LE im Krankenhaus festgestellt, die mit sozialen Faktoren in Verbindung gebracht wurden. Patient:innen mit schwarzer, hispanischer und asiatisch-pazifischer Hautfarbe/ethnischer Zugehörigkeit litten häufiger an einer Hochrisiko-LE als jene mit weißer Hautfarbe/ethnischer Zugehörigkeit. Dies lässt vermuten, dass in diesen Bevölkerungsgruppen vielleicht länger abgewartet wird, bis fortgeschrittene Reperfusionstherapien eingesetzt werden. Diese Unterschiede in der Behandlung scheinen sich auf den klinischen Verlauf und Ergebnisse auszuwirken, denn die Sterblichkeit im Krankenhaus war bei Patienten mit Hochrisiko-LE und „nicht-weißen“ ethnischen Gruppen höher als bei weißen Patient:innen. Außerdem wurden Patienten, die Kriterien eines niedrigeren sozioökonomischen Status erfüllten, seltener mit fortgeschrittenen Reperfusionstherapien behandelt. Darüber hinaus war die Zugehörigkeit zum untersten Einkommensquartil signifikant mit einer höheren Sterblichkeit im Krankenhaus verbunden.

Diese Befunde gelten nicht nur für die LE, sondern auch für andere akute Herz-Kreislauf-Erkrankungen wie den Herzinfarkt. Demografische, ethnische und sozioökonomische Ungleichheiten wurden mit einem eingeschränkten Zugang zu interventionellen Verfahren und ungünstigerem klinischem Verlauf in Verbindung gebracht. (71, 72).

Die beiden Hauptkomponenten der Studie, ethnische Zugehörigkeit und sozioökonomische Benachteiligung, könnten getrennt diskutiert werden.

Erstens gibt es neue Daten, die den Zusammenhang zwischen einer anderen als der weißen Rasse und schlechteren klinischen Ergebnissen bei PE beschreiben. Die Sterblichkeitsraten im Zusammenhang mit LE sind in den USA in den letzten 20 Jahren in der schwarzen Bevölkerung durchgängig höher, und zwar um fast das Zweifache im Vergleich zu den Werten in der weißen Bevölkerung (14). Darüber hinaus deuten die Ergebnisse einer früheren Studie, die auf administrativen Daten aus dem Bundesstaat Illinois basiert, auf häufigere Krankenhauseinweisungen bei schwarzen Patienten als bei weißen Patienten hin, was auch in den Ergebnissen dieser Arbeit festgestellt wurde (64). Die Krankenhauseinweisungen für asiatische/pazifische Inselbewohner und hispanische Patienten waren seltener als jene von weißen Patienten; dieses Ergebnis könnte im Einklang mit den bekannten rassischen Unterschieden bei der VTE-Inzidenz interpretiert werden, könnte aber auch Barrieren beim Zugang zur Gesundheitsversorgung widerspiegeln (65). Phillips et al. zeigten in einer anderen US-Studie mit 10 329 Krankenhausaufenthalten, dass in der schwarzen Bevölkerung ein höherer Schweregrad der LE wahrscheinlicher war, während der Prozentsatz der kathetergestützten oder chirurgischen Eingriffe geringer war. Dennoch unterschieden sich die Sterblichkeitsraten im Krankenhaus nicht zwischen den beiden Gruppen (31). Diese Unterschiede mit einer schlechteren Prognose bei schwarzen Patienten im Vergleich zu ihren weißen Kollegen wurden auch während der COVID-19-Pandemie deutlich, da gezeigt wurde, dass Patienten schwarzer Rasse eine erhöhte Inzidenz von LE im Zusammenhang mit COVID-19 und eine erhöhte übermäßige Sterblichkeit im Zusammenhang mit LE im Zusammenhang mit COVID-19 hatten (97, 98). Douce et al. wiesen auch auf die sozialen Faktoren beim Zugang zur ambulanten Versorgung von tiefen Venenthrombosen hin und zeigten in einer nationalen Studie, dass die ambulante Behandlung von Thrombosen bei schwarzen Teilnehmern halb so häufig war wie bei weißen (66). Es wurden biologische Unterschiede in Bezug auf VTE zwischen verschiedenen Rassen beschrieben, wie z. B. höhere Werte verschiedener hämostatischer und endothelialer Marker (einschließlich Faktor VIII, von Willebrand-Faktor, Plasmin-Antiplasmin und D-Dimer) bei schwarzen Patienten (67). Es ist jedoch möglich, dass gesellschaftliche Maßnahmen, die strukturellen Rassismus widerspiegeln, die oben genannten Unterschiede ebenfalls erklären können. Obwohl die meisten Daten aus den USA stammen, sind sie auch für die deutsche Gesellschaft von großer Bedeutung, die sich zu einer multiethnischen/multikulturellen Gesellschaft entwickelt. Insgesamt deuten unsere Ergebnisse auf rassische und ethnische Unterschiede bei der Behandlung der akuten LE und beim Zugang zu modernen Behandlungsmethoden hin. Diese Ergebnisse stehen im Einklang mit früheren Daten, die über anhaltende Unterschiede

zwischen rassischen/ethnischen Gruppen beim Zugang zur Gesundheitsversorgung, bei der Inanspruchnahme und bei der Erschwinglichkeit von Maßnahmen berichten (69).

Zweitens ist der Einfluss der sozioökonomischen Benachteiligung auf die klinischen Ergebnisse der LE noch nicht umfassend untersucht worden. Sozioökonomisch benachteiligte Patienten erhielten seltener fortgeschrittene Reperfusionstherapien, und obwohl sich dies nicht in eine höhere Sterblichkeit im Krankenhaus niederschlug, wurde über höhere 1-Jahres-Mortalität und 30-Tage-Rückübernahme festgestellt (70). Außerdem scheint ein signifikanter Zusammenhang zwischen der Zugehörigkeit zu einem niedrigen Haushaltseinkommen und einer erhöhten Sterblichkeit im Krankenhaus zu bestehen. Darüber hinaus sind die Verweildauer und die Kosten des Krankenhausaufenthalts bei Patienten, die bestimmte Kriterien der sozioökonomischen Benachteiligung erfüllen, wesentlich länger. Es wurden differenziertere soziale Gesundheitsfaktoren wie der Index der Benachteiligung in der Nachbarschaft beschrieben, die mit schlechteren Gesundheitsergebnissen bei anderen kardiopulmonalen Erkrankungen in Verbindung gebracht wurden (73). In einer Studie mit Patienten, die mit einer LE ins Krankenhaus eingeliefert wurden, wurde festgestellt, dass das Vorhandensein einer sozioökonomischen Benachteiligung in der Nachbarschaft, gemessen anhand des Gebietsbenachteiligungsindex, mit einem Anstieg der 30-Tage-Sterblichkeit um insgesamt 26 % verbunden war (99). Eine wichtige Komponente bei der Behandlung akuter Erkrankungen, einschließlich der LE, ist das Umfeld des Patienten und die örtliche Verfügbarkeit von Gesundheitsressourcen, da die Extrapolation von Behandlungsalgorithmen in verschiedenen Umgebungen schwierig sein kann (74). Krankheitstoleranz und psychosoziale Faktoren könnten sich ebenfalls auf die klinischen Ergebnisse auswirken, indem sie die Behandlung einer akuten Krankheit verzögern, und diese Faktoren könnten je nach Rasse oder sozioökonomischem Status variieren (75). Es ist eine plausible Hypothese, dass wir durch die Verringerung der sozioökonomischen Ungleichheiten tatsächlich die Gesamtkosten für das Gesundheitssystem senken könnten, was zu einer positiven Rückkopplung für die Gesellschaft führt. Dies könnte eine universelle Wahrheit sein, die auch für die LE gilt.

Obwohl ethnische Zugehörigkeit und sozioökonomische Benachteiligung getrennt analysiert wurden, ist es sehr wahrscheinlich, dass sie in hohem Maße miteinander korreliert sind. Diese Wechselbeziehung ist komplex, und es lässt sich nicht mit Sicherheit beurteilen, ob einige Parameter einen größeren Einfluss auf den Zugang zur Behandlung und die klinischen Ergebnisse haben als andere. Die Analyse ergab jedoch, dass die Zusammenhänge zwischen den verschiedenen unabhängigen Faktoren und den abhängigen Faktoren, d. h. weniger fortgeschrittene Therapien und eine höhere Sterblichkeitsrate, statistisch gesehen unabhängig voneinander sind, was darauf hindeutet, dass diese Faktoren synergistisch wirken, d. h. je

mehr Faktoren bei einer Person vorliegen, desto wahrscheinlicher ist ein schlechteres Ergebnis.

Es gibt mehrere Einschränkungen, die den Veröffentlichungen in dieser Arbeit gemeinsam sind. In dieser Arbeit wurden administrative Daten ausgewertet. Es handelt sich um retrospektive Beobachtungsanalysen, aus denen keine kausalen Schlüsse möglich sind; die Interpretation der Ergebnisse muss daher als hypothesengenerierend betrachtet werden. Die Klassifizierung von Krankheiten, Komorbiditäten und Behandlungen wurde anhand von ICD-10-Codes definiert; daher kann eine Fehlklassifizierung nicht ausgeschlossen werden. Darüber hinaus waren die Daten am ehesten administrativ, deswegen besteht die Gefahr von Unterberichterstattung oder Überberichterstattung. LE konnte nicht in die typischen Risikostratifizierungsgruppen, wie niedriges und mittleres Risiko, eingeteilt werden, mit Ausnahme der Hochrisiko-Untergruppe. Außerdem kann nicht festgestellt werden, ob die Faktoren, die ein hohes Risiko definieren, vor oder nach der LE vorhanden waren.

Zusammenfassend kam diese Dissertation zu folgenden Schlussfolgerungen:

1) Die Müttersterblichkeitsrate im Zusammenhang mit PE ist im Zeitraum 2003-2020 unverändert geblieben. Weitere klinische Forschung ist erforderlich, um zu beurteilen, ob und wie Strategien in der öffentlichen Gesundheit, die das Bewusstsein für eine verbesserte VTE-Prävention fördern, oder Fortschritte bei der Diagnose und Behandlung von PE das Risiko des Todes durch LE in dieser gefährdeten Bevölkerungsgruppe verringern würden.
2) Bei älteren und gebrechlichen Patienten mit LE ist der derzeitige Einsatz klassischer Reperfusionstherapien gering. Dem ist so selbst bei Krankenhausaufenthalten für Hochrisiko-LE, was auf die – teils berechtigte - Angst der Ärzt:innen vor Blutungen und perioperativen Komplikationen hinweist. Die Tendenz zum Einsatz von kathetergestützten Therapien ist steigend, und diese neuartigen Modalitäten stellen eine vielversprechende und sichere Alternative zu den klassischen Reperfusionstherapien für diese gefährdete Patientengruppe dar.
3) Es bestehen Ungleichheiten bei der Behandlung der akuten LE in Abhängigkeit von mehreren sozial bedingten Merkmalen. Eine andere Rasse/ethnische Zugehörigkeit als Weiß und ein niedriger sozioökonomischer Status wurden mit einem geringeren Einsatz fortschrittlicher Behandlungsmodalitäten und möglicherweise mit einer höheren Sterblichkeitsrate im Krankenhaus in Verbindung gebracht. Künftige Studien sollten die Kausalität zwischen dem sozioökonomischen Status und den klinischen Ergebnissen untersuchen und die langfristigen Auswirkungen sozialer Ungleichheiten näher beleuchten. Darüber hinaus ist es von entscheidender Bedeutung, sich um eine breite Rekrutierung von Patient:innenen unterschiedlicher ethnischer Herkunft und

unterschiedlichen sozioökonomischen Status zu bemühen und zu erforschen, wie die Belastung durch eine LE und ihre Komplikationen in Minderheitenpopulationen gemildert werden kann.

Zusammenfassung

Die evidenzbasierte Medizin prägt aktuell die Behandlung aller Erkrankungen, darunter auch der akuten LE. Allerdings werden besonders vulnerable und gefährdete Bevölkerungsgruppen wie sozial benachteiligte Menschen, schwangere Frauen und ältere Menschen häufig von Kohortenstudien und randomisierten kontrollierten Studien ausgeschlossen. Ziel dieser Dissertation war, die Epidemiologie, das Management und die Prognose der akuten LE in diesen Populationen zu untersuchen.

In der ersten Publikation wurde die mit LE verbundenen Müttersterblichkeitsraten in den Vereinigten Staaten in den letzten zwei Jahrzehnten untersucht. Zu diesem Zweck wurden öffentliche Vitalregistrierungsdaten (Sterbeurkunden mit Angaben zu den zugrunde liegenden und beitragenden Todesursachen) aus der Mortalitätsdatenbank des Centers for Disease Control and Prevention aus dem Zeitraum von 2003 bis 2020 untersucht und alle mütterlichen Todesfälle mit einem ICD-10 LE-Code in den Sterbeurkunden identifiziert. Insgesamt betrug der Anteil der mütterlichen Todesfälle im Zusammenhang mit LE an der Gesamtzahl der mütterlichen Todesfälle 5,7 %. Die gesamte durch LE bedingte Müttersterblichkeit betrug im Beobachtungszeitraum 1,02 pro 100.000 Lebendgeburten. Die Trends bei der LE-bedingten Müttersterblichkeit blieben von 2003 bis 2020 weitgehend unverändert. Die rohen LE-bedingten Müttersterblichkeitsraten unterschieden sich zwischen den Altersgruppen der Patientinnen (insgesamt 0,61, 1,09 und 3,83 Todesfälle pro 100.000 Lebendgeburten für die Altersgruppen ≤24, 25-39 bzw. ≥40 Jahre) und ethnischen Gruppen (2,89, 0,47, 0,77 und 0,63 Todesfälle pro 100.000 Lebendgeburten bei jeweils schwarzen Nicht-Hispanics, anderen Nicht-Hispanics, weißen Nicht-Hispanics und Hispanics).

In der zweiten Publikation wurde die Sicherheit von Reperfusionstherapien bei älteren und gebrechlichen Patient:innen in der Praxis analysiert. Zu diesem Zweck wurde die US Nationwide Inpatient Sample von 2016 bis 2020 verwendet und Krankenhauseinweisungen von Patienten ≥ 65 Jahre mit PE identifiziert. Es wurde eine Population von Gebrechlichen Patient:innen mithilfe des gebrechlichkeitsdefinierenden Diagnoseindikators „Johns Hopkins Adjusted Clinical Groups“ definiert. Unter 980.245 Krankenhausaufenthalten von Patient:innen ≥ 65 Jahren mit LE (28,0 % gebrechlich) wurden Reperfusionstherapien bei 4,9 % (17,6 % bei Hochrisiko-LE) eingesetzt. Der Einsatz systemischer Thrombolyse blieb stabil, während die kathetergestützte Therapie von 1,7 % im Jahr 2016 auf 3,2 % im Jahr 2020 stieg. Unter allen Krankenhauseinweisungen mit Reperfusion war die kathetergestützte Thrombolyse im Vergleich zur systemischen Thrombolyse mit weniger schweren Blutungen verbunden (5,8 % gegenüber 12,2 %), auch bei gebrechlichen Patienten. Die katheterbasierte Thrombektomie war im Vergleich zur chirurgischen Embolektomie mit einer Verringerung schwerer Blutungen verbunden (11 % vs. 22,4 %), jedoch nicht bei gebrechlichen Patienten. Diese Unterschiede

waren besonders signifikant bei Patienten mit Nicht-Hochrisiko-PE. Auch bei den Gesamtblutungen blieben Unterschiede bestehen.

In der dritten Publikation wurde der Zusammenhang zwischen sozialen Faktoren der Gesundheit, der stationären Behandlung und frühen klinischen Ergebnissen nach akuter LE untersucht. Zu diesem Zweck wurden Krankenhauseinweisungen von Erwachsenen mit akuter PE-Entlassungsdiagnose aus der landesweiten Stichprobe stationärer Patienten in den USA im Zeitraum von 2016 bis 2018 identifiziert. Es wurden insgesamt 1.124.204 Krankenhausaufenthalte mit einer LE-Diagnose analysiert entsprechend eine Krankenhausaufenthalt Rate von 14,9/10.000 erwachsene Personen pro Jahr. Der Einsatz fortschrittlicher Therapien, einschließlich systemischer Thrombolyse, chirurgischer Embolektomie, kathetergestützter Therapien und ECMO, war bei schwarzen und asiatisch-pazifischen Inselbewohner:innen geringer als bei weißen Patient:innen und bei jenen, die über eine staatlich unterstützte Krankenversicherung versichert waren, im Vergleich zu privat versicherten Patienten, obwohl letztere Gruppen die höchste Aufenthaltsdauer und Krankenhauskosten aufwiesen. Die Krankenhaussterblichkeit war im untersten Einkommensquartil höher als im höchsten Einkommensquartil. Unter den Hochrisiko-LE-Patienten hatten Patient:innen aus nicht-weißen ethnischen Gruppen die höchste Krankenhaussterblichkeit.

Schlussfolgerungen der vorliegenden Dissertation sind:

- Die Müttersterblichkeitsrate aufgrund einer LE ist im Zeitraum 2003–2020 nicht gesunken, und dies im Gegensatz zu der LE-bedingten Sterblichkeit in der Allgemeinbevölkerung.
- Während ältere und gebrechliche Bevölkerungsgruppen besonders anfällig für die Reperfusionsbehandlung von LE sind, könnten neuere kathetergestützte Therapien eine sicherere Alternative zu den klassischen Reperfusionstherapien sein.
- Es bestehen Ungleichheiten bei der Anwendung neuartiger Therapien bei akuter PE und eine höhere Krankenhaussterblichkeit bei nicht-weißen Personen, und ein niedriger sozioökonomischer Status ist mit einem selteneren Einsatz neuer Behandlungsmethoden und einer höheren Krankenhaussterblichkeit verbunden.

Auf der Basis dieser Ergebnisse sollten zukünftige Studien:

- beurteilen, ob eine Verbesserung der Prävention venöser Thromboembolien sowie der Diagnose- und Behandlungsstrategien für LE in der Schwangerschaft die Inzidenz der Todesfälle aufgrund von LE in der Bevölkerung senken könnte

- mehr Fokus auf ältere Patient:innen setzen, da diese einen bereits großen und stets wachsenden Anteil der von thromboembolische Ereignissen betroffenen Patient:innen darstellen
- die langfristigen Auswirkungen sozialer Ungleichheiten im LE-Management weiter untersuchen und auf die Notwendigkeit ihrer Aufhebung hinweisen.

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Tabellarischer Lebenslauf

Medizinstudium	
10.2022 – 11.2024	Promotion, Universitätsmedizin der Johannes-Gutenberg-Universität Mainz, Deutschland Arbeitstitel: *Behandlung und Nachsorge der akuten Lungenembolie in besonderen Patientenpopulationen.*
02.2020 – 01.2021	MSc in Medical Research Methodology, Medizinische Schule, Aristoteles Universität Thessaloniki, Griechenland Absolvierte, Note 9,62/10
09.2013 – 07.2019	Medizinische Schule, Aristoteles Universität Thessaloniki, Griechenland Absolvierte, Note 8,67/10 (1,7)
03.2019 – 06.2019	Erasmus Austauschprogram, Georg-August-Universität Göttingen, Germany
10.2016 – 01.2017	Erasmus Austauschprogram Faculté de Médecine, Université de Strasbourg, France
Schulbildung	
09.2010 – 06.2013	Anatolia College, Thessaloniki, Griechenland Note: 19,3/20, *Vraveion and Aristeion Proodou (Exzellenzpreis)*
09.2007 – 06.2010	17. Staatsgymnasium Thessaloniki, Griechenland
Klinische Erfahrung	
seit 05.2023	Assistenzarzt, Kardiologie I, Universitätsmedizin Mainz, Deutschland
07.2020 – 07.2021	Assistenzarzt, Klinik für Innere Medizin, “G. Papanikolaou“ Krankenhaus, Thessaloniki, Griechenland

10.2019 – 07.2020	Militärarzt in der 34. Motorisierten Brigade, Assiros, Greece (Wehrpflicht)
03.2019 – 06.2019	PJ Student, Universitätsmedizin Göttingen
08.2018 – 02.2019	PJ Student, Medizinische Schule, Aristotle Universität Thessaloniki
07.2018	Famulant**,** Adult Congenital Heart Disease Centre, Royal Brompton Hospital, UK
Akademische Erfahrung	
10.2021 – 05.2023	Wissenschaftlicher Mitarbeiter, Centrum für Thrombose und Hämostase, Universitätsmedizin Mainz, Deutschland
02.2017 – 10.2021	Forschungsassistent der 1. Abteilung für Kardiologie, AHEPA Universitätskrankenhaus, Thessaloniki, Griechenland