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Epidemiology and Risk Stratification in Patients with Pulmonary Embolism

PhD Thesis

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List of papers

This PhD thesis is based on the following manuscripts, referred to in the text as papers:

I. Sonne-Holm E, Kjærgaard J, Bang LE, Fosbøl E, Carlsen J, Winther-Jensen M. *Pulmonary embolism: Age specific temporal trends in incidence and mortality in Denmark 1999-2018.* Thrombosis Research. 2022 Feb;210:12-19.

II. Sonne-Holm E, Kjærgaard J, Bang LE, Køber L, Fosbøl E, Carlsen J, Winther-Jensen M. *Educational differences in mortality but not in risk of recurrence following first-time pulmonary embolism: A Danish nationwide register-based study.* Thrombosis Research. 2022 Nov;219:22-29.

III. Sonne-Holm E, Winther-Jensen M, Bang LE, Køber L, Fosbøl E, Carlsen J, Kjærgaard K. *Troponin dependent 30-day mortality in patients with acute pulmonary embolism.* Journal of Thrombosis and Thrombolysis. 2023 Oct;56(3):485-494.

IV. Sonne-Holm E, Kjærgaard J, Bang LE, Køber L, Hassager C, Paulin Beske R, Carlsen J, Winther-Jensen M. *Dynamics of troponins and 30-day mortality in hospitalized patients with pulmonary embolism.* Thrombosis Research. 2025 Jan 22;247:109274.

V. Sonne-Holm E, Winther-Jensen M, Bang LE, Carlsen J, Jawad S, Sommer Ulriksen P, Kjærgaard J. *Pathophysiology and prognostic value of syncope in patients with intermediate-high risk pulmonary embolism.*

Abbreviations

PE:	Pulmonary embolism
RV:	Right ventricle
ESC:	The European Society of Cardiology
CTPA:	Computed tomographic pulmonary angiography
LV:	Left ventricle
PESI:	Pulmonary Embolism Severity Index
sPESI:	Simplified Pulmonary Embolism Severity Index
TnI:	Troponin I
TnT:	Troponin T
ICD:	International classification of diseases
DNPR:	The Danish national person register
CPR:	The central person register
EAR:	The educational attainment register
LABKA:	The clinical laboratory information system
ISCED-11:	International Standard Classification of Education 2011
ECG:	Electrocardiogram
RMS:	Refined Miller score
LVEF:	Left ventricle ejection fraction
TAPSE:	Tricuspid annular plane systolic excursion
TR-gradient:	Tricuspid regurgitation gradient
RBBB:	Right bundle branch block
iRBBB:	Incomplete right bundle branch block
IQR:	Interquartile range
SD:	Standard deviation
eGFR:	Estimated glomerular filtration rate
CRP:	C-reactive protein
BIC:	Bayesian information criterion
BMI:	Body mass index
IRR:	Incidence rate ratio
MRR:	Mortality rate ratio
COPD:	Chronic obstructive pulmonary disease
HR:	Hazard ratio
pO_2:	Partial pressure of oxygen
pCO_2:	Partial pressure of carbon dioxide

Preface

During my time as a Ph.d.-student at Department of Cardiology, Rigshospitalet, I have had the privilege of working with some of the most ambitious and competent professionals in the field.

First and foremost, I want to dedicate a special thanks to Dr. Lia E. Bang, who invited me to join a clinical trial as a Ph.d. student during my tenure as a resident doctor at the Department of Cardiology, Rigshospitalet, in 2019. Without this invitation, and Dr. Bangs incredibly inspiring work as a clinical mentor none the less, this research would not have been possible.

My time as a Ph.d.-student has been led by Dr. Jesper Kjærgaard, to whom I owe a lot. Through his dedicated and highly experienced mentorship, I have learnt much about efficiency, professionalism, and empathy. His passion for the clinic and critical ill patients has deeply influenced me both professionally and personally and I am forever grateful for this insight. The scope of my research and the benefits of my time as a Ph.d. student are due to his guidance, and I could not ask for a more competent and inspiring mentor. I hope our collaboration continues beyond my current position.

Additionally, it has been an honor to work with Dr. Jørn Carlsen, who has provided invaluable support and expertise in his field. I am deeply grateful for his kindness and professionalism throughout this process. I acknowledge Cand.scient. Matilde Winther-Jensen, who has taught me everything I know about statistics. Her guidance and availability have been crucial to this work, and I look forward to many more insightful discussions in the future. I thank Prof. Emil Fosbøl who has contributed with his expertise and knowledge in epidemiological data. And furthermore, the collection of data and materials for the clinical trial, which is part of my Ph.d., would not have been possible without the invaluable competencies of research nurse Mie Christa Larsen.

Finally, I thank my family for their unwavering support, especially my father, whose ambition, professional insights, and drive, have laid the foundation for my research career.
I dedicate this thesis to you.

Emilie Sonne-Holm MD

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INTRODUCTION

PE is a prevalent acute cardiovascular condition affecting a diverse range of patients globally. Epidemiological studies indicate that incidence rates range from 39 to 115 cases per 100,000 individuals annually[1]. Symptoms of PE are varied and nonspecific, ranging from mild to highly severe. A critical pathophysiological element is RV strain, which is caused by pulmonary vascular obstruction and significantly increases the risk of hemodynamic collapse and death[2]. The case fatality rates for PE, which are generally high, depend on the severity of the embolism[3]. Recent analyses, however, have demonstrated a decrease in mortality rates, primarily due to advancements in risk assessment tools and treatment strategies, supported by guidelines[4-9].

The ESC has developed a widely recognized risk assessment tool that classifies PE patients into four categories: low, intermediate-low, intermediate-high, and high risk. This classification is based on the severity of the condition and the associated risk of early death[10]. High-risk PE patients require immediate thrombolytic treatment, while those classified as low risk or intermediate-low risk can often be treated with oral anticoagulants in an outpatient setting. For intermediate-high risk patients, who are hemodynamically stable but show signs of RV strain, treatment approaches have evolved beyond traditional conservative heparin therapy. Recent advancements include reperfusion techniques, such as low-dose systemic thrombolysis[11-13] or catheter-directed treatments[14-16]. However, the issue of determining which PE patients would benefit from advanced treatments strategies is highly debated due to conflicting study results. Thus, additional research is essential to refine risk assessment strategies for PE patients, with the goal of optimizing treatment approaches and improving patient outcomes.

Objectives

The overall aim of this thesis is to describe trends in incidence and survival of PE patients, and furthermore, to identify factors that could improve risk management in acute PE.
We hypothesize:

1. The incidence of acute PE has increased in the Danish population over the past two decades, while mortality rates have decreased.
2. Lower educational attainment is associated with higher risk of recurrence and mortality following acute PE.
3. Higher troponin levels at admission are associated with an increased risk of 30-day mortality in acute PE.
4. Changes in serial troponin concentrations during the acute phase of PE predict 30-day mortality.
5. Syncope in patients with intermediate-high risk PE is associated with a higher risk of in-hospital adverse outcomes compared to those without syncope.

Using data from both national registries and a clinical trial, five studies were conducted with the following specific aims:

1. To assess age-specific trends in the incidence and mortality of acute PE over two decades in Denmark.
2. To evaluate whether socioeconomic position, expressed as highest attained educational level, is associated with risk of recurrence and mortality following acute PE.
3. To investigate if the concentration of troponin measured at admission is associated with the risk of 30-day mortality in patients with acute PE.
4. To identify patterns of serial troponin concentrations during the acute phase of PE and their association with 30-day mortality.
5. To explore the pathophysiology of syncope in intermediate-high risk PE patients and its association with in-hospital adverse outcomes in a clinical trial cohort.

BACKGROUND

Epidemiology

PE is widely recognized as the third most common acute cardiovascular condition globally, surpassed only by myocardial infarction and stroke[17]. In recent decades, the incidence of PE has shown a notable increase, documented across European countries[4-7]. This rising trend is partly attributed to the global increase in life expectancy, which has led to a larger aging population, a group more susceptible to thromboembolic events[18]. Furthermore, the introduction of CTPA in the late 1990s improved the diagnosing of PE by increasing both the accuracy and availability of detection. However, this advancement has also been associated with a tendency towards overdiagnosis[19].

PE presents with a broad spectrum of severity, ranging from asymptomatic cases with a mortality risk of less than one percent, to life-threatening massive embolisms in hemodynamically unstable patients, where the risk of short-term mortality can reach up to 30%[20]. Over the past decades, improvements in risk stratification of PE patients, adherence to clinical guidelines, and the development of optimized treatment strategies have all contributed to a significant reduction in case fatality rates in many Western countries[7,21,22]. Additionally, the decreasing mortality rates may partly reflect a benign increase in the burden of PE cases, likely influenced by the tendency toward overdiagnosis[19].

Given the potential for PE to impose a significant burden on health care systems in the future[23], continuous monitoring of incidence rates, along with the exploration of underlying mechanisms and preventable risk factors, remains crucial.

Risk factors

In addition to advancing age, well-established risk factors of PE include major trauma, surgery, infectious diseases, malignancies, hormonal treatments, pregnancy, and obesity[24]. Despite significant progress in understanding these risk factors, the role of socioeconomic position in the development of PE remains relatively understudied. Previous research has demonstrated a strong association between low socioeconomic position – often measured through educational attainment, occupational status, and household income – and an increased risk of arterial

diseases, such as ischemic heart disease and stroke[25-29]. However, given the limited overlap in risk factors between arterial and venous disease, the association between venous thromboembolism and socioeconomic position has received less attention.

While a few studies from European countries have suggested that individuals with higher socioeconomic status may have a lower risk of developing venous thromboembolism[30-34], including PE, these findings are not yet well-established. Furthermore, although it is widely recognized that socioeconomic position influences overall mortality and morbidity, no studies to date have specifically explored the impact of socioeconomic position on PE recurrence and post-PE mortality. Identifying potential associations between socioeconomic position and PE could have important implications for future strategies in the prevention, management, and long-term care of patients with PE.

Risk classification

When a patient is diagnosed with PE, early risk assessment is essential in order to decide on appropriate treatment strategy. The evaluation of risk is based on the estimated likelihood of in-hospital mortality, which can vary significantly. One of the most critical factors influencing mortality in PE patients is the presence of RV strain. RV strain occurs as a consequence of the sudden obstruction of the pulmonary arteries, leading to impaired RV filling and reduced outflow[35]. If left unresolved, this condition initiates a series of pathological events, ultimately comprising LV filling, reducing the coronary perfusion, and leading to decreased cardiac output[36]. These changes place the patient at high risk of hemodynamic collapse and death (Figure 1).

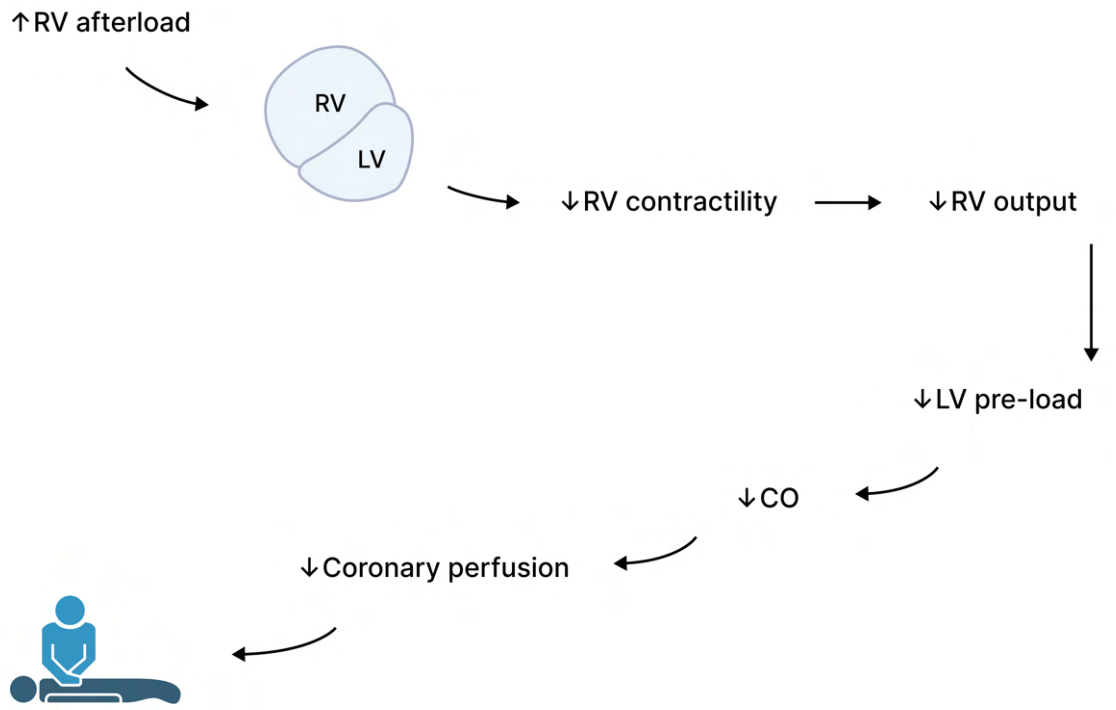

Figure 1. *Key factors contributing to haemodynamic collapse in patients with acute pulmonary embolism. RV: right ventricle, LV: left ventricle, CO: cardiac output. Created with Biorender.com.*

The presence of RV strain, even in hemodynamically stable patients, highlights the importance of its early identification as part of the risk stratification process. Over recent years, multiple risk assessment tools have been proposed to predict outcomes in PE patients, yet the ESC guidelines remain the most widely accepted standard (Figure 2)[10]. According to ESC guidelines, risk assessment incorporates clinical evaluation, imaging, and laboratory markers indicative of RV dysfunction. Additionally, it takes into account aggravating factors and comorbid conditions, which are often quantified using the PESI score[37,38]. The PESI score has been extensively validated and further simplified into a version known as sPESI to facilitate easier clinical use[39,40].

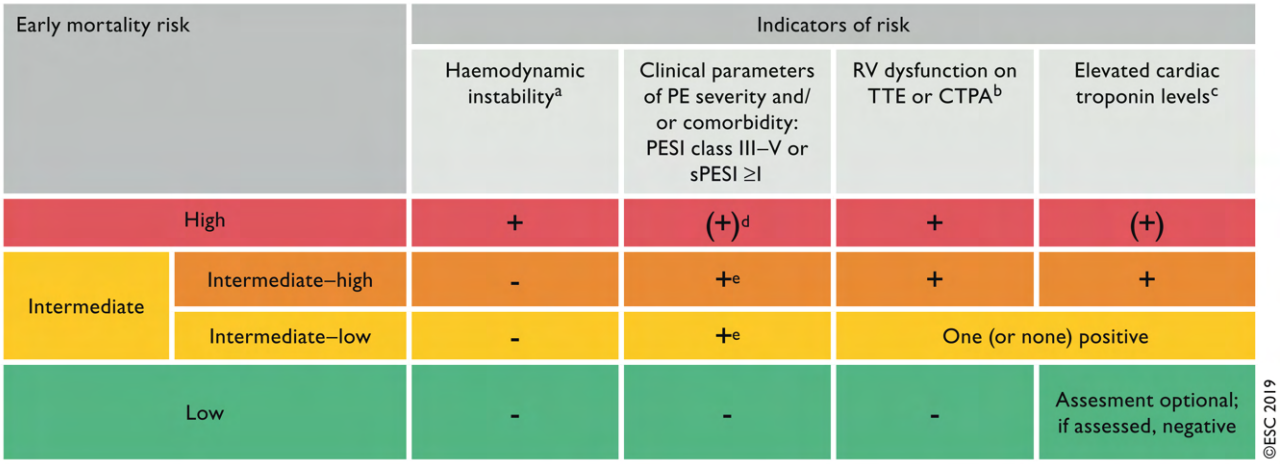

Figure 2. *Classification of pulmonary embolism severity and risk of early death by the European Society of Cardiology. PE: pulmonary embolism, PESI: pulmonary embolism severity index, sPESI: simplified pulmonary embolism severity index, RV: right ventricle, TTE: transthoracic echocardiography, CTPA: computed tomography pulmonary angiogram*[10].

Patients categorized as low or intermediate-low risk can be treated in an outpatient setting with oral anticoagulants, whereas patients with high risk require immediate treatment with rescue thrombolysis[10].

The intermediate-high risk group, however, poses a particular challenge. Traditionally, these patients have been managed conservatively with anticoagulation, usually heparin. However, emerging evidence suggests that despite anticoagulant therapy, a nonsignificant subset of patients remains at a significant risk of clinical deterioration, with 30-day mortality as high as 10%. Consequently, novel treatment options, including low-dose thrombolysis[12,13,41], ultrasound-assisted thrombolysis[14,15,42], and catheter-based embolectomy[43], have recently been introduced to manage these patients more aggressively and possibly prevent clinical deterioration.

Given these developments, there is a growing need for optimized risk assessment tools that can more accurately identify which intermediate-high risk patients would benefit from advanced therapies, while minimizing unnecessary interventions in others. The refinement of these risk models will be critical in improving outcomes for patients with PE.

Troponins

In patients with PE, approximately 30-60% has concentrations of TnI or TnT beyond the upper reference limit at the time of diagnosis. This elevation is an expression of myocardial injury and stress secondary to RV dysfunction[44-47]. Studies have consistently demonstrated that elevated levels of TnI or TnT are associated with an increased risk of short-term mortality in PE patients[45], highlighting their prognostic significance.

Troponin measurements, when combined with echocardiographic evaluation and clinical findings, play a critical role in the initial risk assessment of PE patients. As a result, current ESC guidelines include troponin as a dichotomous variable – categorized simply as elevated or non-elevated – for risk assessment[10]. In contrast, in patients with coronary artery disease, the absolute troponin levels and the pattern of changes over time are key components in evaluating the severity of the event and planning treatment strategies[48]. Despite this, only a limited number of studies have explored the association between specific troponin levels and mortality risk in PE patients[49,50], and yet, no previous studies have investigated the dynamic patterns of repeated troponin measurements and their potential implications for clinical decision-making in this population.

Thus, further research into the potential benefits of extended and dynamic TnI or TnT measurements in PE patients is warranted. Such studies could provide valuable insights and contribute to optimized risk stratification and management strategies in PE care.

Syncope

Syncope, characterized as a sudden, transient loss of consciousness followed by spontaneous complete recovery[51], is a common symptom associated with PE, affecting up to 25% of all patients[52]. Despite its prevalence, the underlying pathophysiological mechanisms remain debated. Proposed explanations include reduced cerebral perfusion secondary to hemodynamic instability, cardiac arrythmias, or vasovagal triggers[53]. The prognostic significance of syncope in the context of PE has been discussed in previous studies, yielding conflicting results[54-59].

A key challenge in interpreting these findings is that many studies have been conducted in heterogenous PE populations, leading to potential confounding by the hemodynamic status at

presentation. This has raised concerns about whether syncope itself directly correlates with adverse outcomes or if it reflects the severity of hemodynamic impact of PE, and as such is reversible with treatment. In patients with intermediate-high risk PE, the prognostic value of syncope remains uncertain. However, understanding this relationship could offer valuable insights and serve as a potential addition to existing risk stratification models, enhancing the ability to predict outcomes and guide treatment strategies in this patient population.

METHODS

Data sources

Paper I-IV

Data on demographics, hospitalizations, health-care related diagnoses, laboratory test results, education and death were extracted from the Danish national registries. Since every Danish citizen is assigned a unique civil registration number at birth, it is possible to link individual information across different datasets using an encrypted server. The DNPR has recorded all hospital admissions in Denmark since 1977. Records include hospital and department details, admission and discharge dates, and up to 20 physician-coded ICD diagnoses[60]. The CPR holds data on death, while the EAR contains information on highest attained level of education[61]. The LABKA research database, established in 1985, contains laboratory test results from hospitals and private clinics. The database has covered most of Denmark since 2013[62]. The validity of the data is demonstrated by previous studies[63,64].

According to Danish law, ethical approval is not required for register based studies. Study I-IV received approval from the Danish Data Protection Agency (approval number: 2007-58-0015).

Paper V

Data is extracted from the randomized clinical trial *"Low-dose thrombolysis, ultrasound-assisted thrombolysis, or heparin for intermediate-high risk pulmonary embolism—the STRATIFY trial".*

The trial is initiated by researchers from Rigshospitalet, Copenhagen University Hospital,

Denmark, during the period 6th of June 2019 until 4th of June 2024. Eligible patients were >18 years of age with a confirmed diagnosis of intermediate-high risk PE and <14 days of symptoms. Patients were included from all cardiology departments and emergency rooms across Zealand, Denmark.

The trial was approved by the Ethics Committee (approval number: H-18013257), the Danish Medicines Agency (approval number: 2017-005075-91) and the Data Protection Agency (approval number: VD-2019-52). Informed consent was obtained prior to trial inclusion.

Study design

Paper I

A national cohort study examining 65,478 patients aged 18 years or older with a first-time in-hospital diagnosis of PE (I26, I260, I260A, I269 and I269A) between 1999 and 2018. The PE could be the primary cause of admission or secondary to other disease requiring hospitalization. The diagnosis was recorded at admission, during hospitalization, in the emergency department, or in an outpatient clinic. Patients' comorbidities were identified based on diagnoses made during previous hospital admissions prior to the PE diagnosis. Information on all-cause mortality within the first year following the diagnosis were recorded.

The study period was divided into four five-years intervals: 1999-2003, 2004-2008, 2009-2013, 2014-2019. Patients were grouped into the following age categories to assess age-specific trends: 18-34, 35-44, 45-54, 55-64, 65-74, 75-84, and ≥85 years.

Paper II

A national cohort study analysing 52,184 patients aged 18 years or older with a first-time in-hospital diagnosis of PE between 1999 and 2018, with available data on educational level. Both primary and secondary PE diagnoses were included, while outpatient clinic contacts were excluded. Comorbidities were defined as preexisting hospital diagnoses within five years. A new in-hospital primary diagnosis of PE within one year, but at least 30 days from the first-time PE diagnosis, was considered a recurrent PE case. All-cause mortality within 30 days and the first year following the primary diagnosis were registered.

The highest level of education attained by patients at the time of their index PE diagnosis was recorded and used as an indicator of socioeconomic status. Education levels were classified according to ISCED-11 categories: basic education (ISCED-11: 1+2), high school/vocational education (ISCED-11: 3+4), short/medium higher education (ISCED-11: 5+6), and long/higher education (ISCED-11: 7+8).

Paper III

A national cohort study of 5,639 patients aged 18 years or older hospitalized with a first-time PE diagnosis between 2013 and 2018 and available data on TnI/TnT measured within one day prior to one day after admission. Only primary PE diagnoses registered at hospital admission or in an emergency room were included. Comorbidities were defined as preexisting hospital diagnoses within the last five years, and 30-day all-cause mortality was recorded.
Individual peak levels of TnI and/or TnT were documented. Due to the varied use of troponin assays across Denmark, eleven different types of measurements (TnI or TnT, unit and upper threshold) were included (Figure 3). The cohort was first divided into two groups based on whether the peak level of TnI/TnT was above the individual upper threshold or not. Secondly, the cohort was divided into quintiles of increasing TnI/TnT concentrations, with each assay handled separately.

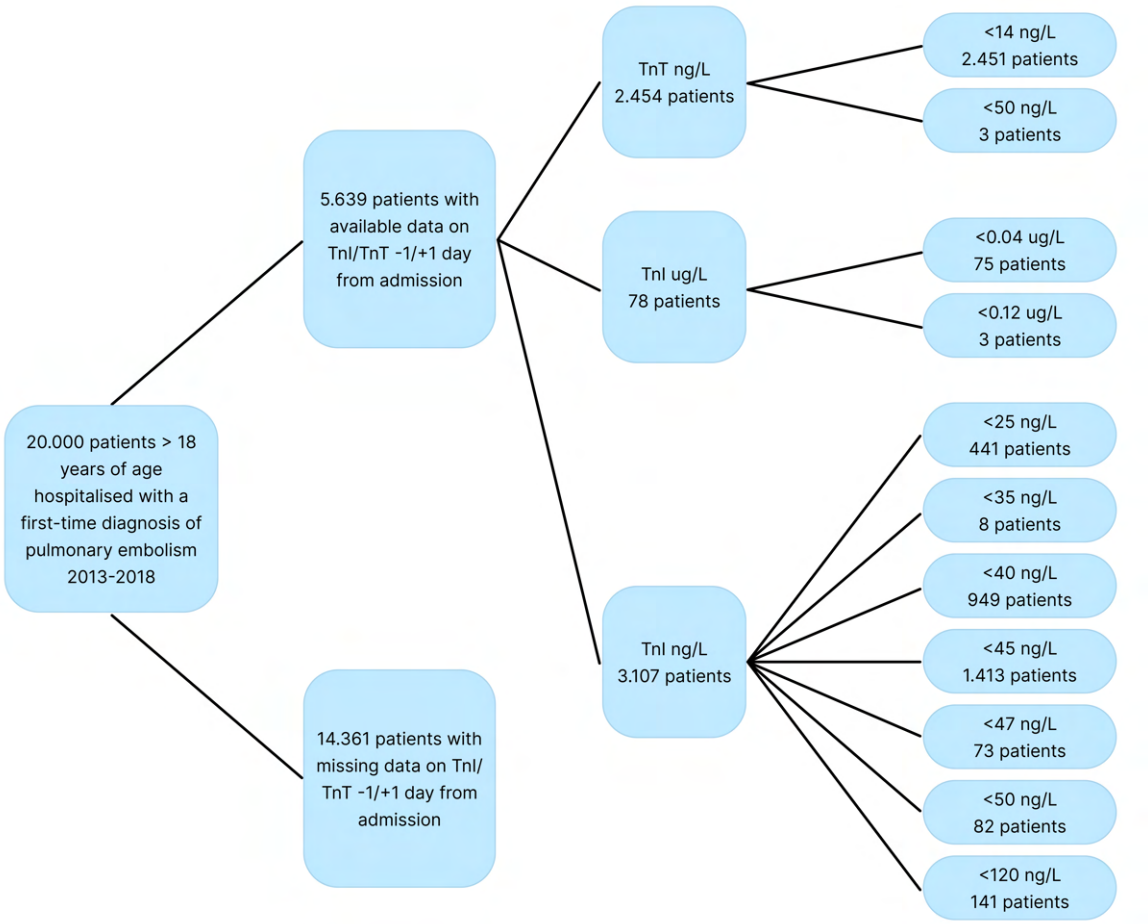

Figure 3. *Data inclusion process. The 11 patient groups based on different assays are illustrated to the right. TnI: troponin I, TnT: troponin T. Paper III.*

Paper IV

A national cohort study investigating 2,862 patients aged 18 years or older with a first-time PE diagnosis between 2013 and 2018, and repeated measurements of TnI or TnT in the acute phase of PE. Only primary diagnoses registered at admission or in the emergency room were included. A first measurement of either TnI or TnT was to be performed within one day prior to one day after admission, followed by at least one repeated measurement of TnI/TnT within the next three days. Comorbidity was defined as all hospital diagnoses within the past five years and, and all-cause 30-day mortality was recorded.

The cohort were divided in to two non-overlapping groups based on repeated measurements of either TnI or TnT (Figure 4). Due to large fluctuations in troponin levels, concentrations were converted into a 10% logarithmic value.

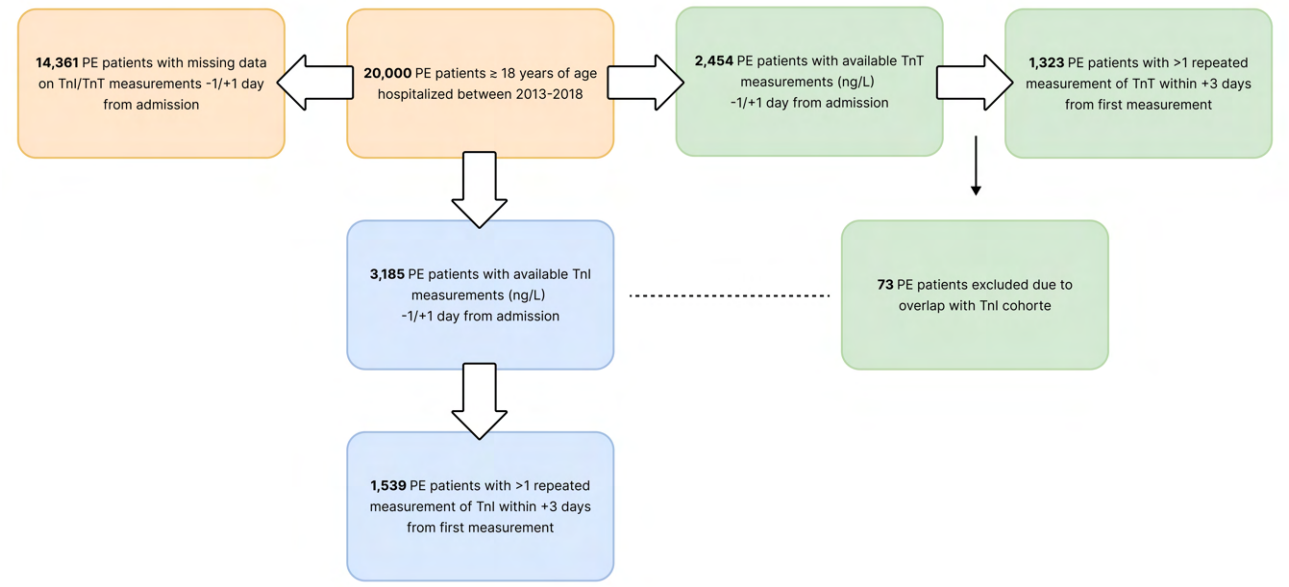

Figure 4. *Data inclusion. PE: pulmonary embolism, TnI: troponin I, TnT: troponin T. Paper IV.*

Paper V

A cohort study of 210 patients aged 18 years or older with a confirmed diagnosis of intermediate-high risk PE. Data on syncope as part of initial PE symptoms, demographic information, and clinical features upon admission were collected. All patients underwent diagnostic CTPA, bedside echocardiography, performed by the cardiologist on call, and an ECG within the first 24 hours. A blinded radiologist evaluated the CTPA to estimate clot burden using RMS, RV/LV ratio measurements, and the presence of saddle embolus. The echocardiography was assessed for LVEF, TAPSE and TR-gradient. ECGs were analysed for arrythmias, S1Q3T3 pattern, negative T-waves V1-V3 and RBBB/iRBBB. The sPESI score was calculated for each patient.

The cohort were divided into two groups based on the presence or absence of syncope and followed until in-hospital death, rescue thrombolysis or discharge.

Statistical methods

This section provides a brief summary of the statistical methods used across the various studies, followed by methods specific to each individual study. Detailed descriptions are available in the manuscripts.

Categorical demographic and baseline data are presented as proportions, while continuous variables are reported as medians with IQR or means with SD. The chi-squared test was used for comparing categorical variables, and ANOVA was used for continuous variables. A two-sided p-value ≤ 0.05 was considered significant.
All analyses were performed using SAS 9.4 or R 3.6.1, with all figures generated in R 3.6.1.

Paper I

Incidence rates for each time-period and age group were calculated per 100,000 person years using the Danish population aged over 18 as a reference group. One-year mortality rates were expressed per 10 person years for each time-period and age group. Time trends in incidence and mortality rates were assessed using a Cochran-Mantel-Haenzsel test. Using the first calendar period as a reference, incidence and mortality rate ratios per calendar period were calculated and adjusted in two steps: first for age and then additionally for age, sex and comorbidity.

Paper II

For each educational level, a cumulative incidence function for both all-cause mortality and recurrence of PE within the first year were calculated and tested using Gray's test.
A multivariable adjusted absolute risk regression model[65] was used to evaluate the impact of educational level on risk of PE recurrence and/or death within one year. This model calculated the absolute relative risk by comparing cumulative incidences across educational groups, using basic education (elementary school + middle school) as the reference, while adjusting for age, sex, comorbidities, and year of diagnosis.

Paper III

Cumulative 30-day mortality curves and log-rank tests were used to compare differences between patients with and without troponin concentration above upper threshold, as well as differences across quintiles of increasing troponin concentration. A Cox proportional hazards model, adjusted for age, sex, comorbidities, and levels of haemoglobin, eGFR and CRP, was conducted to investigate the effect of troponin concentrations above upper threshold on the risk of 30-day mortality and differences in 30-day mortality across quintiles.

Paper IV

Three distinct trajectories of repeated measurements of troponins were identified using latent class trajectory models[66]. A spline model over quartiles of time, with a random intercept and three trajectories, best fitted the TnI and TnT data based on lowest possible BIC, trajectory plots, and the number of patients allocated to each trajectory. The cohort was then divided into three groups based on these identified trajectories. A Cox regression model, adjusted for age, sex, comorbidities, and eGFR, was used to examine the association between the posterior probability of belonging to one of the three trajectories and the risk of 30-day mortality.

Paper V

A multivariate logistic regression model was used to examine the individual effect of relevant syncope risk factors including age, sex, BMI, arrythmias at index ECG, RMS and RV/LV ratio from baseline CTPA. The association between syncope and in-hospital mortality was visualised using a Kaplan-Meier plot. A multivariate regression analysis, adjusted for study treatment, sPESI-score and sex, was conducted to examine the association between syncope and a composite endpoint of rescue thrombolysis or in-hospital death.

RESULTS

Main findings of each study are summarized in the following sections. Detailed descriptions are available in the manuscripts.

Paper I

From 1999 to 2018 the overall number of first-time PE cases per five-year period increased threefold, from 9,359 to 27,000 cases. The incidence of PE increased significantly over the observed time across all age groups, $p < 0.001$ (Figure 5). During the study period, incidence rates doubled among the youngest patients aged 18-34 and 35-44 years, rising from 10 to 18 and from 18 to 35 per 100,000 person-years, respectively. For middle-aged groups (45-54 and 55-64 years), the incidence rate tripled, increasing from 26 to 63 and from 42 to 123 per 100,000 person-years. In the older age groups - 65-74, 75-85, and over 85 years - incidence

rates also doubled, with increases from 92 to 299, 166 to 383, and 155 to 417 per 100,000 person-years, respectively.

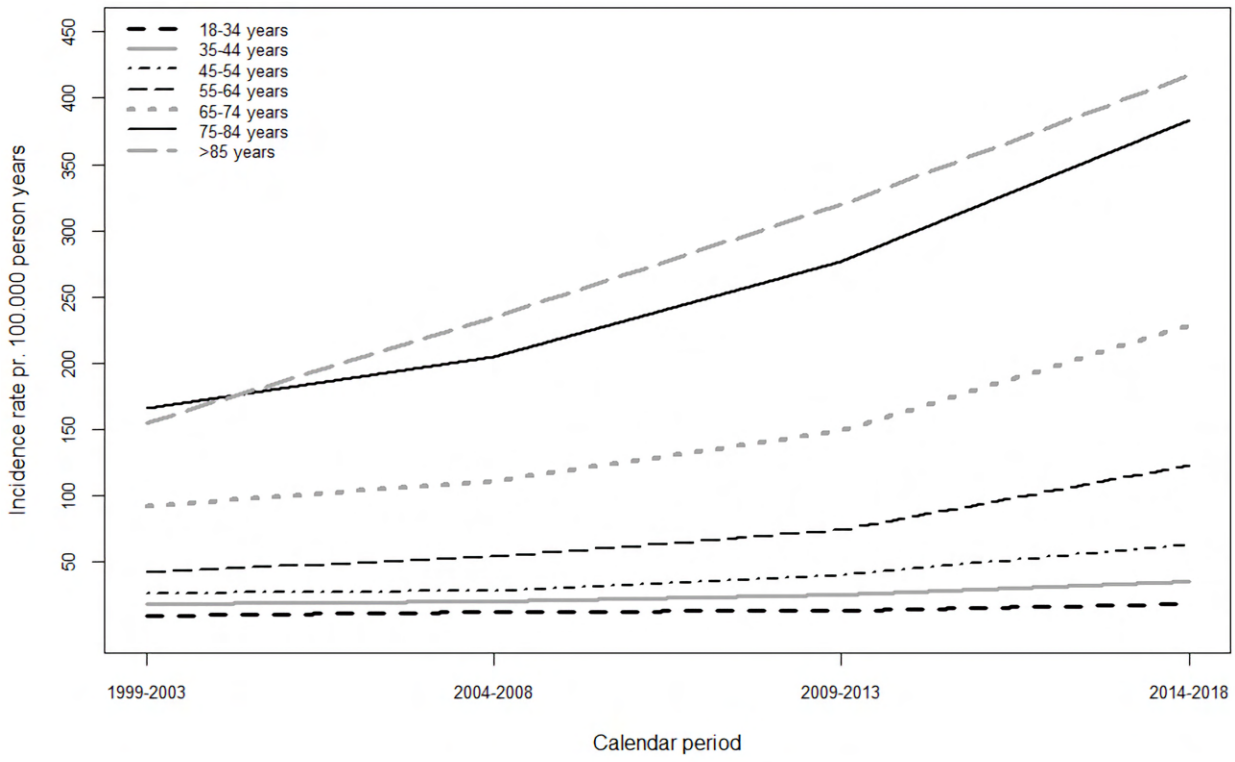

Figure 5. *Age-specific temporal incidence rates of pulmonary embolism per calendar period. Paper I.*

Mortality decreased significantly across all age groups during the study period, p <0.001 (Figure 6). The largest decreases in mortality were observed in the 18–34-year age group, from 0.59 to 0.21 per 10 person years, and in the 75–84-year age group, from 7.26 to 2.96 per 10 person years.

The IRR for the study period 1999-2003 was 1.24 (95% CI: 1.21-1.28) when compared to the earliest period 1999-2003, increasing to 1.72 (95% CI: 1.68-1.77) for 2009-2013 and 2.62 (95% CI: 2.55-2.69) for 2014-2018. After adjusting for patient age and sex, there was no substantial change in IRR for specific time periods (2004-2008: IRR 1.22 (95% CI: 1.10-1.26), 2009-2013: IRR 1.63 (95% CI: 1.59-1.68), 2014-2018: IRR 2.40 (95% CI: 2.34-2.46). However, when adjusting for both age, sex and comorbidities, the increasing effect of time on PE incidence diminished (2004-2008: IRR 1.16 (95 % CI: 1.13-1.20), 2009-2013: IRR 1.31 (95% CI: 1.27-1.34), 2014-2018: IRR 1.61 (95% CI: 1.56-1.65).

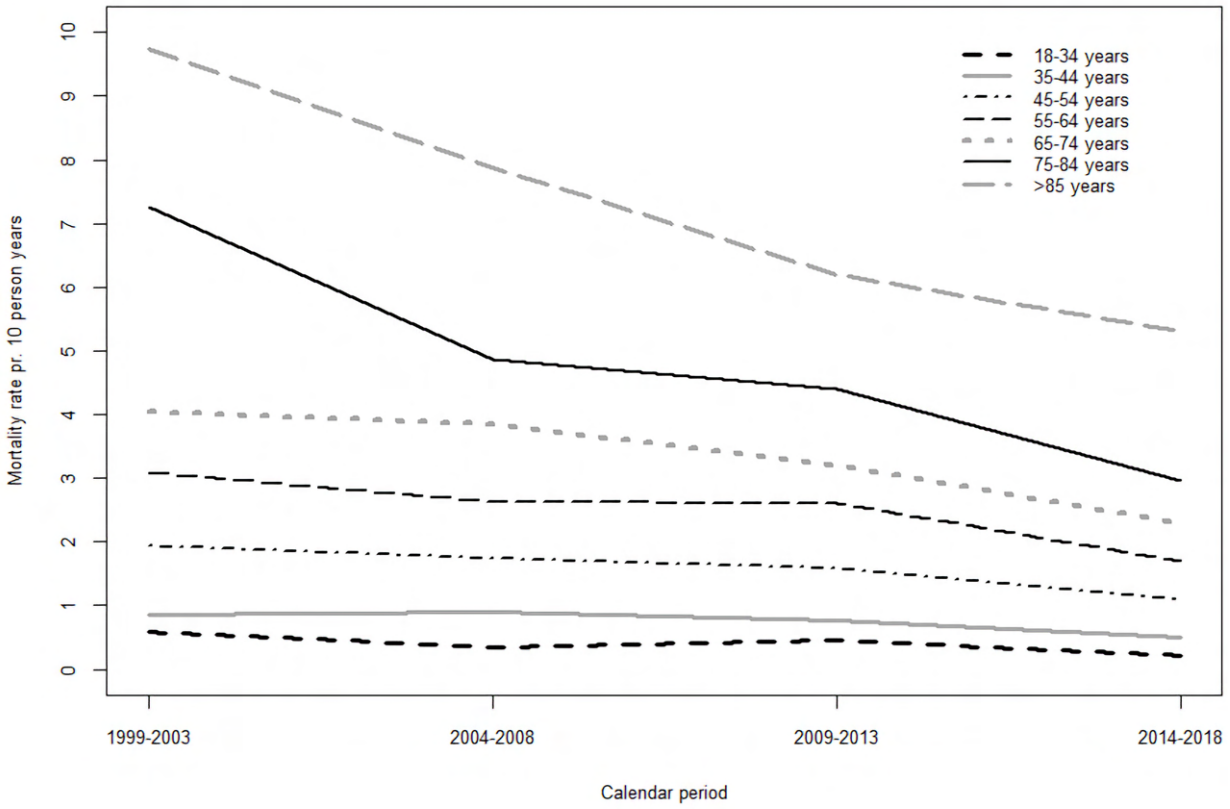

Figure 6. *Age-specific temporal 1-year mortality rates following pulmonary embolism per calendar period. Paper I.*

The MRR for the study period 1999-2003 was 0.86 (95% CI: 0.82-0.91) compared to 1999-2003, 0.78 (95 % CI: 0.74-0.82) for 2009-2013, and 0.56 (95% CI: 0.53-0.59). Adjusting for age and sex, the MRR was almost unaffected (2004-2008: MRR 0.82 (95% CI: 0.77-0.86), 2009-2013: MRR 0.71 (95% CI: 0.67.0.75), 2014-2018: MRR: 0.51 (95% CI: 0.48-0.54)). However, adjusting for age, sex and comorbidities, amplified the decreasing effect of time on mortality (2004-2008: MRR 0.84 (95% CI: 0.80-0.89), 2009-2013: MRR 0.60 (95% CI: 0.56-0.63), 2014-2018: MRR 0.31 (95% CI: 0.30-0.33).

Paper II

Of the 52,184 identified PE cases, 22,708 (44%) had completed basic education, 19,809 (38%) had completed high school or vocational education, 7,257 (14%) had attained short or medium higher education, and 2,410 (4%) had completed long higher education.

A recurrent PE event within the first year occurred in 1,685 patients. The proportion of recurrence was 4 % for patients with basic education or high school/vocational education and 5 % for those with short/medium higher and long higher education (p = 0.459). We found no differences in the cumulative incidence of recurrence across educational levels (Gray's test p = 0.371) (Figure 7). An absolute risk regression model confirmed that educational level did not affect the risk of recurrent PE after adjusting for age, sex, comorbidities and year of PE diagnosis. The relative absolute risk of PE recurrence was 1.01 (95% CI: 0.89-1.13) for high school/vocational education compared to basic education, 1.02 (95 % CI: 0.87-1.19) for short/medium higher education and 0.94 (95% CI: 0.70-1.25) for long higher education.

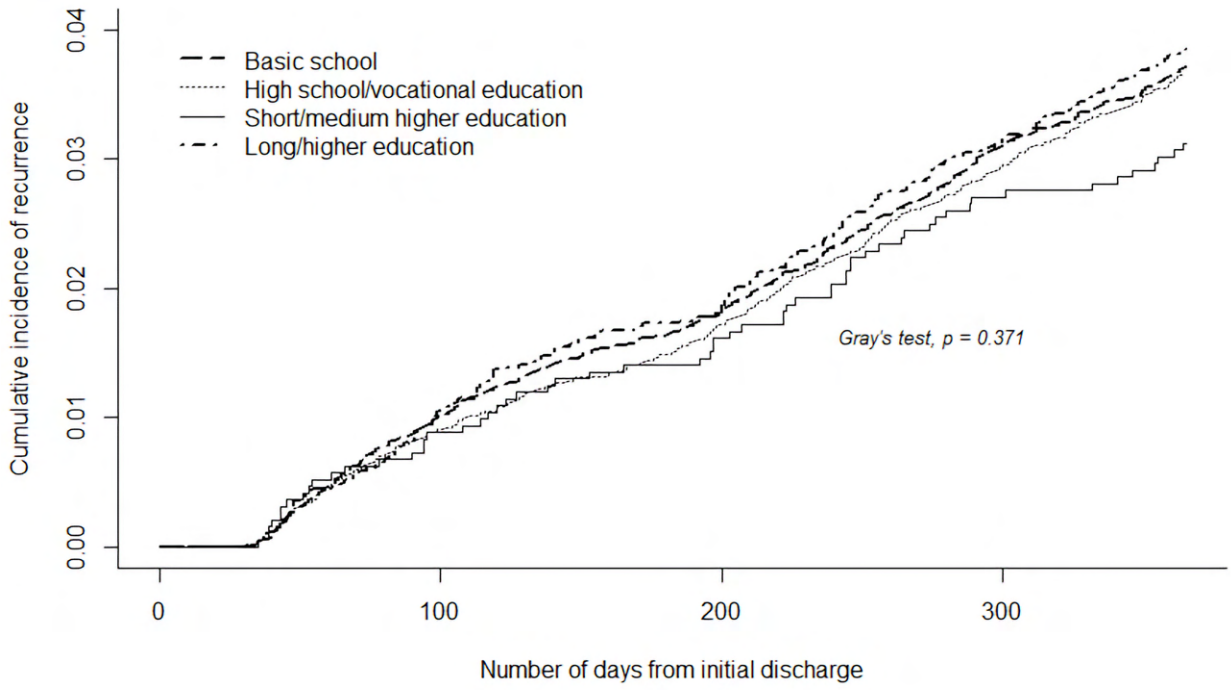

Figure 7. *Unadjusted cumulative incidence for recurrence of pulmonary embolism across level of education. Paper II.*

The proportion of patients who died within the first 30 days following their PE diagnosis varied significantly by educational level, with 15 % for basic education, 11 % for high school/vocational education, 9 % for short/medium higher education, and 8 % for long higher education (p <0.001). Within the first year, all-cause mortality rates across the educational groups were 32 %, 26 %, 23 % and 20 %, respectively. Examining the cumulative incidence of all-cause death

within the first year confirmed the decreasing effect of higher educational level (Gray's test p <0.001) (Figure 8).

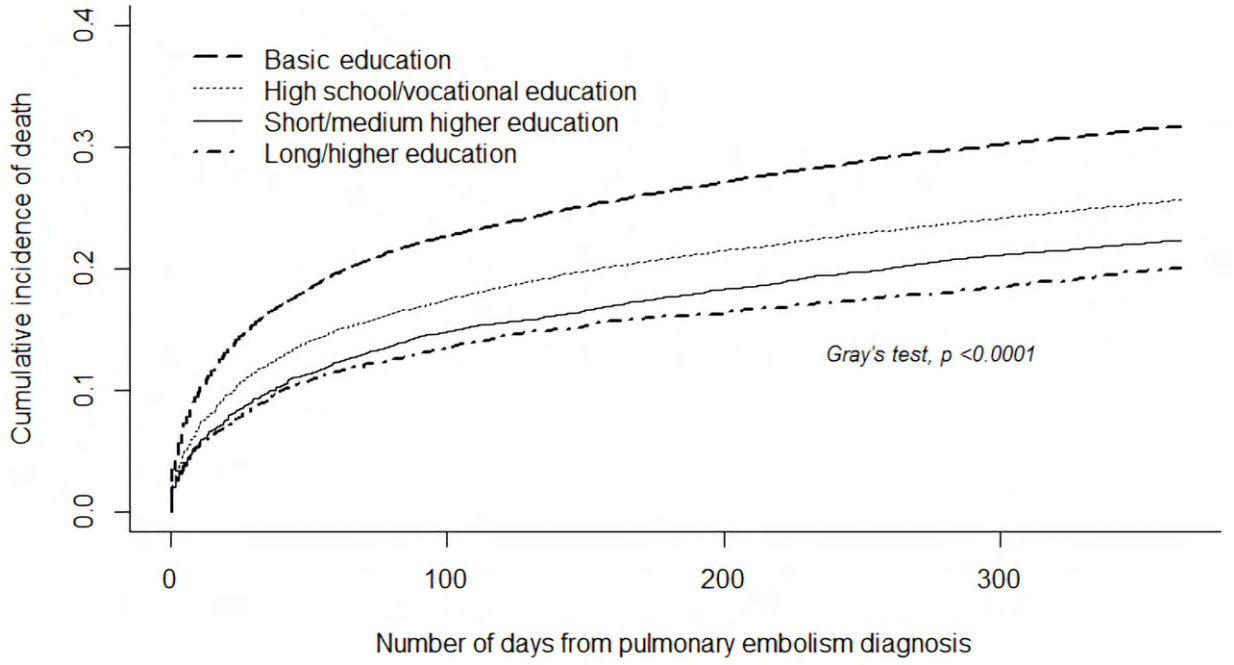

Figure 8. *Unadjusted cumulative incidence of 1-year mortality across level of education. Paper II.*

After adjusting for age, sex, comorbidities, and year of diagnosis, the absolute risk of death within one year was reduced by a factor 0.93 (95% CI: 0.90-0.96) for high school/vocational education compared to basic education, 0.88 (95% CI: 0.84-0.92) for short/medium higher education, and 0.83 (95% CI: 0.77-0.90) for long higher education.

Paper III

Between 2013 to 2018, we identified 3,185 cases of PE in patients over 18 years of age with TnI measurements and 2,545 cases with TnT measurements, all measured within one day before after admission. Overall, 3,278 patients (58 %) had troponin levels above the individual upper threshold at time of admission. Compared to patients with troponin levels within the normal reference range, those with elevated troponin were generally older (median age: 74 vs. 67 years) with a similar distribution of sex in both groups (50 % female). Patients with elevated

troponin had a higher prevalence of comorbidities, including previous myocardial infarction (8% versus 6%), cancer (18% versus 15%), heart failure (8% versus 6%), COPD (10% versus 8%), and renal disease (5% versus 6%). However, a history of deep venous thrombosis was more common in patients with normal troponin level (19% vs. 15%). The median eGFR was lower in patients with elevated troponin levels compared to those without (68 vs. 83 ml/min), and CRP levels were higher (35 vs. 25 mg/L). A significant difference in 30-day all-cause mortality was observed between the two groups (11% vs. 3%), a finding supported by an adjusted Cox regression analysis ($HR_{elevated\ troponin}$ 2.74; 95% CI: 1.94–3.86).

In the second part of the analysis, patients were divided into five equal-sized groups based on increasing troponin levels. The distribution of sex remained consistent across all quintiles (approximately 50% female in each group), while age increased with higher troponin levels, from a median of 63 years in the 1st quintile to 74 years in the 5th quintile. The prevalence of ischemic heart disease increased across the quintiles (11%, 18%, 18%, 15% and 12% from the 1st to the 5th quintile respectively), as did the prevalence of heart failure (4%, 8%, 11%, 9% and 7%). eGFR levels decreased across the quintiles (85 ml/min, 81 ml/min, 73 ml/min, 71 ml/min and 67 ml/min), while CRP levels increased (23 mg/L, 24 mg/L, 32 mg/L, 36 mg/L and 36 mg/L). All-cause mortality within 30 days of admission also increased with higher troponin levels, from 1% in the 1st quintile to 15% in the 5th quintile (Figure 9). This trend was further supported by an adjusted Cox regression analysis, using the 1st quintile as the reference group: 2nd quintile HR: 0.84 (95% CI: 0.36-1.95), 3rd quintile HR: 3.74 (95% CI: 1.94-7.24), 4th quintile HR: 4.67 (95% CI: 2.44-8.96), and 5th quintile HR: 6.55 (95% CI: 3.46-12.38).

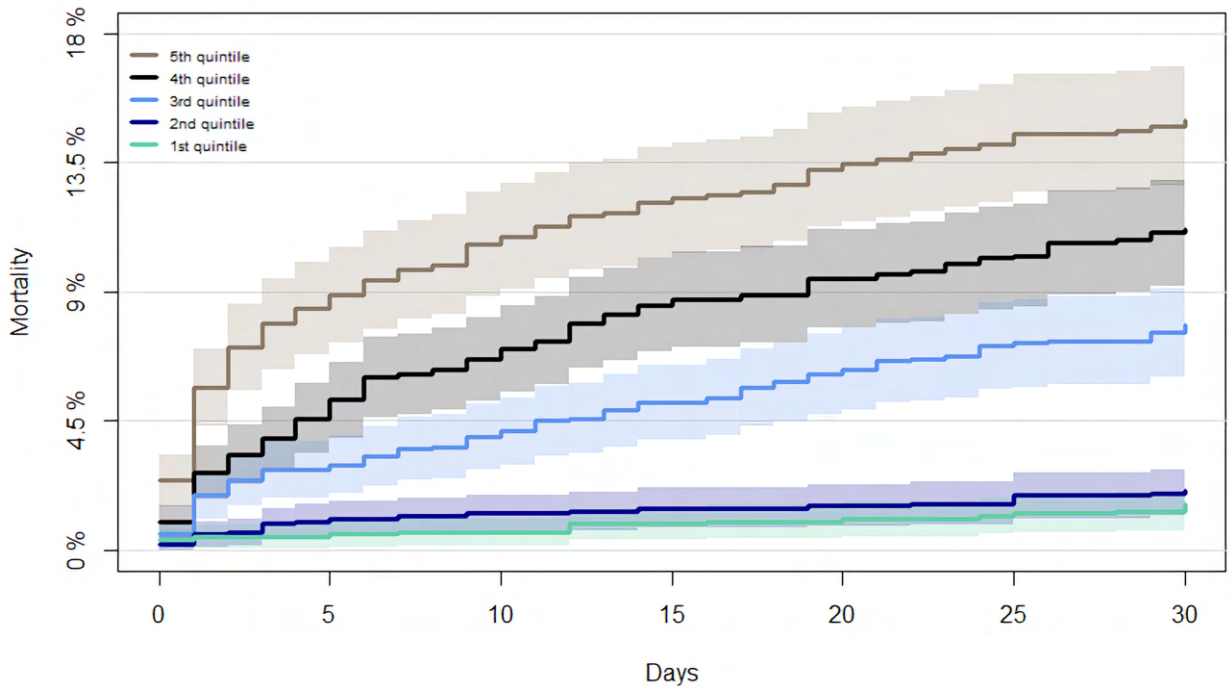

Figure 9. *Cumulative 30-day mortality across level of troponin. Paper III.*

Paper IV

Between 2013 and 2018, a total of 1,539 PE patients aged 18 years or older, who had at least two TnI measurements within three days of admission, were identified, along with 1,332 patients who had repeated TnT measurements. Altogether, 3,799 troponin measurements were analysed. There were no significant differences in age (median 72 years) or sex (50% female) when comparing the TnI and TnT cohorts. In both groups, 7 % of patients died within 30 days of admission.

Based on latent class trajectory modelling three distinct troponin trajectories could be identified in both cohorts (Figure 10). Despite small variations in number of patients allocated to each trajectory, the overall troponin patterns were consistent across the cohorts. In both groups, trajectory I exhibited consistently low levels of TnI (median 15 ng/L) or TnT (median 18 ng/L) throughout the three-day observation period (n_{TnI} = 286, 18 % and n_{TnT} = 472, 36%). Trajectory II, which comprised the majority of patients (n_{TnI} = 1,076, 70 % and n_{TnT} = 724, 55%), showed an initially elevated TnI (o hour median 140 ng/L) or TnT (0 hour median 86 ng/L),

followed by a plateau and gradual decline in TnI (7 hour median 119 ng/L, 20 hour median 148 ng/L) or TnT (6 hour median 79 ng/L, 21 hour median 77 ng/L). Trajectory III (n_{TnI} = 177, 12% and n_{TnT} = 127, 10%) was characterized by initially high TnI or TnT levels, followed by a rapid rise in TnI (0 hour median 111 ng/L, 7 hour median 1,065 ng/L) or TnT (0 hour median 85 ng/L, 6 hour median 342 ng/L) within the first 10 hours, and then a subsequent decline in TnI (20 hour median 964 ng/L) or TnT (21 hour median 265 ng/L) within the first 24 hours.

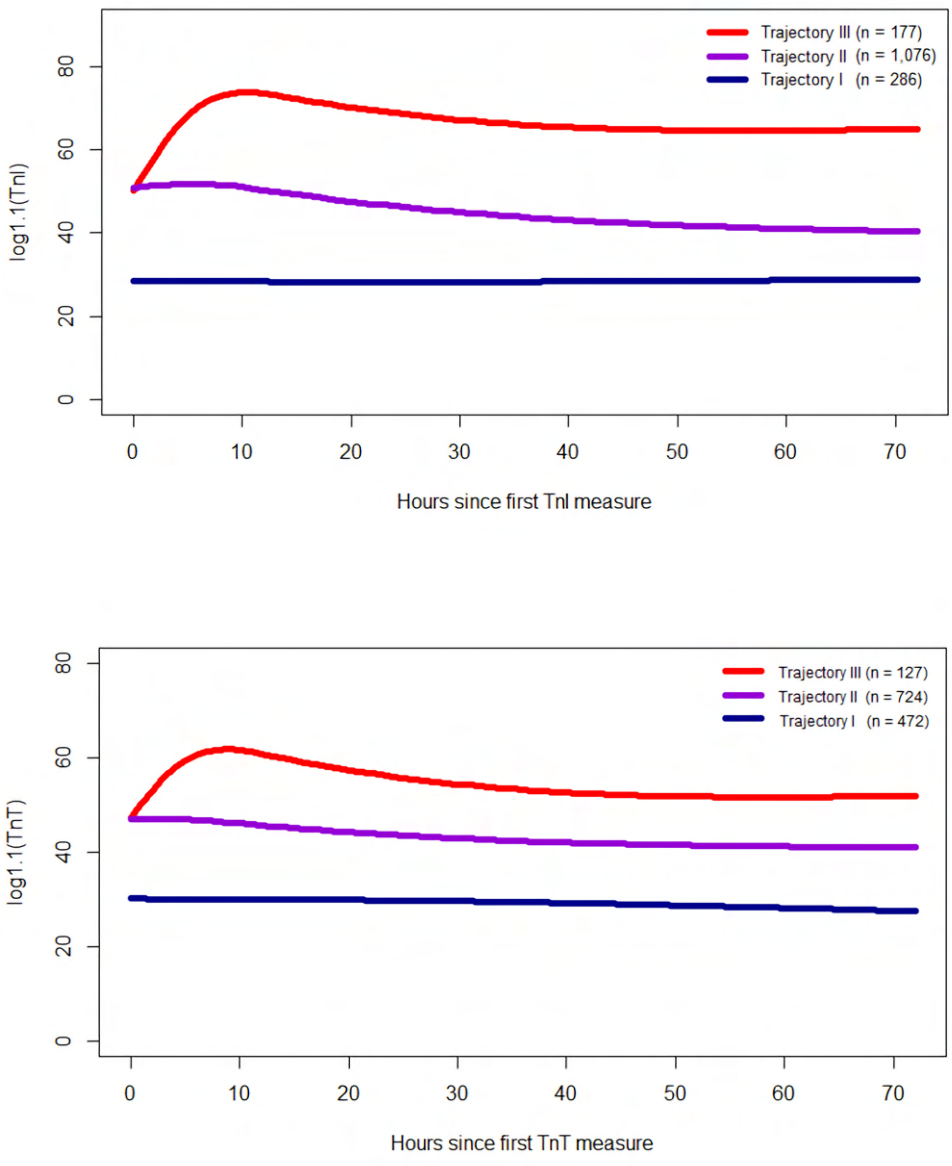

Figure 10. *Identification of three TnI (top) and TnT (bottom) trajectories using latent class trajectory modelling in PE patients. TnI: troponin I, TnT: troponin T. Paper IV.*

Baseline characteristics were similar across the three trajectories in terms of sex and comorbidities, though patient age increased with trajectory level, ranging from 67/70 years in trajectory I to 73/75 years in trajectory III for the TnI and TnT cohorts, respectively.
The 30-day all-cause mortality rates were significantly higher in trajectories II and II compared to trajectory I in both the TnI cohort (3%, 7%, and 18% for trajectories I, II and II, respectively) and the TnT cohort (1%, 9% and 20% for trajectory I-III). The median time to death shortened as the trajectory level increased, with trajectory I having a median of 10/14 days, trajectory II with 3/6 days and trajectory III with 3/3 days for the TnI and TnT cohort, respectively.
In the TnI cohort, patients in trajectory II had a sevenfold higher risk of 30-day all-cause mortality compared to those in trajectory I (HR 7.42, 95% CI 1.00-54.84), while patients in trajectory III exhibited a sixteen times higher risk (HR 16.42, 95% CI 2.42-127.29). Similarly, in the TnT cohort, patients in trajectory II had a threefold higher risk of 30-day mortality compared to trajectory I (HR 2.93, 95% CI 1.17-7.33), with those in trajectory III showing an eightfold increased risk (HR 8.21, 95% CI 2.78-24.19).

Paper V

A total of 210 patients with intermediate-high risk PE were included in this study. Among them, 39 patients (19%) reported experiencing syncope. A comparison of baseline characteristics between patients with and without syncope revealed that syncope was more common in younger male patients (66% male, mean age 63 years). Other demographics did not differ significantly between the groups. Clinical findings at admission were generally similar, with the exception of systolic blood pressure, which was significantly lower in patients with syncope (mean 129 mmHg) compared to those without (mean 137 mmHg) ($p = 0.04$), although still within normal range for both groups. There were no significant differences in respiratory status between the groups, though patients with syncope had a slightly lower median blood pH (7.41) compared to those without syncope (7.44) ($p = 0.01$), despite no differences in pO_2 and pCO_2 levels.
Arrythmias, particularly atrial fibrillation, were more frequently observed in patients with syncope (10%) compared to those without (3%) ($p = 0.04$). However, ECG findings indicative of RV strain did not differ significantly between the groups. The clot burden, expressed as mean

RMS measured from the diagnostic CTPA, was higher in patients with syncope (mean RMS 21) compared to those without (mean RMS 19) (p = 0.04). Additionally, the mean RV/LV ratio was significantly increased in patients with syncope (1.6), compared to those without (1.4) (p <0.001).

Multivariate logistic regression analysis revealed that only younger age (OR 0.96, 95% CI 0.93-0.99), lower BMI (OR 0.92, 95% CI 0.85-0.99), and an increased RV/LV ratio (OR 5.24, 95% CI 1.62-17.01) were independently associated with syncope.

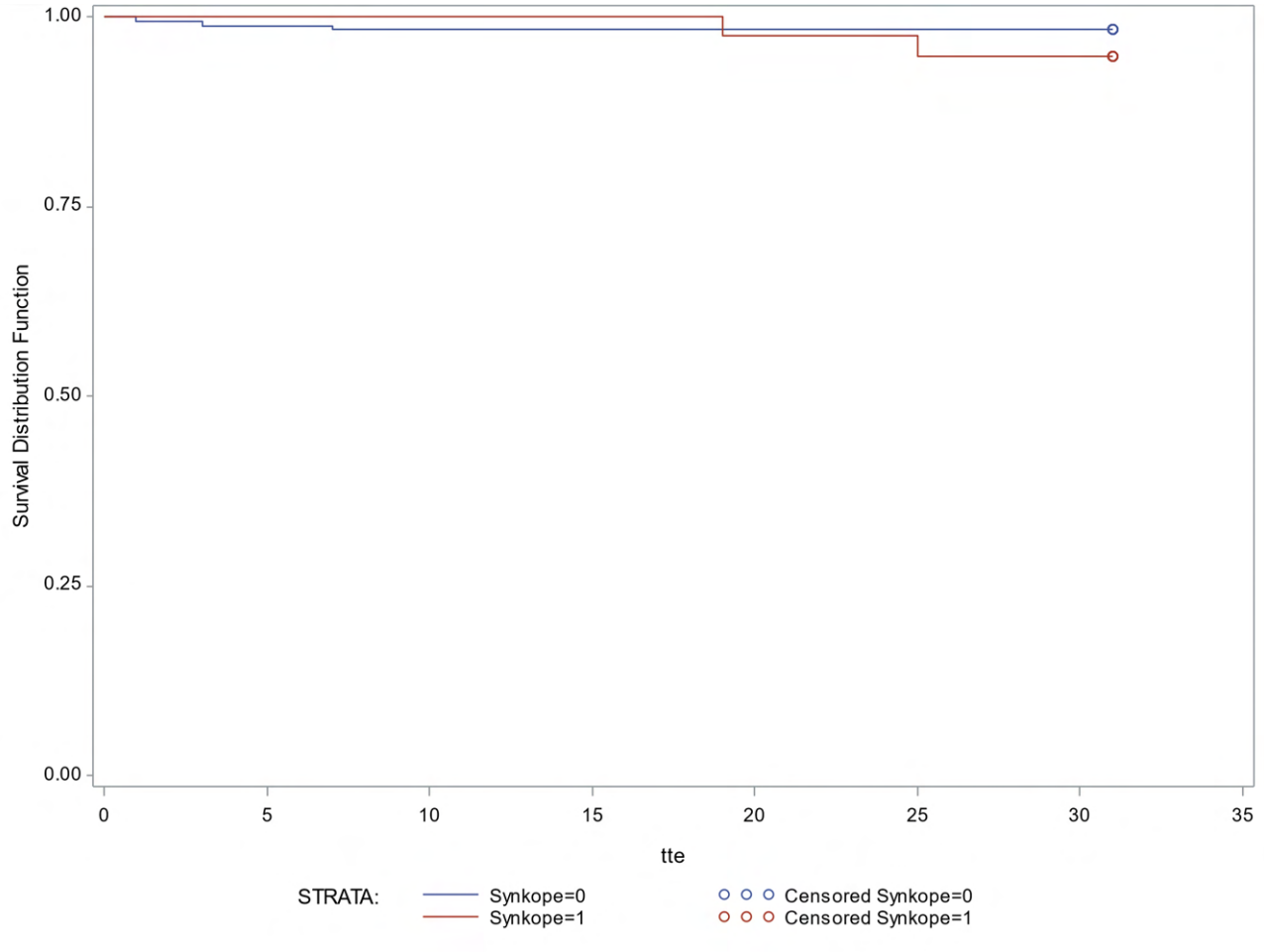

Figure 11. *Kaplan Meier survival curve comparing intermediate-high risk pulmonary embolism patients with and without syncope. Paper V.*

Within the overall cohort, five in-hospital deaths and five cases of administration of rescue thrombolysis were reported (Figure 11). A multivariate regression analysis assessing the

relationship between syncope and a composite endpoint of in-hospital death and rescue thrombolysis, revealed that patients with syncope had an OR of 9.28 (95% CI: 2.04-42.32, p = 0.004) compared to those without after adjustment for sex, study treatment and sPESI score.

DISCUSSION

The primary aims of the thesis were to examine temporal trends in the incidence and survival of PE and to identify factors associated with an increased risk of adverse outcomes, ultimately improving risk assessment strategies.

Between 1999 and 2018, the incidence of PE rose significantly across all age-groups, while the 1-year mortality rate steadily declined. Although educational level, as a marker of social class, did not affect the risk of PE recurrence, individuals with only basic education had a notably higher risk of mortality after a PE event. Additionally, elevated troponin levels at the time of PE diagnosis were strongly linked to increased mortality. Three distinct patterns in repeated troponin measurements were identified, with an early rise in troponin concentration significantly associated with higher 30-day mortality, compared to patients with stable, low levels. Finally, syncope as an early symptom of PE was linked to increased RV strain in patients with intermediate-high risk PE and was also associated with a higher likelihood of adverse in-hospital outcomes.

Temporal trends in incidence and mortality

Previous studies from Western countries have consistently reported an increasing temporal incidence of PE[7,67-71], a trend that aligns with the findings of this thesis. The growing incidence may, in part, be attributed to the aging global population, as evidenced by the increasing mean age of patients diagnosed with PE over time. Moreover, the introduction of CTPA in the late 1990s significantly transformed PE diagnostics[69]. Due to its precision and widespread availability, there is concern about potential overdiagnosis of PE, leading to a rise in incidental findings of clinically insignificant PE cases[19,72]. This concern is supported by our finding of a 25% increase in PE diagnoses among patients treated in outpatient settings, likely linked to routine CT evaluations in cancer care or other chronic diseases.

Our analysis also revealed that the observed rise in PE incidence is influenced by comorbid conditions. Adjusting for these comorbidities significantly reduced the IRR, suggesting that the temporal increase in PE cases is largely driven by changes in the prevalence and severity of these conditions. For instance, cancer and its treatment are well-documented risk factors for thromboembolic events, including PE[73,74]. With the increasing global burden of cancer, the expanded use of cancer therapies, and the growing reliance on CT imaging for disease monitoring, the association between cancer and PE has strengthened, as reflected both in our results and in other studies[75].

Additionally, obesity, a critical and growing health issue in many Western countries, particularly among younger populations, is a significant risk factor for thrombosis[76]. Hypercoagulability and venous stasis in the lower extremities are key mechanisms contributing to the elevated risk of thromboembolic events in obese individuals[77,78]. Although this study faced limitations in accurately capturing obesity via ICD codes, likely underestimating the true prevalence of obesity[79], we still observed an increasing proportion of obese patients within our cohort. This trend could partly explain the increasing incidence of PE, even among younger age groups.

Mortality following PE decreased significantly across all age-groups in this study, in accordance with existing literature[7,22,80]. This decline may reflect the shift toward detecting less severe cases of PE, due to advancements in diagnostic techniques as discussed above. However, the decreasing trend in PE mortality also highlights the impact of improved patient management, including early risk stratification, adherence to treatment guidelines, and the development of advanced therapeutic options. In this thesis, the mortality rate ratios were amplified after adjusting for age, sex, and comorbidities, further suggesting that the fatality rate of PE itself has declined due to these advancements in care.

Impact of socioeconomic status

As the incidence of PE continues to rise, it becomes increasingly important to optimize risk assessment and treatment strategies to maintain a downward trend in case fatality rates. Exploring factors associated with increased short-term complications, such as socioeconomic status, is essential in this effort.

The influence of socioeconomic status on overall morbidity and mortality is well-documented[81-83], yet it has been less frequently examined in relation to PE. A prior Danish study did investigate the impact of socioeconomic factors on venous thromboembolism, finding that individuals with higher levels of education, income, and employment had a 30% lower risk of experiencing a first-time venous thromboembolism compared to those with lower socioeconomic status[34]. While the exact mechanisms remain speculative, it is suggested that differences in health-related behaviour may play a significant role. Individuals with lower socioeconomic status may have reduced access to preventive health-care services, including regular check-ups and screening and vaccination programs[84-86].

Several risk factors for PE, such as obesity, physical inactivity, and trauma, are more prevalent in individuals with lower socioeconomic status[87,88]. Psychosocial stress, which is often associated with lower social class, may also exacerbate PE risk by promoting an imbalance in coagulation and inflammation, thus increasing procoagulant activity[89-91].

Despite these potential pathophysiological links between PE and socioeconomic position, no previous studies have explored how social class impacts the risk of recurrent PE. Recurrence is often influenced by treatment discontinuation and the patient's overall risk profile[92], which may be affected by educational status. However, in our study, we found no significant difference in the 1-year recurrence rate of PE, which remained between 4-5%, regardless of educational level. Due to the lack of registration, we were unable to assess patient risk profiles or treatment compliance, both of which are key factors that could have contributed to the observed outcomes, and thus remains an important limitation to the study.

Our findings revealed that 30-day mortality was significantly higher among patient with basic education (15%) compared to those with long higher education (8%). This inverse correlation between educational level and mortality persisted at every time point during the first year following PE diagnosis. Even after adjusting for sex, age comorbidity and the year of PE diagnosis, the association between lower educational attainment and increased mortality remained highly significant. Therefore, a greater comorbidity burden alone does not appear to fully explain the higher mortality risk in patients with lower education. Delayed access to medical care among socially disadvantaged patients, potentially due to lower health awareness and symptom recognition, may be a contributing factor to the observed mortality disparity[93].

Another possible explanation could involve differences in the quality of care, as patients with

lower socioeconomic status may be more likely to be treated at low-volume hospitals, where clinical expertise may be less developed[94,95].

Given these findings, it remains clear that socioeconomic status is an important factor to consider in the management and follow-up of PE. Tailored approaches to care that account for social disparities may help to improve outcomes in these vulnerable populations.

Troponin and risk assessment

Troponins are well-established biomarkers in risk stratification for PE and have been incorporated into the ESC risk stratification tool[10]. A troponin level exceeding the upper threshold at the time of PE diagnosis is a critical factor, as it has been shown to significantly increase the 30-day mortality risk[45]. However, in patients with unstable coronary artery disease, it is well-known that the specific increase in troponin concentration assessed through repeated measurements, correlates with the risk of adverse events within the first 24 hours[96]. Despite its utility, the simplified application of troponins in PE risk assessment, is partly due to lack of relevant studies on the extended use of troponin measurements in this context.

We found an increase in crude mortality risk, which rose from 1% in patients with troponin levels in the lowest quintile to 16% in those in the highest quintile. Interestingly, no significant difference in mortality was observed between patients in the first and second quintiles. These findings are valid after adjusting for key confounding variables, including sex, age, comorbidity, haemoglobin level, eGFR and CRP. This trend is consistent with prior research by Konstantinides et al., who categorized troponin concentrations into low, moderate and high ranges, and demonstrated a stepwise increase in in-hospital mortality, clinical complications, and incidence of recurrent PE in patients with higher troponin levels compared to those with only moderate elevation[49]. Similar, other studies have identified a direct link between elevated troponin concentrations and the severity of PE, as well as adverse in-hospital outcomes[50,97].

A notable challenge in using troponins for risk stratification is the variation in assay methods across institutions, both nationally and internationally, making the establishment of universal cut-off values for troponin concentration categories difficult. Additionally, some PE patients may exhibit a delayed rise in troponin levels, likely due to gradual RV failure. This underscores the potential value of repeated measurements troponin measurements, which may enhance

the identification of PE patients in high risk of adverse outcomes. However, only limited research has investigated the kinetics of serial troponin measurements in this population. Müller-Bardorf et al. reported that in four out of nine patients, TnT measurements were initially within normal ranges upon admission but increased to elevated levels within eight hours, with no elevation persisting beyond 40 hours[98]. Similarly, Ferrari et al. highlighted a significant risk of misclassifying PE severity when relying solely on initial troponin levels, with 15% of patients exhibiting normal troponin concentrations at first assessment, only to have elevated levels at subsequent measurements. Their findings suggested that TnI peaks were typically reached within eight hours[99]. Unfortunately, due to the small sample sizes in these studies, no definitive conclusions could be drawn regarding the mortality risk associated with delayed troponin elevation.

In this thesis, we identified three differing dynamic patterns of troponins similar in both the TnI and TnT cohort. Approximately 10-12% of patients exhibited a peak increase in TnI/TnT concentration within 8-10 hours after the initial assessment (trajectory III). This likely reflects a more severe thrombus burden, leading to progressive RV strain. Most patients, however, had elevated TnI/TnT at first measurement, followed by a steady decline in subsequent concentrations (trajectory II).

In terms of clinical outcomes, patients with elevated but stable levels of TnI/TnT (trajectory II) had a three to sevenfold higher risk of short-term mortality compared to those with consistently low levels (trajectory I). Furthermore, patients exhibiting a steep increase in TnI/TnT (trajectory III) had an eight to sixteen times higher mortality risk. Thus, these results emphasize the prognostic importance of troponin dynamics in PE patients, underscoring the necessity of serial measurements within the first 24 hours of admission to accurately assess patient risk.

Syncope in intermediate-high risk patients

Syncope has been widely discussed for its potential prognostic significance in PE. In this thesis, we identified syncope in approximately one fifth of patients with intermediate-high risk PE as part of their pre-hospital presentation, which is consistent with findings from previous studies[52,54]. The present thesis focuses exclusively on patients with intermediate-high risk PE,

thereby excluding hemodynamic instability as a confounding factor – a factor that has been a limitation in other studies involving mixed PE populations[100].

In this thesis we found an increased RV/LV ratio, to be independently associated with syncope. This suggests that syncope, in a cohort of hemodynamically stable patients, may represent a manifestation of the most severe PE cases. While clot burden and RV/LV ratio are only moderately correlated, RV failure is influenced by both cardiac and respiratory reserves[2,101]. Our finding that lower BMI is independently associated with syncope underscores the role of reduced physiological reserve, which may heighten susceptibility to sudden hemodynamic changes in cases of severe pulmonary obstruction.

Although previous studies have identified older age and comorbidities as factors increasing the likelihood of syncope in PE patients[102], the current thesis does not support this. Interestingly, younger patients were more prone to syncope, which may indicate a reduced pulmonary collateral arterial supply or a diminished LV resilience against elevated RV pressure. This could increase their vulnerability to hemodynamic stress in the context of PE.

In one-way analysis syncope was associated with the presence of arrythmias, particularly atrial fibrillation, on the index ECG. However, it remains speculative whether the arrythmias in the exact moment of syncope, the Bezold-Jarisch reflex[103], or transient drop in blood pressure could explain the connection between syncope and increased RV strain. Further investigation is needed to clarify the precise mechanisms involved.

The prognostic significance of syncope in PE remains a topic of ongoing debate[55,57-59,104,105]. Due to the relatively small sample size in this thesis, we were unable to establish a direct link between syncope and in-hospital mortality risk. However, syncope was found to increase the combined risk of in-hospital mortality and the need for rescue thrombolysis almost eightfold, even after adjustment for sPESI score. This suggests that syncope could serve as a critical marker of severity in hemodynamically stable PE patients.

The modified FAST score (H-FABP (or high-sensitive troponin T), Syncope, Tachycardia score) has been proposed as a model for identifying the most severe cases among hemodynamically stable PE patients, incorporating the prognostic relevance of syncope[58,106,107]. While the score has been validated in observational studies[108], it has not yet been tested in randomized clinical trials aimed at guiding therapeutic decisions.

Thus, syncope appears to represent a subset of hemodynamically stable PE patients with significant RV strain and an elevated risk of adverse in-hospital outcomes. Future clinical trials should explore whether incorporating syncope into risk assessment models could improve the stratification and management of this subgroup of PE patients.

LIMITATIONS

The included studies have limitations that should be considered when interpreting the results. First and foremost, study I-IV are based on data from Danish national registries and thus, conclusions are built on associations and not causalities. Specific limitations affecting each study is addressed in the following sections.

Paper I

Due to the retrospective nature of the data collection, it is not possible to distinguish whether the observed increases in PE incidence, comorbidities, and other health-related factors are due to changes in registration practices over time or represent actual trends. However, since financial incentives for enhancing registration practices in Denmark were implemented before our study period, this alone cannot account for the significant rise in PE incidence observed during the middle of our study period.

Paper II

In this study, socioeconomic status was defined by the highest level of education attained at the time of PE diagnosis. Given the diverse age range of patients in PE populations, relying solely on occupational status and household income may not accurately reflect socioeconomic position. However, a limitation related to educational status arises for younger patients who may not have completed their education by the time of diagnosis. Nonetheless, a sensitivity analysis showed that the association between education and the risk of death and recurrence following PE remained consistent with the main findings when excluding patients younger than 40 years of age.

Paper III and IV

These studies focus on unselected PE populations, as data on hemodynamic status and echocardiographic findings are not available from the retrospective data collection. As a result, we cannot determine whether troponin concentrations and their dynamics improve prognostic potential when combined with other relevant factors. The use of various troponin assays across different regions in Denmark restricts our ability to establish specific cut-off values in Paper III and to include specific intercepts in our model in Paper IV. Additionally, due to the lack of information regarding the rationale for measuring multiple TnI or TnT concentrations during the acute phase of PE, its potential prognostic significance remains unaddressed in Paper IV.

Paper V

The study cohort is relatively small, with limited exposures and events, which restricts our ability to draw strong conclusions regarding the pathophysiology and prognostic significance of syncope. Thus, the results of the multivariate analyses should be interpreted cautiously and validated in other cohorts.

CONCLUSIONS

Paper I

In this comprehensive population-based nationwide Danish study, we observed a consistent rise in the incidence of PE from 1999 to 2018, accompanied by a steady decline in 1-year mortality rates across all age groups. Although the increasing incidence could be partially attributed to advancements in diagnostic accuracy, the growing prevalence of comorbidities that are known risk factors for PE should not be overlooked. This underscores the importance of ongoing efforts toward the early prevention of PE.

Paper II

In this nationwide population-based study from 1998 to 2018, we identified notable disparities in both 30-day and 1-year mortality following a first-time PE based on educational level. Nevertheless, no significant differences in the risk of recurrent PE within the first year were observed across the education groups. The increased mortality risk among patients with basic education was not explained by a higher burden of comorbidities, underscoring the importance of providing targeted, socially tailored follow-up care for PE patients.

Paper III

This comprehensive register-based study underscores the prognostic value of elevated troponin levels at diagnosis in acute PE patients. Additionally, we observed a stronger association between higher troponin levels and an increased risk of 30-day mortality. This insight could play a critical role in advancing risk stratification of PE patients, however, further confirmation through future therapeutic trials is necessary.

Paper IV

This nationwide register-based study is the first to identify distinct patterns in TnI and TnT concentrations among unselected PE patients. We show that a steep rise in TnI or TnT levels within six to ten hours following diagnosis is linked to a higher risk of 30-day mortality,

compared to PE patients with consistently low and stable levels. This finding suggests that early serial troponin sampling could improve the risk assessment of PE patients and warrant further investigation in future research.

Paper V

This clinical trial-based study shows that syncope in patients with intermediate-high risk PE is linked to greater RV strain and an elevated risk of adverse in-hospital outcomes. These findings emphasize the prognostic importance of syncope in this patient group, underscoring the need for closer monitoring and potentially more aggressive treatment approaches. Future prospective trials should explore whether syncope should be incorporated into enhanced risk assessment models for intermediate-high risk PE patients to optimize patient outcomes.

PERSPECTIVES

Early risk assessment is crucial in patients with PE due to the wide clinical spectrum and associated risks. Effective risk evaluation allows for the selection of appropriate treatment strategies and the optimization of patient outcomes. This thesis focuses on improving risk assessment by incorporating an extended use of clinical parameters related to the severity of PE. However, it is important to note that our findings, primarily derived from register-based data, are hypothesis-generating and require validation in future randomized trials. The most effective and clinically relevant combinations of factors associated with PE mortality has yet to be established, highlighting the need for further research in this area.

Over the years, the array of treatment options for PE patients has expanded significantly. This is particularly true for patients classified as intermediate-high risk PE patients, who, given their increased risk of hemodynamic deterioration and mortality, can be offered a variety of pharmacological and invasive treatment alternatives beyond standard anticoagulation. Ongoing and future trials are crucial to identify which treatment options represents the best balance between minimizing complications and maximizing efficacy, ultimately ensuring optimal outcomes for patients.

SUMMARY

Background: PE is a prevalent acute cardiovascular condition affecting a diverse global population. With an ageing demographic and improved diagnostic tools, the burden of PE on healthcare systems is expected to grow. Optimizing risk assessment tools and clinical guidelines is crucial to maintain the decreasing trend in case fatality and to ensure that new, advanced therapies are accessible for those in need.
The thesis thus investigates the following key aspects of PE:

1. Age-specific trends in the incidence and mortality over two decades. (Paper I)
2. The relationship between socioeconomic position, indicated by educational attainment, and the risk of PE recurrence and mortality. (Paper II)
3. The correlation between troponin levels at admission and 30-day mortality risk. (Paper III)
4. Patterns of troponin development during the acute phase of PE and their association with 30-day mortality. (Paper IV)
5. The pathophysiology behind syncope in intermediate-high risk PE patients and its association with in-hospital adverse outcomes. (Paper V)

Methods: Data for Paper I-IV were obtained from Danish national registries, involving demographics, hospitalizations, diagnoses, laboratory results, education, and mortality, linked via unique civil registration numbers. Paper V sourced data from the randomized clinical trial STRATIFY, conducted at Rigshospitalet, Copenhagen University Hospital, involving patients ≥18 years with confirmed intermediate-high risk PE.
Paper I is a national cohort study of 65,478 patients ≥18 years diagnosed with first-time PE between 1999 and 2018, categorized by age and study period to assess trends in incidence and all-cause mortality. Paper II includes 52,184 patients ≥18 years diagnosed with PE in the same period, exploring recurrent PE and mortality across educational levels. Paper III examines 5,639 patients diagnosed with PE from 2013 to 2018, focusing on TnI and TnT levels measured at admission and risk of 30-day mortality. Patients were divided by whether their troponin levels exceeded upper reference threshold and further stratified by troponin concentration quintiles. Paper IV involves 2,871 patients from the same cohort with repeated troponins measurements in the acute phase of PE, analysing the dynamics and their association with 30-day mortality.
Paper V is a prospective study of 210 patients with intermediate-high risk PE, documenting syncope as a pre-hospital symptom and its association with clot burden, RV/LV ratio on CTPA, echocardiographic parameters, and ECG findings. The cohort was divided into two groups based on the presence of syncope, and patients were followed until in-hospital death, rescue thrombolysis or discharge.

Results: Between 1999 and 2018, the incidence of first-time PE tripled across all age groups, while mortality rates significantly decreased. Adjustments for age, sex, and comorbidities had a modest effect on these trends.
In examining prognostic factors, no significant difference in the risk of PE recurrence across level of education was found, however, individuals with higher education demonstrated lower 30-day and 1-year mortality rates, compared to patients with basic education, even after accounting for demographic variables.
Elevated troponin levels in PE patients were strongly associated with higher mortality, with a dose-response relationship indicating that patients with increasing troponin levels faced significantly higher 30-day all-cause mortality. This finding was further expanded by identifying three distinct troponin trajectories. Patients with early spikes in troponin levels exhibited an eight to sixteen fold increase in 30-day mortality compared to those patients with stable, low levels.
Lastly, intermediate-high risk PE patients who experienced syncope demonstrated greater RV/LV ratio on CTPA. Syncope was associated with a significantly higher risk of in-hospital death or the need for rescue thrombolysis.

Conclusion: The significant increase in PE incidence alongside a decrease in mortality rates over the past two decades highlights the need for ongoing prevention efforts and optimization of risk assessment tools. The disparities in mortality rates based on educational levels, troponin levels, and presence of syncope indicates potential areas for enhanced risk stratification, ultimately improving clinical managing and patient outcomes.

DANSK RESUMÉ (DANISH SUMMARY)

Baggrund: Lungeemboli (LE) er en almindelig akut kardiovaskulær tilstand, som berør en heterogen global befolkning. Med en aldrende demografisk sammensætning og forbedrede diagnostiske muligheder forventes det, at belastningen af LE på sundhedssystemet vil stige. Optimering af risikovurderingsværktøjer og kliniske retningslinjer er afgørende for at opretholde den forbedrede overlevelse og sikre, at nye avancerede behandlinger er tilgængelige for patienter med behov.
Afhandlingen undersøger derfor følgende centrale aspekter af LE:

1. Tendenser i forekomst og dødelighed over to årtier. (Artikel I)
2. Forholdet mellem socioøkonomisk status, angivet ved uddannelsesniveau, og risikoen for recidiv samt død. (Artikel II)
3. Korrelationen mellem troponin-niveau ved indlæggelse og risikoen for 30-dages død. (Artikel III)
4. Mønstre i udviklingen af troponin i den akutte fase af LE og deres association med 30-dages død. (Artikel IV)
5. Patofysiologien bag synkope hos patienter med intermediær-høj risiko LE og associationen til adverse events under indlæggelse. (Artikel V)

Metode: Data til artikel I-IV blev indhentet fra danske nationale registre, der omfatter information om demografi, indlæggelser, diagnoser, laboratorieresultater, uddannelse og død, alle kombineret via patientens unikke CPR-nummer. Artikel V beror på data fra det randomiserede kliniske forsøg STRATIFY, udført på Rigshospitalet, involverende patienter ≥18 år med bekræftet intermediær-høj risiko LE.
Artikel I er et nationalt kohorte studie af 65,478 patienter ≥18 år diagnosticeret med førstegangs LE mellem 1999 og 2018 kategoriseret efter alder og studieperiode for at vurdere tendenser i forekomst og dødelighed. Artikel II inkluderer 52,184 patienter diagnosticeret med LE i samme periode og undersøger recidiv samt dødelighed betinget af uddannelsesniveau. Artikel III undersøger 5,639 patienter med diagnosticeret LE i perioden 2013-2018 med fokus på troponin I eller T niveau målt ved indlæggelse, stratificeret efter kvintiler af troponin koncentration og disses association med 30-dages mortalitet. Artikel IV involverer 2,871 patienter fra samme kohorte med gentagne troponin målinger i den akutte fase af LE, og analyserer dynamiske mønstre og disses association med 30-dages mortalitet.
Artikel V er et prospektivt studie af 210 patienter med intermediær-høj risiko LE, der undersøger associationen mellem synkope og trombebyrde, forholdet mellem højre og venstre ventrikels diameter, ekkokardiografiske parametre og elektrokardiogram fund samt risikoen for død under indlæggelse eller op konvertering til fulddosis trombolyse.

Resultater: Mellem 1999 og 2018 tredobledes forekomsten af LE uanset aldersgruppe, mens dødeligheden faldt signifikant. Justering for alder, køn og komorbiditeter havde en beskeden effekt på disse tendenser. Ved undersøgelse af prognostiske faktorer blev der ikke fundet signifikante forskelle i risikoen for LE recidiv afhængig af uddannelsesniveau, men individer med højere uddannelsesniveau udviste lavere 30-dages og 1-års mortalitet sammenlignet med patienter med grunduddannelse, selv efter justering for demografiske variable.
Forhøjede troponin niveauer hos LE patienter var stærkt korreleret til højere dødelighed med et dosis-responsforhold, der indikerer, at patienter med stigende troponinniveauer har en signifikant højere risiko for 30-dages død. Tre forskellige troponinforløb blev ydermere identificeret og afslørede, at patienter med tidlige abrupte stigninger i troponinniveau har en 8 til 16 gange forhøjet risiko for 30-dages død sammenlignet med patienter med stabile lave niveauer.
Patienter med intermediær-høj risiko LE og synkope havde en signifikant øget ratio mellem højre og venstre ventrikel på baseline CT-skanning. Synkope var forbundet med en signifikant højere risiko for død under indlæggelse og behov for fulddosis trombolyse.

Konklusion: Den markante stigning i forekomsten af LE sammen med et fald i dødeligheden over de seneste to årtier understreger behovet for forsatte forebyggelsesindsatser og optimering af risikovurderingsværktøjer. Ulighederne i dødelighed baseret på uddannelsesniveau, troponin-niveau og tilstedeværelsen af synkope indikerer potentielle områder for forbedret risiko stratificering, hvilket kan bidrage til forbedret klinisk behandling og patient overlevelse.

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APPENDIX

PAPER I

Pulmonary embolism: Age specific temporal trends in incidence and mortality in Denmark 1999-2018. Sonne-Holm E, Kjærgaard J, Bang LE, Fosbøl E, Carlsen J, Winther-Jensen M. Thrombosis Research. 2022 Feb;210:12-19.

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Pulmonary embolism: Age specific temporal trends in incidence and mortality in Denmark 1999–2018

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ABSTRACT

Background: Through the last two decades the prevention, diagnosis and treatment of pulmonary embolism (PE) has evolved along with demographic changes. The influence of these current transformations is important in the assessment of the future burden of PE. We aimed to describe age specific temporal trends in incidence of first-time PE and subsequent mortality.

Methods: We identified patients ≥18 years of age with a first-time in-hospital diagnosis of PE in Danish national registers. By dividing patients into seven age groups (18–34, 35–44, 45–54, 55–65, 65–74, 75–84, >85 years), age specific incidence and 1-year mortality rates were calculated for four different calendar periods between 1999 and 2018.

Results: From 1999 to 2018 65,478 patients with a first-time PE were identified. PE incidence per 100,000 person years increased during the study period in all age-groups (18–34 years: 10 to 18, 35–44 years: 18 to 35, 45–54: 26 to 63, 55–64 years: 42 to 123, 65–74 years: 92 to 229, 75–84 years: 166 to 383 and >85 years: 155 to 417), p_{trend} <0.0001 for all. During the study period 1-year mortality rate decreased from 4 to 2 per 10 person years in patients aged 65–74 years and this trend was found in all age groups (p_{trend} = 0.0001 for all).

Conclusion: Despite a decreasing mortality rate, incidence rate of PE increased in Denmark across all age groups from 1999 to 2018, reflecting improved sensitivity of diagnostic methods and changes in the burden of comorbid conditions, all together warranting a continuing need for early prevention of PE.

1. Introduction

Pulmonary embolism (PE) is the third most common acute cardiac condition [1] with an annual incidence rate ranging from 39 to 115 per 100,000 person years in epidemiological studies [2]. PE has a wide morbidity range, from the asymptomatic and incidentally discovered where 30-day mortality is less than 1%, to massive acute PE that often lead to progressive shock and death with a 90-day mortality ranging up to 30% [3].

With the introduction of Computed Tomographic Pulmonary Angiography (CTPA) around 1998, the detection of PE has improved [4]. Enhanced use of this and other similar diagnostic procedures is assumed to have increased the documented incidence of PE [5].

Risk factors convincingly demonstrated for PE include increasing age, malignancy, prolonged immobility, major surgery, obesity, use of hormonal contraception and postmenopausal treatment among women [6]. The occurrence and management of these different predisposing factors of PE have changed over the last decades. General life expectancy has increased by more than two years per decade during the past century in high-income countries such as Denmark leading to a growing elderly population prone to thromboembolic disease [7]. Malignancy, diagnosed or occult, and its treatment is known to be thrombogenic and the burden of cancer has increased markedly during the last decades [8]. Furthermore, obesity is positively associated with venous thromboembolism, and has become a significant challenge in Western society and health care system [9]. At the same time, awareness on the risk of thromboembolism post-surgery has improved leading to routine use of perioperative anticoagulation prophylaxis and early postoperative mobilization [10]. Lastly, in Denmark, national recommendations regarding the use of estrogen-containing oral contraceptive agents has

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changed around 2012 in order to lower the associated thrombogenic risk in women of reproductive age [11,12].

At present, it is unknown whether these currents trends in the management and prevention of PE and its risk factors have affected PE incidence and subsequent survival in different age groups in Denmark over the last two decades.

The aims of the study are 1) to examine temporal changes in age specific incidence rates of first-time acute PE in Denmark in the period 1999–2018 and 2) to determine temporal changes in age specific 1-year mortality rates following first-time acute PE in the same time period.

2. Methods

In this national study we identified patients ≥18 years of age with a first-time in-hospital diagnosis of PE between 1st of January 1999 and 31st of December 2018 using the Danish National Patient Register (DNRP). The DNPR covers data on all hospital admissions in Denmark since 1977 and since 1995, outpatient clinic contacts and emergency department contacts have also been included. Records include patients' unique civil registration numbers, admitting hospital and department, dates of admission and discharge and up to 20 diagnoses coded by physicians in charge of the patient admission and discharge. Diagnoses are coded using the International Classification of Diseases (ICD) codes. From 1995 the 10th revision, ICD10, replaced ICD8 [13]. According to Danish practice, the first-listed diagnosis in the patient record (A-diagnosis) is the main reason for the hospital contact. Any possible complications occurring during hospitalization are coded secondly (B-diagnosis). Our study population consisted of patients with an A-or B-first-time diagnosis of PE registered initially at hospital admission, during hospitalization, in the emergency department or at an outpatient clinic. We defined comorbidities as in-hospital diagnoses before the diagnosis of first-time PE. Information on all-cause mortality in the first year after the PE diagnosis was extracted from the Central Person Register.

In Denmark, a financial incentive has been introduced since 1996 to ensure accurate registration of diagnoses in the health care system. Most of the diagnoses of cardiovascular disorders, including codes for PE, have been shown to have a high validity [14,15]. According to Sundbøll et al. the positive predictive value of the ICD10 code for a primary diagnosis of first-time PE had a high positive predictive value of 95%. Less well validated is a secondary diagnosis of first-time PE with a positive predictive value of 67% and an outpatient diagnosis of PE with a positive predictive value of only 50% [15].

2.1. Statistical methods

The study period from 1999 to 2018 was grouped into four 5-year periods (1999–2003, 2004–2008, 2009–2013, 2014–2019). Temporal trends in baseline distributions of age-groups (18–34, 35–44, 45–54, 55–64, 65–74, 75–84, >85 years) and comorbidities (ischemic heart disease (IHD), heart failure (HF), previous acute myocardial infarction (AMI), cancer, atrial fibrillation (AFLI), obesity, diabetes, renal disease, chronic obstructive pulmonary disease (COPD), stroke/transient ischemic attack (TIA), peripheral arterial disease (PAD), hypertension and deep venous thrombosis (DVT)) were examined using Cochran-Mantel-Haenzsel and Cochran Armitage trend tests.

Assuming a Poisson distribution of data, incidence rates of PE in the various age-groups were calculated for each five-year calendar period. The entire Danish population ≥18 years of age were used as reference group. Incidence rates were specified as per 100,000 person years.

Rates of 1-year mortality were calculated for each calendar period in the different age-groups and were specified as per 10 person years. The trend in incidence and mortality rate in the various age groups were tested using a Cochran-Mantel-Haenzsel test.

To evaluate the potential effect of other factors associated with PE, incidence rate ratios and mortality rate ratios were calculated across calendar periods using the first calendar period as a reference and adjusted in two steps for 1) age and sex and 2) age, sex, IHD, CHF, AMI, cancer, AFLI, obesity, diabetes, renal disease, COPD, stroke/TIA, PAD, hypertension and DVT.

All analyses were performed in SAS 9.4 and figures were generated in R 3.6.1. A two-sided p-value of <0.05 was considered statistically significant.

2.2. Ethics

The Danish Data Protection Agency approved this study (2007-58-0015, internal reference GEH-2014-015, I-suite: 02733). Register studies do not require ethical approval in Denmark. Data was accessed via an encrypted server hosted by Statistics Denmark and all data was anonymized, and patient identity thereby protected.

3. Results

During the study period 1999–2018, 65,478 patients were diagnosed with first-time PE. The proportion of PE cases in women declined from 55% in first calendar period, 1999–2003, to 51% in the fourth calendar period, 2014–2018. The number of patients increased almost threefold during the observation period from 9359 in first period to 27,000 in the fourth period ($p < 0.0001$). Mean age increased significantly during the study period from 66 years of age to 68 years ($p < 0.0001$) (Table 1).

The proportion of PE diagnoses registered as A-diagnoses increased slightly from 68% to 70% from the first to the fourth calendar period ($p < 0.0001$) and the number of PE diagnoses registered in an outpatient clinic doubled from 26% to 51% ($p < 0.0001$).

In the youngest age groups, 18–34 years and 35–44 years, we found a significant decrease in the proportion of PE cases during the study period from 6% to 4% ($p < 0.0001$) and from 7% to 5% ($p < 0.0001$) respectively. In the age groups 45–54 and 55–64 years no significant changes in the proportion of patients during the study period were observed and the two age groups represented approximately 10% and 15% of PE patients respectively. The proportion of patients aged 65–74 years increased significantly from 22% to 28% during the study period ($p < 0.0001$). Among the oldest >85 years of age, no significant changes were observed, and the group represented approximately 15% of the patients (Fig. 1).

The proportion of patients diagnosed with IHD, cancer, AFLI, obesity, diabetes, renal disease, COPD, stroke/TIA, hypertension and DVT prior to their PE increased significantly from first to fourth period (Table 1). The proportion of patients with cancer prior to their PE almost doubled during the study period from 12% to 24% ($p < 0.0001$). The proportion of obese patients increased from 2% in first period to 6% in the fourth period ($p < 0.0001$). The proportion of patients diagnosed with DVT prior to their PE increased significantly from 15% to 22% ($p < 0.0001$). CHF were the only comorbidity diagnosis which showed a decreasing trend during the study period, from 14% to 9% ($p < 0.0001$).

Incidence of PE rose with increasing age (Fig. 2). In general, PE incidence increased across all age groups from 1999 to 2018 ($p < 0.0001$). Among the youngest patients, 18–34 and 35–44 years of age, incidence almost doubled and rose from 10 and 18 per 100,000 person years in first calendar period respectively to 18 and 35 per 100,000 person years in the fourth calendar period. In the middle-aged patient groups, 45–54 and 55–64 years of age, incidence almost tripled and increased from 26 and 42 per 100,000 person years to 63 and 123 per 100,000 person years respectively. Among the older age groups, 65–74, 75–84 and >85 years of age, incidence rates a little more than doubled during the study period and the increases were thus not as steep as in the middle-aged groups (Fig. 2). Incidence rose from 92 to 299 per 100,000 person years in the group aged 65–74 years, from 166 to 383 per 100,00 person years in the group aged 75–85 years and from 155 to 417 per 100,000 person years in the group aged >85 years.

Increasing rates of 1-year mortality were associated with higher age

Table 1
Changes in baseline patient characteristics of patients with pulmonary embolism between 1999 and 2018 stratified per calendar period. *P*-values from Cochran-Armitage trend test. IHD: ischemic heart disease, CHF: congestive heart failure, AMI: acute myocardial infarction, AFLI: atrial fibrillation, COPD: chronic obstructive pulmonary disease, TIA: transitory ischemic attack, PAD: peripheral arterial disease, DVT: deep vein thrombosis.

	1999–2003	2004–2008	2009–2013	2014–2018	P-value
N	9359	12,033	17,086	27,000	<0.0001
Female	5170 (55)	6633 (55)	9103 (53)	13,667 (51)	<0.0001
A-diagnosis	6352 (68)	8078 (67)	11,672 (68)	18,892 (70)	<0.0001
Outpatient contact	2406 (26)	3860 (32)	5750 (34)	13,691 (51)	<0.0001
Mean age (SD)	66 (17)	68 (17)	68 (16)	68 (16)	<0.0001
18–34 years	575 (6)	654 (5)	744 (4)	1099 (4)	<0.0001
35–44 years	679 (7)	798 (7)	941 (6)	1243 (5)	<0.0001
45–54 years	957 (10)	1018 (9)	1531 (9)	2470 (9)	0,0717
55–64 years	1417 (15)	1977 (16)	2570 (15)	4207 (16)	0,9724
65–74 years	2039 (22)	2685 (22)	4391 (26)	7501 (28)	<0.0001
75–84 years	2533 (27)	3117 (26)	4349 (26)	6940 (26)	0,0281
>85 years	1159 (12)	1784 (15)	2560 (15)	3450 (13)	0,8687
IHD	1226 (13)	1660 (14)	2776 (16)	4134 (15)	<0.0001
CHF	1301 (14)	1499 (13)	1916 (11)	2555 (9)	<0.0001
AMI	674 (7)	948 (8)	1375 (8)	1850 (7)	0.0364
Cancer	1114 (12)	1888 (16)	3941 (23)	6567 (24)	<0.0001
Atrial fibrillation	858 (9)	1285 (11)	2174 (13)	3140 (12)	<0.0001
Obesity	225 (2)	502 (4)	965 (6)	1702 (6)	<0.0001
Diabetes	491 (5)	747 (6)	1447 (9)	2795 (10)	<0.0001
Renal disease	181 (2)	416 (4)	719 (4)	1668 (6)	<0.0001
COPD	1008 (11)	1314 (11)	2206 (13)	3488 (13)	<0.0001
Stroke/TCI	942 (10)	1309 (11)	2000 (12)	3177 (12)	<0.0001
PAD	507 (5)	682 (6)	953 (6)	1282 (5)	0.0007
Hypertension	910 (10)	2151 (18)	4795 (28)	9044 (34)	<0.0001
DVT	1401 (15)	1965 (16)	3026 (18)	5825 (22)	<0.0001

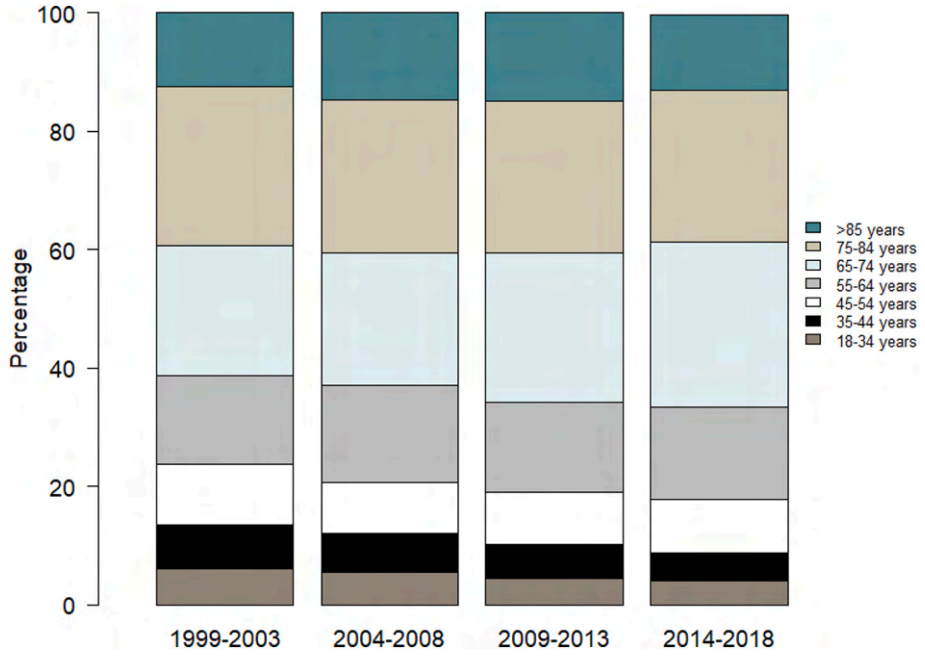

Fig. 1. Distribution of age groups among patients with pulmonary embolism in four calendar periods during 1999–2018.

(Fig. 3) and decreased significantly across all age groups during the study period ($p < 0.0001$). Those who experienced the largest decrease in mortality rate were the group of patients aged 18–34 and 75–84 years. In these groups mortality rate decreased from 0.59 and 7.26 per 10 person years in the first calendar period to 0.21 and 2.96 per 10 person years in the fourth calendar period (Fig. 3).

The increasing incidence rates and decreasing mortality rates across all age groups during the study period were found in both men and women when stratifying for sex (Figs. 4 and 5, appendix).

The increasing trend in incidence rate across calendar periods were almost unaffected on adjustment for age and sex. However, when further adjustment for prior IHD, CHF, AMI, cancer, AFLI, obesity, diabetes, renal disease, COPD, stroke/TIA, PAD, hypertension and DVT the trend was markedly minimized (Table 2). When adjusting mortality rate for age and sex, the decreasing trend across calendar period were almost unaffected, but when further adjustment for prior comorbidity, the decreasing trend were amplified (Table 3).

4. Discussion

In this nationwide study of the entire Danish population we observed an almost threefold increase in number of first-time PE cases from 1999

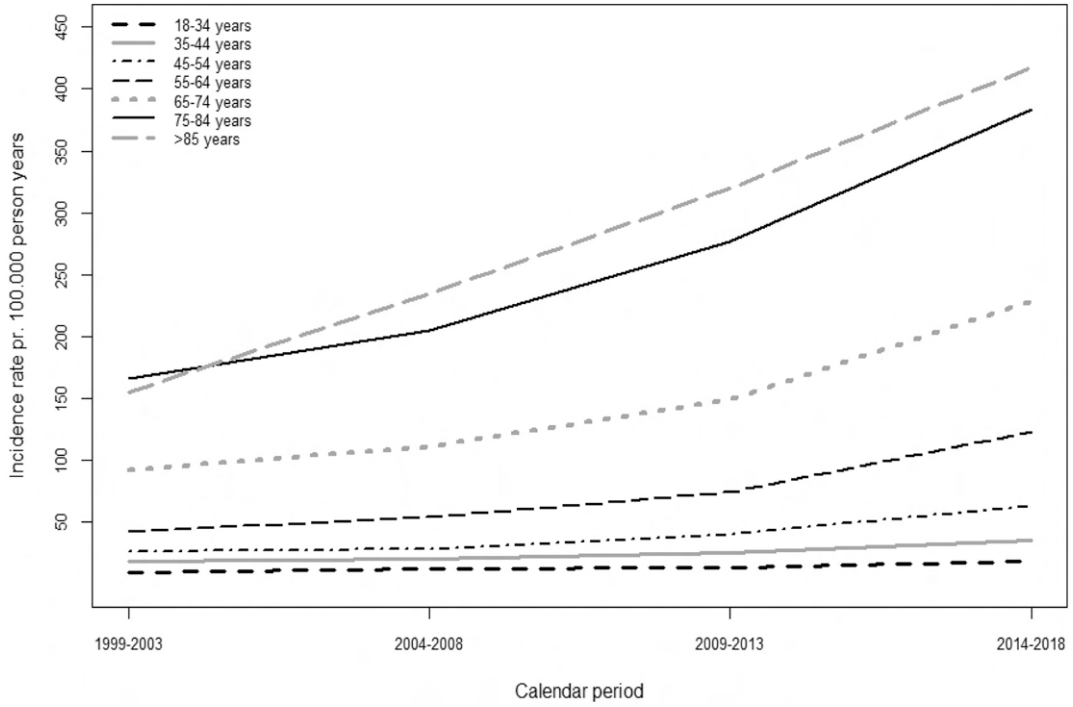

Fig. 2. Temporal incidence rates of pulmonary embolism per calendar period for age groups 18–34, 35–44, 45–54, 55–64, 65–74, 75–84 and >85 years. Incidence increased in all age groups, $p < 0.0001$.

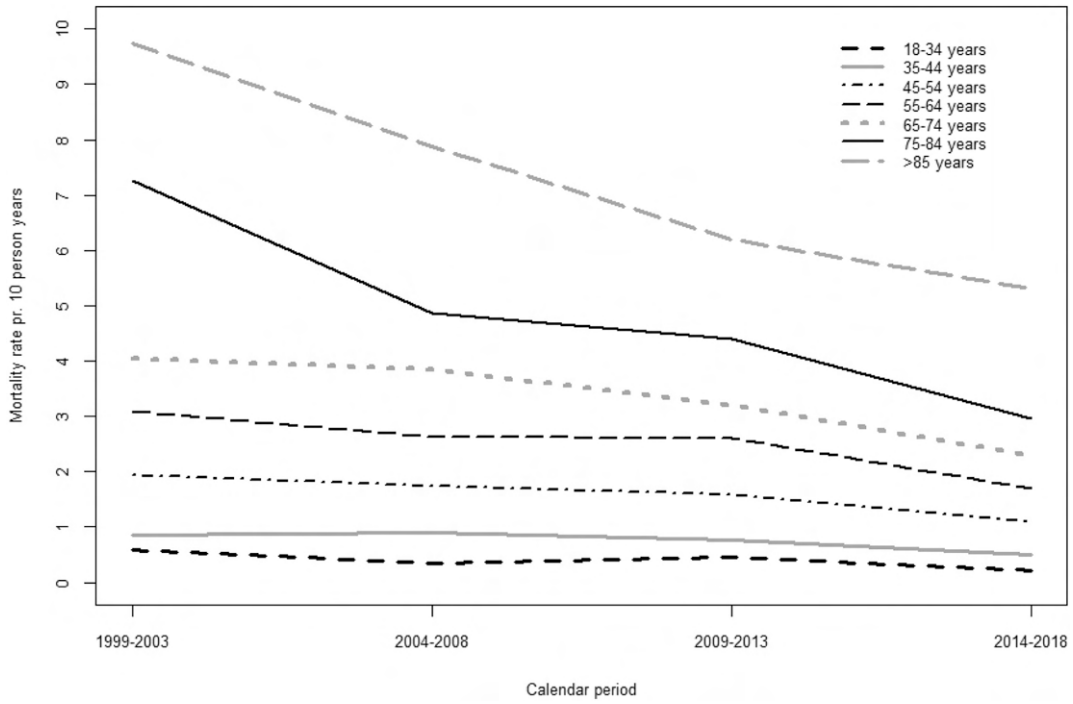

Fig. 3. Temporal 1-year mortality rates following pulmonary embolism per calendar period for age groups 18–34, 35–44, 45–54, 55–64, 65–74, 75–84 and >85 years. Mortality decreased in all age groups, $p < 0.0001$.

to 2018. Mean age at event increased significantly from 66 to 68 years. We observed a decrease in the proportion of women resulting in an almost equal distribution of the sexes in the last calendar period. The incidence of PE increased markedly with age regardless of calendar period. The annual incidence rate of PE increased across all age groups in the study period and post PE 1-year mortality was significantly decreasing across all age groups.

Our finding that temporal incidence rates of PE increased across all age groups during the study period, is in accordance with previous studies, all suggesting a continuing upward trend in the incidence of PE [16–21]. We demonstrate this trend nationwide in Denmark through a 20-year period. This trend is likely to be multifactorial.

First, the widespread use of non-invasive imaging, especially CTPA, has changed the diagnostic approach to PE through the last decades

Table 2
Adjusted incidence rate ratios for pulmonary embolism.

	Unadjusted		Age- and sex- adjusted		Multivariable adjusted[a]	
	IRR (95% CI)	P-value	IRR (95% CI)	P-value	IRR (95% CI)	P-value
1999–2003	Ref.		Ref.		Ref.	
2004–2008	1.24 (1.21–1.28)	<0.0001	1.22 (1.19–1.26)	<0.0001	1.16 (1.13–1.20)	<0.0001
2009–2013	1.72 (1.68–1.77)	<0.0001	1.63 (1.59–1.68)	<0.0001	1.31 (1.27–1.34)	<0.0001
2014–2018	2.62 (2.55–2.69)	<0.0001	2.40 (2.34–2.46)	<0.0001	1.61 (1.56–1.65)	<0.0001

IRR: incidence rate ratio, CI: confidence interval.
[a] Adjusted for sex, age, ischemic heart disease, congestive heart failure, acute myocardial infarction, cancer, atrial fibrillation, obesity, diabetes, renal disease, chronic obstructive pulmonary disease, stroke/transient ischemic attack, peripheral arterial disease, hypertension, deep vein thrombosis.

Table 3
Adjusted mortality rate ratios for pulmonary embolism.

	Unadjusted		Age- and sex- adjusted		Multivariable adjusted[a]	
	MRR (95% CI)	P-value	MRR (95% CI)	P-value	MRR (95% CI)	P-value
1999–2003	Ref.		Ref.		Ref.	
2004–2008	0.86 (0.82–0.91)	<0.0001	0.82 (0.77–0.86)	<0.0001	0.84 (0.80–0.89)	<0.0001
2009–2013	0.78 (0.74–0.82)	<0.0001	0.71 (0.67–0.75)	<0.0001	0.60 (0.56–0.63)	<0.0001
2014–2018	0.56 (0.53–0.59)	<0.0001	0.51 (0.48–0.54)	<0.0001	0.31 (0.30–0.33)	<0.0001

MRR: mortality rate ratio, CI: confidence interval.
[a] Adjusted for sex, age, ischemic heart disease, congestive heart failure, acute myocardial infarction, cancer, atrial fibrillation, obesity, diabetes, renal disease, chronic obstructive pulmonary disease, stroke/transient ischemic attack, peripheral arterial disease, hypertension, deep vein thrombosis.

[3,4]. A French study by Delluc et al. showed that in 1998, 4.4% of PE cases were diagnosed using CTPA as compared with 73.7% in 2013 [18]. Due to the accuracy and accessibility of the procedures, concerns about overdiagnosis of clinically insignificant subsegmental PE has been raised [5,22]. The change in diagnostic approach may have led to a growing awareness of PE as an important public-health problem leading to referral of additional patients for evaluation [23]. Furthermore, among patients undergoing thoracic CT for unrelated reasons, previous studies have found that incidental emboli are detected in 4% of cases [24], in 17% of patients older than 80 years [25] and in 24% of asymptomatic trauma patients [26]. In our study we observed a 25% increase in the number of PE diagnoses registered in an outpatient clinic during the study period. This could reflect an increased proportion of incidental findings of PE in unrelated outpatient CT scans, highlighting that the dramatic increase in incidence of PE during the last two decades found in this study is partly explained by the widespread availability of noninvasive modalities.

Secondly, the observed increase in PE incidence may reflect changes in the burden of comorbid conditions known to be PE risk factors. This is supported by our finding, that IRR across calendar periods was significantly diminished upon adjustment for comorbidity. The substantial thromboembolic risk associated with confirmed or presumed malignancy is well documented [3,6,19,20,27]. Advanced cancers, specific types of cancer (breast, lung, brain, pelvis, rectum, pancreas and gastrointestinal tract) and the administration of chemotherapy is known to be associated with an increased risk of PE [28]. In our study we found an increasing proportion of patients with cancer among patients with PE. This is in accordance with a recent study by Valerio et al., showing that the prevalence of cancer in patients from northern Italy with PE-related death increased from 39% in 2008 to 46% in 2019 [29]. Information on comorbidity were obtained from death certificates and not previously registered hospital admission, as in our study. However, the increasing trend in the occurrence of the association between cancer and PE is comparable and probably reflects not only a growing burden of cancer globally but also an enhanced tendency to screen for PE in cancer patients due to the accessibility of imaging diagnostics as mentioned above.

The proportion of obesity among PE patients increased significantly during our study period. In line with other studies, Steffen et al. found that abdominal obesity doubled the risk of developing venous thromboembolism in both men and women [30]. The risk is thought to be mediated by a prothrombogenic state of hypercoagulability and endothelial cell injury as well as stasis in the lower extremities [31]. Obesity and less physical activity among the younger segment of western population is of growing concern and might in part explain our finding of an increasing incidence rate of PE in the groups less than 55 years of age [32].

The increases in PE incidence in our study seems to be unaffected by the changes in national recommendations around 2012 [12] favoring less thrombogenic second-generation oral contraceptives and the general improvement in routine use of perioperative anticoagulation prophylaxis and early mobilization in surgical departments [33]. The advantages from these actions might be outweighed by the increased and refined diagnostic approach as mentioned above.

Our finding, that PE is a disease primarily affecting the elderly, is well established [5,16–19,21,34], and might be explained by age related changes in peripheral vein vascular biology promoting both an increased tendency for local thrombosis and venous thrombus growth and embolization [34]. With an increasing elderly population, our results may suggest that the burden of PE is of future growing concern.

In accordance with several previous studies [21,35,36], we found a continuous decreasing rate of 1-year mortality across all age groups in the study period. It is noteworthy that our results rely on all-cause 1-year mortality obtained from a central register and is thus not immediately comparable to studies examining the trend in PE-specific mortality rate extracted from specific death certificates [35]. However, we find that all-cause 1-year mortality provides a good and clinically relevant estimate of the prognosis of PE patients.

In opposition to this result, a novel study from 2021 by Barco et al. examined age- and sex-specific PE-related mortality in the USA and Canada between 2000 and 2018 by calculating crude PE-related mortality rates for individual years dividing the number of PE-related deaths by the total population [37]. The study did not provide information on incidence data. In accordance with our results, the study found a decreasing trend in PE-related mortality from 2000 until 2006 across all age groups. However, from 2006 to 2018 PE-related mortality increased among young and middle-aged patients with no obvious explanation. The rising trend in PE incidence among young as well as middle-aged patients from 2006 to 2018 in the present study, may indicate, though not immediately comparable to US data, that a rising incidence may be a

reasonable explanation to the finding by Barco et al. The improvement in mortality found in our study, may in part be due to a larger proportion of clinically insignificant cases of PE, supporting the theory of over-diagnosis due to advances in the diagnostic approach and thus suggesting a primarily benign incremental burden of PE. Additionally, the observed decreasing trend in mortality possibly reflect improved management of the disease due to the practice of guidelines, risk stratification and enhanced treatment, all together improving patient outcomes. These considerations are confirmed by observing the amplification of the decreasing trend in PE mortality when adjusting for age, sex and comorbidities. The improvement in 1-year mortality following PE is thus not a question about improved treatment and fatality of comorbidities associated with PE, but rather a reflection of lower fatality of PE itself developed over the last two decades.

5. Strengths and limitations

Due to the widespread and thorough registration nationwide in the Danish health care system, this register-based study constitutes one of the largest retrospective studies of PE. Registries are complete from 1999 and onward, whereby this study is up to date with latest trends in PE incidence and mortality.

However, confounding and the inadequacy of proving causal relations are the major challenges in register-based studies. Due to the retrospective collection of data, we are not able to distinguish between enhanced registration practice or a true increase in comorbid burden and PE. The financial incentive in the registration practice of diagnoses in the Danish health care system was, however, introduced prior to our study period and does therefor not explain the steep increase in PE incidence that we found from the middle of our study period and onwards.

In this study we identified patients with first-time PE registered as a primary diagnosis, a secondary diagnosis and as an outpatient diagnosis. According to Sundbøll et al. only the primary diagnosis of first-time PE has a very high positive predictive value. These patients made up around 70% of all first-time PE cases. The proportion of first-time PE diagnoses made in an outpatient clinic rose from 30% to 50% in the last calendar period and since the positive predictive value of these PE diagnoses is only 50%, we must assume that the number of miscoded PE cases has maximum increased from around 15% to 25% in 2014–2018. Though not an insignificant increase in potential not true PE cases, this consideration only explains a smaller part of the substantial development in PE incidence.

A special concern regarding the registration of obesity should be mentioned. In our study we categorized patients as obese based on the ICD-10 code DE66. The ICD codes for obesity has very poor sensitivity proven by a Canadian study, thus underestimating the true prevalence of obesity [38]. Furthermore, an ICD-code does not specify the degree of obesity. Unfortunately, our study did not provide information on patients' body mass index, which leads us to assume, that our registered prevalence and severity of obesity is equally underestimated.

6. Conclusion

In this up-to-date population based nationwide Danish study we found an overall continuous increasing temporal trend in the incidence of PE alongside a decreasing rate in associated 1-year mortality across all age groups between 1999 and 2018. While the incidence increase may be partially due to improved sensitivity of diagnostic methods, changes in the burden of comorbid conditions known to be PE risk factors is not to be neglected and highlights the need for continued efforts in early prevention of PE.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

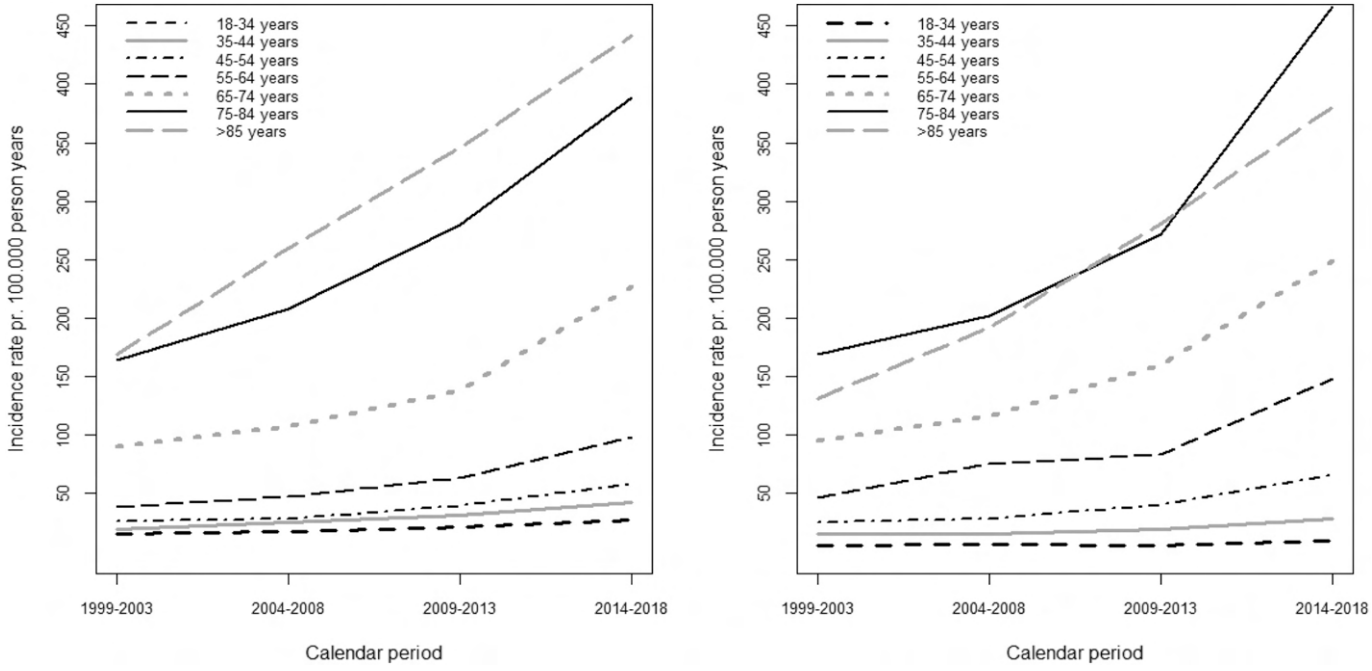

Fig. 4. Temporal incidence rates of pulmonary embolism per calendar period in women (left) and men (right) for age groups 18–34, 35–44, 45–54, 55–64, 65–74, 75–84 and >85 years. Incidence increased in all age groups in both sexes, $p < 0.0001$.

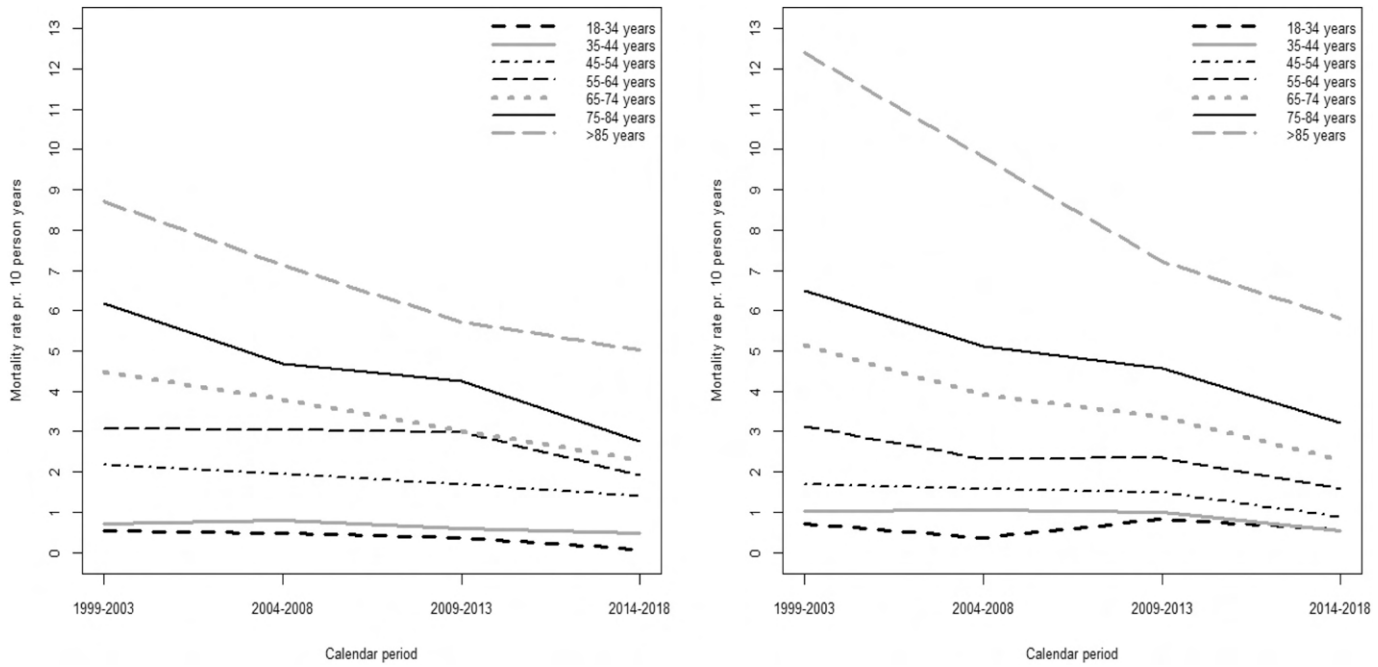

Fig. 5. Temporal 1-year mortality rates following pulmonary embolism per calendar period in women (left) and men (right) for age groups 18–34, 35–44, 45–54, 55–64, 65–74, 75–84 and >85 years. Mortality decreased in all age groups in both sexes, p = 0.0001.

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PAPER II

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Full Length Article

Educational differences in mortality but not in risk of recurrence following first-time pulmonary embolism: A Danish nationwide register-based study

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ABSTRACT

Background: Several studies agree that high socioeconomic position is protective against risk of PE. However, socioeconomic impact on outcomes from PE is not known. In this paper we aimed to compare differences in risk of recurrence and mortality within the first year following a first-time PE across level of education.
Methods: Using Danish national registers, patients ≥18 years of age hospitalized with a first-time PE between 1998 and 2018 were registered. Based on International Standard Classification of Education system 2011 patients were divided into four levels of education. Risk of recurrence and death across educational level were assessed by cumulative incidence curves and multivariable adjusted absolute risk regression analyses.
Results: In total, 22,708 patients with basic education (60 % women, median age 73 years), 19,809 with high school/vocational education (43 % women, median age 67 years), 7257 with short/medium higher education (54 % women, median age 65 years) and 2410 with long higher education (34 % women, median age 64 years) were hospitalized for PE. Risk of recurrence was not influenced by increasing educational level (relative absolute risk (RAR) 0.97, [95 % confidence interval (CI), 0.85–1.11], RAR 1.01 [95 % CI, 0.85–1.19], RAR 0.81 [95 % CI, 0.60–1.09]) compared to basic education, however, risk of death decreased with increasing level of education (RAR 0.93 [95 % CI, 0.90–0.96], RAR 0.88 [95 % CI, 0.83–0.92], RAR 0.83 [95 % CI, 0.76–0.89]).
Conclusion: Significant educational differences exist in mortality following PE, warranting a need for socially differentiated efforts targeted towards patients with low educational status.

1. Introduction

Pulmonary embolism (PE) is a venous thromboembolic and potentially fatal cardiovascular disorder with incidence rates ranging from 39 to 115 per 100,000 person years and 30-day mortality rates extending to 15% [1]. An increasing tendency in annual incidence rate over time suggests that the burden of PE is of growing concern [2–7]. Well known risk factors for PE include advancing age, surgery, major trauma, immobilization, infection, hormonal therapy, pregnancy, obesity and malignancy [1,8–10].

In arterial disease such as ischemic heart disease and stroke, the influence of socioeconomic position is well known and addressed in several studies, all showing that low income and short education is associated with both increased disease incidences and higher mortality [11–13]. The inequality seems to be explained by a larger burden of cardiovascular risk factors, such as hypertension, hypercholesterolemia and smoking, more prevalent in individuals with low socioeconomic position [14,15]. Due to few overlapping risk factors between arterial and venous disease, less is known about the association between socioeconomic position and PE. Few studies have examined the association between socioeconomic status and incidence of PE, all identifying high socioeconomic position as protective against the risk of PE [16–21]. However, the potential effect of socioeconomic position on mortality risk and risk of recurrent PE has not yet been thoroughly examined.

In this nationwide study we thus aimed to assess the impact of socioeconomic position on outcomes from first-time PE in Denmark

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between 1998 and 2018 by examining the association between highest attained educational level and 1) recurrence of PE within the first year following first-time PE and 2) all-cause 30-days and 1-year mortality.

2. Methods

In this nationwide study, we used the Danish National Patient Register (DNPR) to identify patients ≥18 years of age with a first-time in-hospital diagnosis of PE between 1st of January 1998 and 31st of December 2018. Since 1977 data on all hospital admissions in Denmark has been covered by the DNPR and from 1995 outpatient contacts and emergency department contacts have been added to the register. Patients' unique civil registration number, admitting hospital and department, dates of admission and discharge as well as diagnoses coded by physicians in charge of the patient admission and discharge are included in the records. Diagnoses are coded using the International Classification of Diseases (ICD) codes, where the 10th revision, ICD10, has been used since 1995 [22]. In the Danish health care system, the first listed diagnosis in the patient record (the A-diagnosis) is the main reason for the hospital contact. The B-diagnoses are coded secondly as any complications or other medical conditions occurring during the hospital admission. Our study population consisted of patients hospitalized with an A- or B-diagnosis of first-time PE. Existing comorbidities were defined as in-hospital diagnoses within 5 years prior to the diagnosis of first-time PE. Recurrence of PE was registered as a new in-hospital A-diagnosis of PE within one year but minimum >30 days from initial discharge, to ensure that a readmission was due to actual recurrent PE. Using the Central Person Register we gathered information on all-cause mortality within one year following the first-time PE diagnosis. Thus, two different starting points was used for the registration of recurrence (>30 days from discharge) and death (days from PE diagnosis) respectively to ensure the most accurate registration of events in a competing risk setting. Information on patients' highest attained level of education at time of their first-time PE was obtained from the Educational Attainment Register. All information is stored according to Statistic Denmark's educational classification system DISCED-15 which ensures accurate detail on educational status [23]. The information is translatable to the International Standard Classification of Education system 2011 (ISCED-11) [24].

To ensure accurate registration of diagnoses in the health care system a financial incentive has been introduced in Denmark since 1996 [25]. The coding of diagnoses of cardiovascular disorders, including codes for PE, has a high validity [26,27]. The positive predictive value of a primary (A-diagnosis) ICD10 code for first-time PE is 95 % according to Sundbøll et al., and only 67 % for a secondary (B-diagnosis) diagnosis. A primary diagnosis of a recurrent PE has a positive predictive value of 88% [27].

2.1. Statistical methods

We used the individual highest attained educational level at time of first-time PE diagnosis as a marker of socioeconomic position. Education was divided into 4 levels to ensure sufficient details: basic education (ISCED-11: 1 + 2), high school/vocational education (ISCED-11: 3 + 4), short/medium higher education (ISCED-11: 5 + 6) and long higher education (ISCED-11: 7 + 8). Differences between educational level and median age, sex, comorbidities (ischemic heart disease (IHD), heart failure (HF), previous acute myocardial infarct (AMI), cancer, diabetes, renal disease, chronic obstructive pulmonary disease (COPD), stroke and transient cerebral ischemia (TIA), hypertension and deep venous thrombosis (DVT)), median days of hospitalization, recurrence of PE within one year following first-time PE, 30-days and 1-year all-cause mortality were examined using Cochran Armitage Trend tests and Mann Whitney *U* tests.

Cumulative incidence functions for each educational level were calculated for both all-cause mortality and recurrence of PE within the first year following first-time PE and differences across educational level were examined using Gray's test. We performed a sensitivity analysis including only patients >40 years of age to assess the impact of educational level among the youngest patients.

To examine the influence of educational level on 1-year risk of recurrence of PE >30 days from initial discharge among patients alive and 1-year all-cause mortality following first-time PE we used a multivariable adjusted absolute risk regression model. Such a model is appropriate in a competing risk framework where the absolute risk of an event is of interest. The model quantifies the expected change of a predicted absolute risk of an event for a change of a predictor's value given fixed values for other predictor variables [28]. In this case, we do that in one model by calculating the absolute relative risk as a ratio between cumulative incidences in the different educational groups using basic education as a reference group and at the same time adjusting for other relevant patient related variables (age, sex, comorbidities and year of PE diagnosis).

All analyses were performed in SAS 9.4 and *R* 3.6.1. Figures were performed in *R* 3.6.1. A two-sided *p*-value of <0.05 was considered statistically significant.

2.2. Ethics

This study was approved by the Danish Data Protection Agency (2007-58-0015, internal reference GEH-2014-015, I-suite: 02733). In Denmark, register studies do not require ethical approval. Data for this study was accessed via an encrypted server hosted by Statistics Denmark with anonymized data, and patients' identities were thereby protected.

3. Results

3.1. Study population

During the study period from 1998 to 2018 we identified 57,519 patients hospitalized with a first-time diagnosis of PE and 52,184 with available data on educational level. In this group of patients, 22,708 (44 %) completed a basic education, 19,809 (38 %) completed high school or a vocational education, 7257 (14 %) completed a short or medium high education and only 2410 (4 %) completed a long higher education. Women represented 60 % of patients among those with a basic education, compared to only 43 %, 54 % and 34 % in the groups with more advanced educational levels respectively. Median patient age was 73 years among those with basic education and significantly lower (67, 65 and 64 years) among the other educational groups (Table 1).

The proportion of patients with IHD, HF, AMI, diabetes, renal disease stroke/TIA and hypertension confirmed prior to their first-time PE diagnosis were significantly different across level of education, revealing that the higher level of education the lower burden of comorbidity (Table 1).

The median number of days of hospitalization decreased with increasing level of education. Patients with basic education were hospitalized for 5 days on average whereas patients with high school/vocational education, short/medium high education and long higher education were hospitalized for 4, 4 and 3 days respectively ($p < 0.001$) (Table 1).

3.2. Recurrence

We identified 1685 cases of recurrent PE occurring within >30 days from initial discharge until 365 days from first-time PE diagnosis. There were no differences in risk of recurrence across level of education. In each group approximately 4–5 % of patients still alive between 30 days from initial discharge and 1 year following their first-time PE diagnosis experienced a recurrent event of PE ($p = 0.459$) (Table 1). Fig. 1 shows the cumulative incidence of recurrence of PE >30 days from discharge across the four levels of education ($p = 0.371$).

Table 1
Baseline results for patients with first-time pulmonary embolism between 1998 and 2018 stratified by level of education. IQR: interquartile range, SD: standard deviation, IHD: ischemic heart disease, HF: heart failure, AMI: acute myocardial infarction, COPD: chronic obstructive pulmonary disease, TIA: transitory ischemic attack, DVT: deep vein thrombosis.

	Basic education	High school/vocational education	Short/medium higher education	Long higher education	P-value
N	22,708	19,809	7257	2410	
Women (%)	13,603 (60)	8566 (43)	3926 (54)	827 (34)	<0.001
Median age (IQR)	73 (16)	67 (20)	65 (22)	64 (26)	<0.001
IHD (%)	3314 (15)	2360 (12)	679 (9)	185 (8)	<0.001
HF (%)	2431 (11)	1425 (7)	398 (6)	137 (6)	<0.001
AMI (%)	1723 (8)	1283 (7)	323 (5)	101 (4)	<0.001
Cancer (%)	4282 (19)	4208 (21)	1551 (21)	456 (19)	<0.001
Diabetes (%)	1963 (9)	1357 (7)	366 (5)	103 (4)	<0.001
Renal disease (%)	968 (4)	713 (4)	236 (3)	70 (3)	<0.001
COPD (%)	3044 (13)	1775 (9)	477 (7)	100 (4)	<0.001
Stroke/TIA (%)	2620 (12)	1735 (9)	560 (8)	178 (7)	<0.001
Hypertension (%)	5771 (25)	4228 (21)	1328 (18)	365 (15)	<0.001
DVT (%)	3230 (14)	3016 (15)	1082 (15)	346 (14)	0.117
Median days of hospitalization (IQR)	5 (8)	4 (8)	4 (7)	3 (6)	<0.001
30 day mortality (%)	3450 (15)	2255 (11)	660 (9)	204 (8)	<0.001
1 year mortality (%)	7336 (32)	5202 (26)	1649 (23)	491 (20)	<0.001
1 year recurrence (%)	712 (5)	658 (5)	247 (4)	68 (4)	0.459

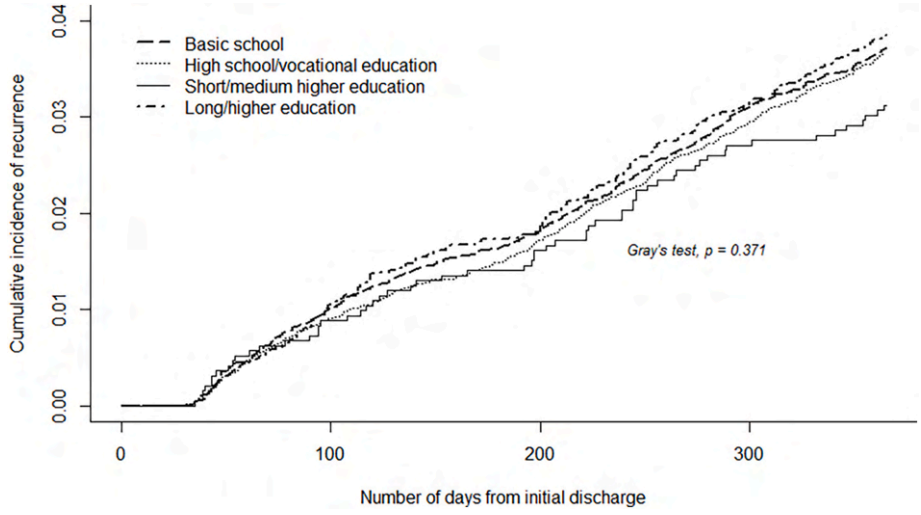

Fig. 1. Unadjusted cumulative incidence curve for recurrence of pulmonary embolism within >30 days from initial discharge until 12 months following first-time pulmonary embolism diagnosis across level of education. Cumulative incidence of recurrence of pulmonary embolism did not differ across educational level, Gray's test, $p = 0.371$ ($n_{basic\ education} = 712$, $n_{high\ school/vocational\ education} = 658$, $n_{short/medium\ higher\ education} = 247$ and $n_{long\ higher\ education} = 68$).

Results from the multivariable adjusted absolute risk regression model revealed that educational level did not independently affect the risk of recurrence of PE within the first year (Fig. 2). Being diagnosed with first-time PE during the calendar periods 2002–2005, 2006–2009, 2010–2013 and 2014–2018 decreased the absolute risk of recurrence of PE within the first year, by a factor 0.75 (0.63;0.89), 0.55 (0.47;0.66), 0.61 (0.51;0.73) and 0.39 (0.33;0.47) respectively compared to a first-time PE diagnosed in 1998 to 2001. Increasing age and suffering from diabetes and COPD lowered the risk of recurrence of PE. Lastly, the absolute risk of recurrence decreased by a factor 0.81 (0.68; 0.95) for patients with a previous DVT.

3.3. Mortality

All cause 30-days and 1-year mortality following first-time PE varied across educational level. Risk of 30-day mortality were 15 % (3450 patients) among those with basic education, 11 % (2255 patients) among patients with high school/vocational education, 9 % (660 patients) among patients with short/medium high education and 8 % (204 patients) in the group with long higher education risk of all-cause death within 1 year following admission was 32 %, 26 %, 23 % and 20 % respectively (Table 1).

Fig. 3 shows the cumulative incidence of all-cause death within the first year following the first-time PE diagnosis.

The absolute risk of death among patients not suffering from relapse within one year following first-time PE decreased with increasing level of education, leaving patients with high school/vocational education with an absolute risk of death reduced by a factor 0.93 (0.90;0.96), short/medium higher education with a reduced absolute risk by a factor 0.88 (0.83;0.92) and long higher education with a reduced absolute risk by a factor 0.83 (0.76;0.89), all compared to patients with basic education(Fig. 4). The results were obtained after adjustment for age, sex, comorbidities and year of diagnosis. Year of diagnosis also reduced the absolute risk of death within one year. Patients diagnosed between 2014 and 2018 had a reduced absolute risk of death by a factor 0.68 (0.63; 0.73) compared to patients diagnosed between 1998 and 2001. Suffering from heart failure, cancer, diabetes, renal disease, COPD, stroke/TIA and hypertension was all associated with an increased absolute risk of death, but a prior diagnosis of DVT lowered the risk by a factor 0.88 (0.84;0.92).

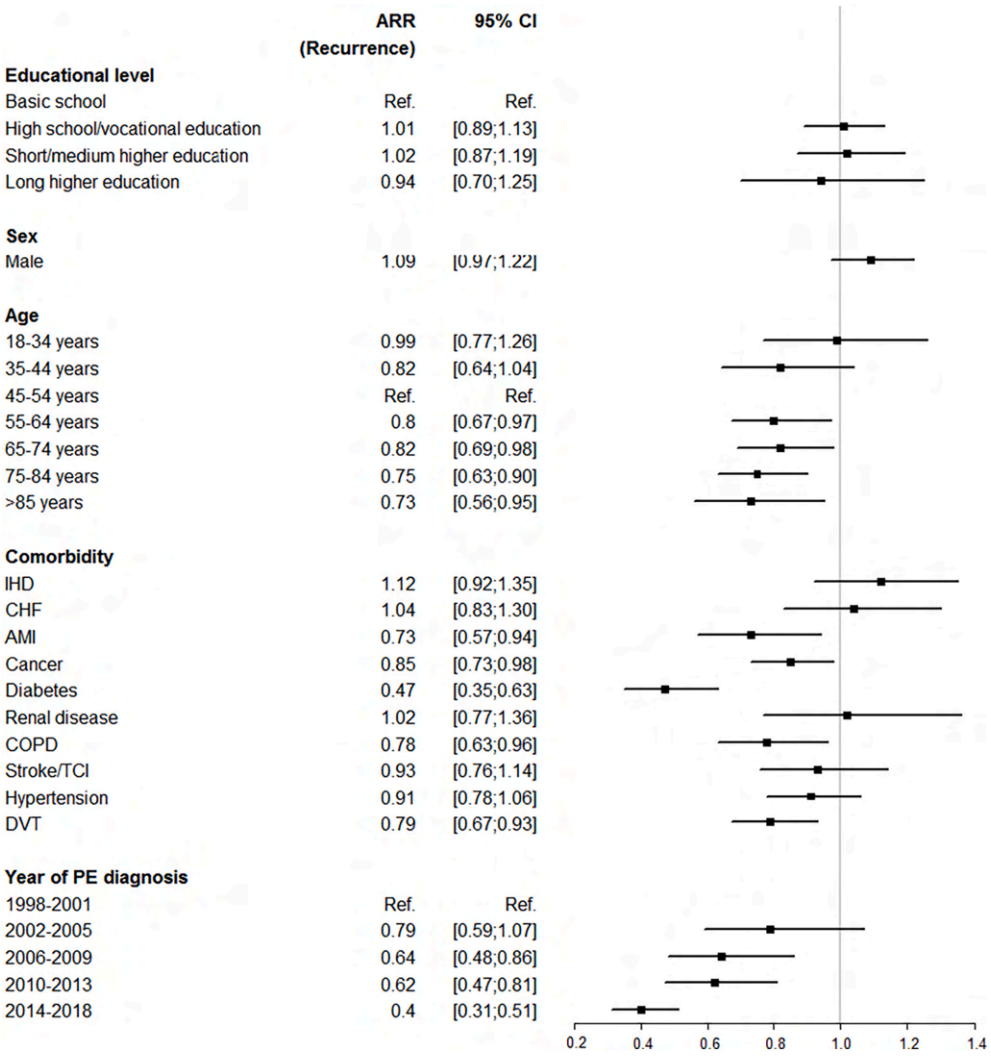

Fig. 2. Relative absolute risk of recurrence of pulmonary embolism after >30 days from discharge until 12 months following first-time pulmonary embolism diagnosis. Each result is adjusted for every other patient related category in the figure (sex, age, educational level, comorbidity and year of pulmonary embolism diagnosis). IHD: ischemic heart disease, HF: heart failure, AMI: acute myocardial infarction, COPD: chronic obstructive pulmonary disease, TIA: transitory ischemic attack, DVT: deep vein thrombosis, PE: pulmonary embolism.

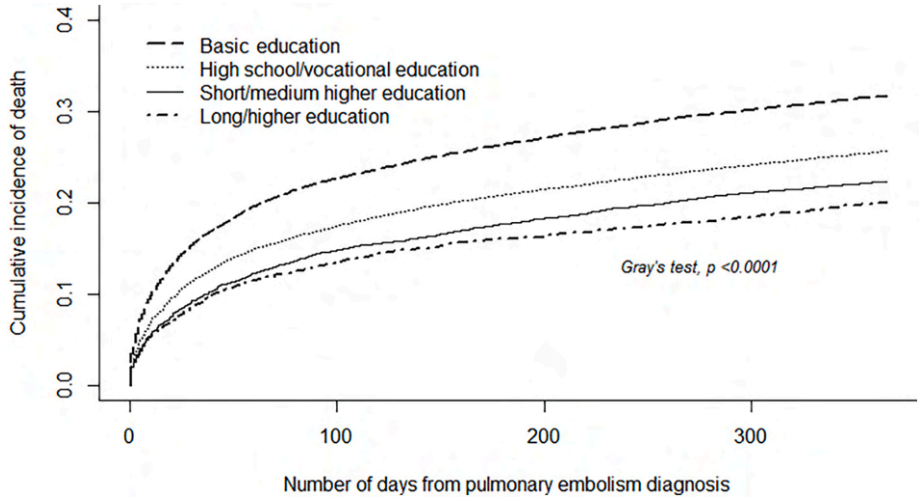

Fig. 3. Unadjusted cumulative incidence curve for death within 12 months from first-time pulmonary embolism diagnosis across level of education. Cumulative incidence of death did differ significantly across educational level, Gray's test, $p < 0.0001$ ($n_{\text{basic education}} = 7336$, $n_{\text{high school/vocational education}} = 5202$, $n_{\text{short/medium higher education}} = 1649$ and $n_{\text{long higher education}} = 491$).

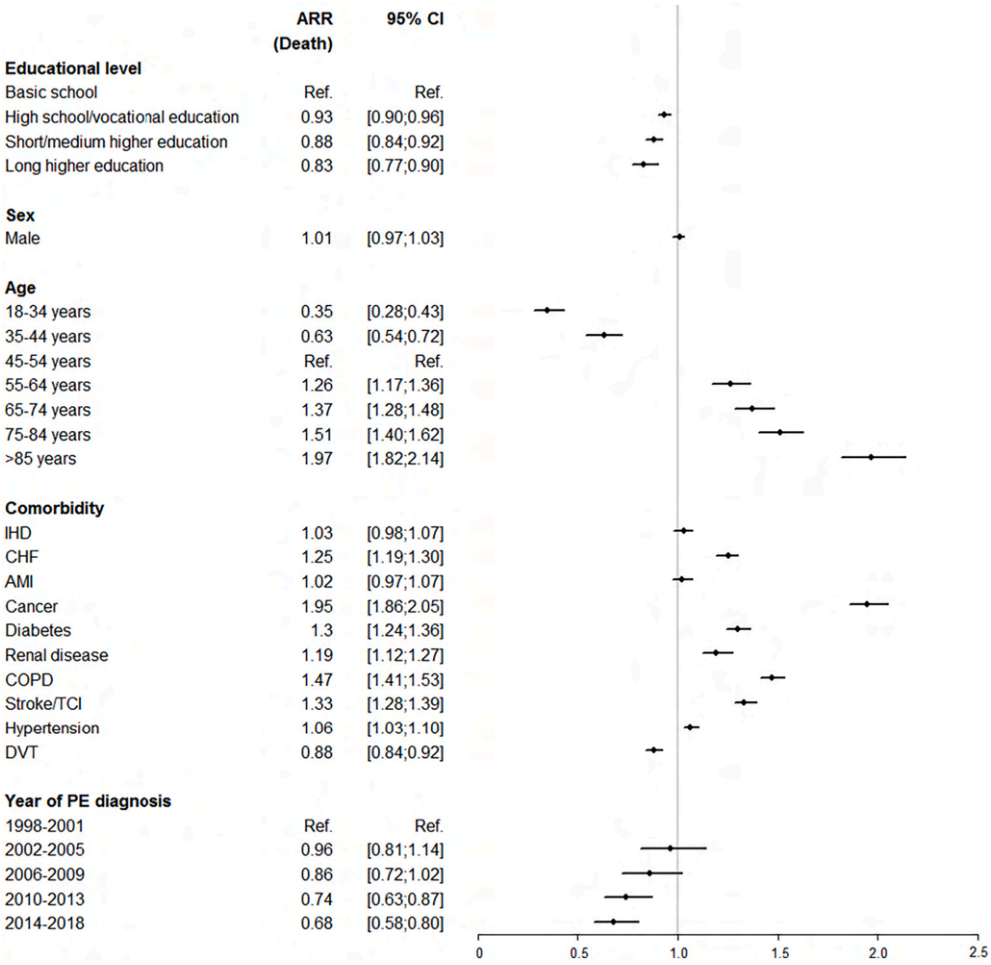

Fig. 4. Relative absolute risk of death within 12 months following first-time pulmonary embolism. Each result is adjusted for every other patient related variable in the figure (sex, age, educational level, comorbidity and year of pulmonary embolism diagnosis). IHD: ischemic heart disease, HF: heart failure, AMI: acute myocardial infarction, COPD: chronic obstructive pulmonary disease, TIA: transitory ischemic attack, DVT: deep vein thrombosis, PE: pulmonary embolism.

3.4. Sensitivity analyses

To address the potential skew of data caused by the youngest patients, who at time of their first-time PE diagnosis not yet had attained their highest level of education, we performed separate analyses including only the 48,647 patients >40 years of age. The associations between educational level and recurrence and death from PE from these analyses were equal to our main results (results not shown). Furthermore, we found a higher proportion of patients with a basic education in the pre-war generations compared to the younger generations, suggesting differing educational possibilities related to age. However, since the results from our multivariable adjusted absolute relative risk regression analysis revealed, that a significant educational effect on mortality risk exist even after adjustment for patient age, we do not consider the effect of educational possibilities in a given generation to influence our main result.

We identified 5355 patients with PE and missing data on educational level. Median age in this group of patients was 84 years and thus, 50 % of the patients died within the first year following their PE diagnosis.

4. Discussion

In this nationwide Danish register study between 1998 and 2018, patients hospitalized with a first-time PE and a basic education were mainly women with higher mean age and a greater burden of comorbidity compared to patients with higher educational levels. Risk of recurrence of PE within the first year following admission did not differ across educational status, however, the absolute risk of all-cause 30-day and 1-year mortality decreased significantly with increasing educational level. These two findings were confirmed in two models adjusting for age, sex, year of diagnosis and existing, relevant comorbidity.

The association between socioeconomic position and health can be challenging to study due to user fees and health insurances often being necessary for medical attention in health care sectors worldwide. However, the free equal access to health care services in Denmark ensures that socioeconomic position is not a direct obstacle in receiving medical and preventive treatment and thus, makes the Danish health care system relevant for an exploration of the association. In this study we only included patients hospitalized with PE, thus excluding PE low risk patients treated in an outpatient clinic.

A recent Danish study by Jørgensen et al. [21] found that low educational level, low income and unemployment were more common among patients with venous thromboembolism compared to matched controls. Compared with low levels, high educational level, high income, and high employment status were associated with an approximately 30 % decreased risk of first-time venous thromboembolism, even after adjusting for comorbidities [21]. Mechanisms leading to a decreased risk of first-time PE among higher educated individuals are largely unknown. Education as a specific measure of socioeconomic position, is thought to impact the ability to turn information into behavioral awareness among adults [29] and thus acts protectively through appropriate lifestyle, health perception and low iatrotropic

threshold for presenting for medical attention. Individuals with basic education are characterized by lower health care utilization such as vaccination- and screening programs as well as preventive visits in the health care system making individuals vulnerable to more complex and severe illness [30,31] increasing the likelihood of PE. In addition, recognized risk factors of PE such as obesity [32] and immobilization due to trauma/injuries [33] are more common among socially disadvantaged individuals. In Denmark, a persistent absolute and relative social inequality in overweight and obesity is well-known [34] and could especially account for the increased occurrence of PE among patients with basic education due to the increased risk of stasis conditioned by obesity. Smoking, as another important contributor to social inequality in health [35], is only indirectly associated to the risk of PE through the development of smoking-attributable diseases such as cancer [36], and is therefore not considered a major determinant of the association between educational level and PE. We found a greater burden of comorbidities and a longer duration of hospitalization among PE patients with basic education. This finding could be explained by the higher median age in this group compared to the other educational groups, suggesting a time trend in educational possibilities during that last decades.

In addition, some studies have found increased levels of procoagulant and inflammatory factors in patients with low socioeconomic status presumably mediated through lifestyle patterns but also psychosocial stress disturbing the hemostatic profile and increasing the risk of atherosclerosis and thrombosis [37–39]. A study by Rosengren et al. showed that men who reported persistent stress in midlife were more likely to be diagnosed with PE whereas high-socioeconomic status, measured by occupational class, was protective [18].

The rate of recurrence of PE is determined by discontinuation of treatment and features of index PE. A study by Agnelli et al. found that the recurrence rate after discontinuation of treatment was ~2.5 % per year after PE associated with transient risk factors (trauma, fracture, surgery, oral contraceptives, or pregnancy). For PE occurring in the absence of any transient risk factors the recurrence rate was 4.5% [40]. In our study, 1-year risk of recurrence was 4–5 % but unfortunately, our study did not provide information on neither discontinuation of treatment nor the risk status of the patients. Due to limitations in our data, we were only able to define recurrence as a PE readmission >30 days from initial discharge. This means that our results of recurrence risk only apply to those patients still alive >30 days from discharge. Since 30-day mortality varies significantly between educational groups, our finding should be interpreted with caution. The patient group with low education and increased 30-day mortality will be less exposed to recurrent events of PE compared to patients with high education and low 30-day mortality and thus, potentially equalizing the difference in recurrence rates between the groups. The reduced risk of recurrence among older patients and patients suffering from diabetes or COPD, could possibly be explained by index-event bias. When the risk of an index event (here PE) and a recurrent event shares the same risk factors, paradoxes are expected, because they are induced by conditioning the analyses on the occurrence of the index event [41]. We did not find any differences in risk across level of education, though it is generally believed that longer education facilitates the understanding of therapeutic measures, resulting in better compliance and higher commitment to treatment [29]. Whether or not this lack of association could be due to index-event bias is only a speculation.

The strong influence of socioeconomic factors on morbidity and mortality in general is well established and thoroughly discussed [42–44], however, when it comes to the association between socioeconomic position and death from PE, literature is sparse. A recent study by Wadhera et al. found no differences in short-term mortality rates when comparing socioeconomically disadvantaged older adults (>65 years of age) hospitalized for PE in the United States with their more affluent counterparts, however, they found a higher one-year mortality rate comparing the two groups [45]. Social disadvantage was defined as enrollment in "Medicaid", a national program providing health coverage to low-income people. In our study, we observed all-cause mortality to be inversely correlated with educational level at any given time point within the first year following first-time PE. Among patients with basic education, risk of 30-day mortality was almost twice as high (15 %) compared to patients with a long higher education (8 %). The poor 30-day prognosis among patients less educated could reflect a delayed referral to the hospital due to a low iatrotropic threshold as seen in cancer patients, which is not only representative for Danish patients but for socioeconomically deprived patients worldwide [46]. Furthermore, a study from 2019 by the RIETE investigators, showed an inverse association between annual hospital volume of PE and outcomes among patients with PE [47]. The association was probably explained by lack of clinical expertise among clinicians at low volume hospitals. Since hospital volume often correlates with socioeconomical status and educational level of patient uptake [48], this association might provide an explanation to our finding of reduced 30-day mortality among the higher educated patient group. However, in Danish cities, the patient uptake can be quite socioeconomically diverse and not necessarily generalizable. The association between educational level and death was highly significant even after adjusting for sex, age, comorbidity, and year of PE diagnosis. This finding is of particular interest since it excludes heavier comorbid burden to only explain the increased risk of PE associated 1-year mortality among patients with lower educational level.

Our finding that both risk of recurrence and mortality have decreased significantly during the last two decades are in line with results from a previous Danish nationwide study [7]. A benign incremental burden of PE due to increased use of easily available diagnostics and new and improved treatment options for the condition seems to explain this positive time trend making PE patients less prone to complicating and fatal outcomes.

Though not proving any causal relations between education and mortality following PE, our results are, to our knowledge, among the first to recognize level of education as a highly important marker of 30-day mortality risk following first-time PE. This finding illustrates a need for considering level of education in the planning of in-hospital monitoring and follow-up regimens of PE patients.

4.1. Strengths and limitations

Due to thorough national registration in the Danish Health care system this register-based study constitutes one of the largest national retrospective studies of the association between outcomes following a first-time PE and socioeconomic position, here defined by highest attained level of education. The impact of socioeconomic position on PE outcomes is a rarely explored topic and has mainly been studied in subpopulations and less frequently at national level.

Socioeconomic position is defined by multiple variables such as income, education, and occupational status, which are weakly to moderately correlated and represents different aspects on effect on health [29]. In this study we used highest attained educational level at time of event as a marker of socioeconomic level. We believe that in a health care system with free and equal access, level of education, rather than household income, has a greater influence on health risk and behavior explained by differences in ability to understand, adapt and commit to medical treatment and information [49]. Furthermore, in a study population with a median age above retirement age, socioeconomic markers such as occupational status and household income could be misleading.

Patients with missing data on educational level had a median age of 84 years, suggesting a lack of registration practice among the oldest individuals. We do not consider these missing data as having a significant effect on our conclusions.

One limitation to educational status as an exposure variable concerns the youngest patients, who at time of their PE diagnosis have not yet attained their highest level of education. As mentioned previously, we

found the same associations between educational level and recurrence and death from PE among patients >40 years of age compared to the whole patient population. Thus, we do not consider highest attained level among the youngest patients in this study as a significant challenge to the study design.

Lastly, confounding and the inadequacy of proving causal relations are the major challenges in register-based studies. This study does not provide information on patient related data such as smoking, alcohol consumption and body mass index which all could be valuable explainers to the association between educational status and outcomes from PE. Due to the very poor sensitivity of ICD codes for obesity proven by a Kuhle et al. [50], this register based study is not able to accurately correlate obesity to level of education and PE. Future studies are needed to further investigate the causal relation between educational status and PE.

5. Conclusion

In this population-based nationwide study from 1998 to 2018, we found significant educational differences in 30-day and 1-year mortality following a first-time PE. There were no differences in risk of recurrent PE within one year across educational level. The decreased mortality risk among patients with high education is not explained by less comorbidity burden, and thus, our results indicate an important need for socially differentiated efforts targeted towards patients with basic education in PE follow-up regimens.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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PAPER III

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Troponin dependent 30-day mortality in patients with acute pulmonary embolism

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Abstract
Background: Troponin concentrations above upper reference are associated with increased mortality in patients with pulmonary embolism (PE). We aimed to assess whether risk of 30-day mortality increases in a dose-response relationship with concentration of troponin. Methods: Using Danish national registries, we identified patients ≥ 18 years of age hospitalized with first-time PE between 2013 and 2018 and available troponin measurements − 1/+1 day from admission. Patients were stratified into quintiles by increasing troponin concentration. Risk of 30-day mortality was assessed performing cumulative mortality curves and Cox regression model comparing the troponin quintiles. Results: We identified 5,639 PE patients of which 3,278 (58%) had a troponin concentration above upper reference. These patients were older (74 years), 50% male and with heavier comorbidity compared to patients with non-elevated troponin. We found increasing 30-day mortality with increasing troponin concentration (1% in 1st quintile (95% CI 0.5–1.5%), 2% in 2nd quintile (95% CI 1-2.5%), 8% in 3rd quintile (95% CI 5–9%), 11% in 4th quintile (95% CI 9–13%) and 15% in 5th quintile (95% CI 13–16%), confirmed in a Cox model comparing 1st quintile with 2nd quintile (HR 1.09; 95% CI 0.58–2.02), 3rd quintile (HR 3.68; 95% CI 2.20–6.15), 4th quintile (HR 5.51; 95% CI 3.34–9.10) and 5th quintile (HR 8.09; 95% CI 4.95–13.23). Conclusion: 30-day mortality was strongly associated with troponin concentration useful for improving risk stratification, treatment strategies and outcomes in PE patients.

Keywords Epidemiology · Mortality · Risk assessment · Pulmonary embolism · Troponin

Introduction

Pulmonary embolism (PE) is the third most common acute cardiovascular condition worldwide [1] with increasing incidence rates [2] ranging from 39 to 115 per 100,000 person years [3]. The condition can be fatal with 30-day mortality reaching as high as 15% [1]. A critical determinant of outcome in acute PE is right ventricular (RV) failure, defined as a rapidly progressive syndrome resulting from impaired RV filling and/or reduced RV flow output due to sudden pulmonary obstruction [4]. Dilatation of the RV eventually impacts the filling of the left ventricle (LV) and coronary perfusion and thus reduces cardiac output leading to systemic hypotension, hemodynamic instability and ultimately death [5]. However, absence of hemodynamic instability does not exclude beginning and/or progressing RV dysfunction, and early risk assessment of PE patients is essential [6].

Troponin I and T (TnI and TnT) serves as markers of myocardial injury caused by ischemic damage, toxic effects, or hemodynamic stress. In patients with PE, 30–60% have elevated levels of troponin TnI and/or TnT [7–10] as a consequence of RV dysfunction. Troponin concentrations above threshold are associated with increased risk of mortality in both unselected PE patients and in those, who are

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hemodynamically stable at presentation [8]. Troponin positivity in combination with echocardiographic and clinical findings, thus serves as an important tool for early risk assessment and choice of treatment strategy in patients with acute PE [1].

However, with new and promising treatment methods for especially hemodynamic stable PE patients (e.g., low-dose thrombolysis, ultrasound catheter-based thrombolysis) [11–16], optimization of risk stratification is important for early identification of patients at increased risk of hemodynamic deterioration and death.

We therefore aimed to assess (1) the association between concentrations of TnI/TnT above threshold and 30-day all-cause mortality among patients with first-time PE and (2) the proportionality between 30-day all-cause mortality and concentration of TnI/TnT using quintiles.

Methods

Using the Danish National Patient Register (DNPR), we identified patients ≥ 18 years of age admitted to the hospital with a first-time diagnosis of PE between 1st of January 2013 and 31st of December 2018. In Denmark all citizens have a unique civil registration number, used by all authorities as a number for identification. All hospital admissions, emergency department contacts and outpatient clinic contacts in Denmark since 1977 are covered in the DNPR. Patients' civil registration number, admitting hospital and department, dates of admission and discharge and diagnoses coded by physicians in charge are included in the records. All diagnoses are coded using the International Classification of Diseases (ICD) coding system [17] and with the replacement of the 8th edition, ICD8, with the 10th edition in 1995, ICD10 is used in this study. In our study population, only patients with a primary diagnosis of a first-time PE were included. The diagnosis could be registered initially at hospital admission or in the emergency department. Most diagnoses of cardiovascular disorders, including codes for PE, has a high validity (the ICD-code for a first-time PE has a positive predictive value of 88% in Danish registries) [18, 19]. Comorbidity was defined as any in-hospital diagnoses appearing within 5 years prior to the diagnosis of first-time PE in the DNPR. From the Central Person Register (CPR) we gathered information on all-cause 30-day mortality following the first-time PE diagnosis.

The clinical laboratory information system (LABKA) research database implemented in 1985 contains laboratory test results performed in private clinics and hospital departments covering most regions in Denmark since 2013 [20]. Information is recorded in a uniform way according to the international Nomenclature, Properties and Units (NPU) coding system. By linking PE patients identified from the DNPR to the LABKA research database, we retrieved information on levels of TnT and TnI measured within one day prior to one day after admission for first-time PE. We identified one group of patients with measurements of TnT in nanogram per litre (ng/L) and two different upper reference levels (< 14 ng/L and < 50 ng/L). A second patient group had measurements of TnT in microgram per litre (µg/L) completed with two different upper reference levels (< 0.05 µg/L and < 0.12 µg/L) and finally a third patient group had TnI in ng/L performed with 7 different upper reference levels (< 25 ng/L, < 35 ng/L, < 40 ng/L, < 45 ng/L, < 47 ng/L, < 50 ng/L and < 120 ng/L) (see Fig. 1). Unfortunately, our data did not allow any insights into the specific assay used.

Statistical methods

Peak level of TnI and/or TnT per patient measured within one day prior to one day after admission for first-time PE were registered. Patients were dichotomized based on whether TnI/TnT concentration was elevated or not. Elevation was defined as a peak measurement with a concentration above individual upper reference level. Differences between patients with troponin above and under upper threshold with regards to median age, sex, comorbidities (ischemic heart disease (IHD), previous acute myocardial infarct (AMI), cancer, heart failure (HF), chronic obstructive pulmonary disease (COPD), renal disease, deep venous thrombosis (DVT)), median level of relevant biochemistry at time of PE diagnosis (haemoglobin (Hb), estimated glomerular filtration rate (eGFR) and C-reactive protein (CRP)) and 30-day mortality were examined using chi-squared for categorical variables and ANOVA tests for continuous variables.

We performed cumulative mortality curves and a log-rank test to compare differences in 30-day mortality from time of PE diagnosis between patients with elevated and non-elevated troponin. To investigate the individual effect of an elevated concentration of TnI/TnT on 30-day mortality we performed a cox proportional hazard model adjusting for age, sex, relevant pre-existing comorbidity (IHD, AMI, cancer, HF, COPD, renal disease and DVT) and biochemistry at time of PE diagnosis (Hb, eGFR and CRP). Concentrations of Hb, eGFR and CRP were divided into three levels (low, medium and high) based on tertiles.

Handling each assay separately, we further evaluated whether risk of 30-day mortality were proportional with the concentration of TnI/TnT, by dividing measurements into quintiles. We only included the eight different troponin analysis groups with > 50 patients each (see Fig. 1) and thus, the 5,625 troponin measurements were divided into five equal sized groups of approximately 1,100 patients by

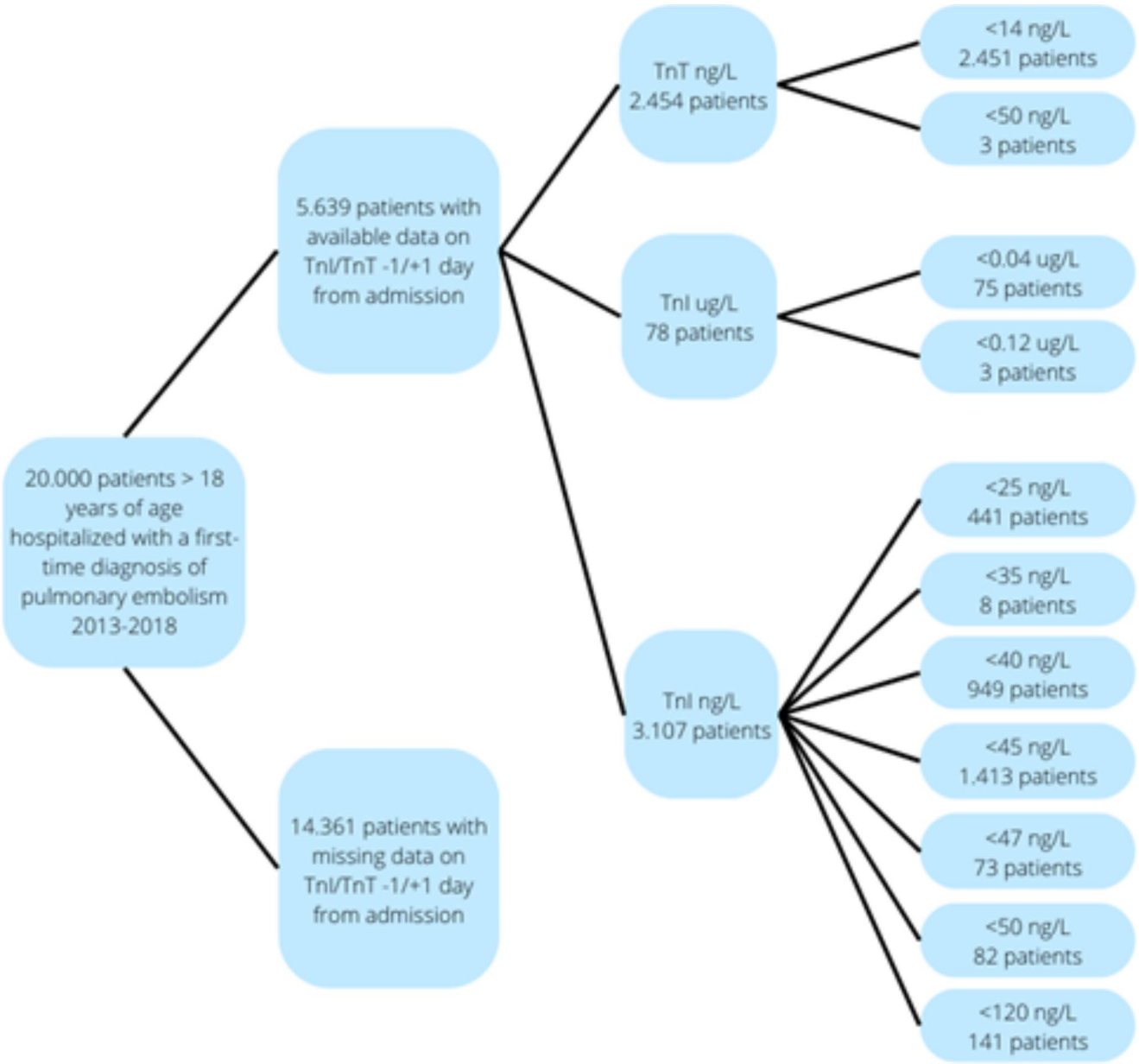

Fig. 1 Flowchart showing data inclusion. The 11 identified patient groups based on different type of measurements (troponin I or T, unit and upper reference limit) are illustrated to the right

increasing concentration of troponin. Differences between each quintile regarding median age, sex, comorbidities and 30-day mortality were examined using Cochran Armitage Trend test for continuous variables and Mann Whitney U tests for categorical variables. Additionally, we assessed mortality using a cumulative mortality plot and a cox proportional hazard model adjusting for age, sex, and relevant pre-existing comorbidity to confirm differences in 30-day mortality between quintiles.

All dataset preparation was performed in SAS 9.4 and analyses and figures were performed in R 3.6.1. A two-sided p-value of < 0.05 was considered statistically significant.

Ethics

This study was approved by the Danish Data Protection Agency (2007-58-0015, internal reference GEH-2014-015, I-suite: 02733). In Denmark, register studies do not require ethical approval. Data for this study was accessed via an encrypted server hosted by Statistics Denmark with anonymized data, and patients' identities and sensitive information were thereby protected.

Results

From 2013 to 2018 we identified 20,000 patients ≥ 18 years of age hospitalized with a first-time PE diagnosis in Denmark. No information on clinical parameters were available, and thus, patients were unselected regarding hemodynamic status. Among these patients, only 5,639 had a measurement of TnI (3,185 patients) or TnT (2,454 patients) completed within + 1/-1 day from admission (74% of measurements performed on the day of admission). Based on individual upper reference limit, 58% of patients (3,278 patients) had an elevated concentration of troponin, while 42% (2,361 patients) had a concentration within normal reference range (Table 1). There were no differences in the distribution of sex between the two patient groups (50% male in both). Patients with elevated troponin were older (median age 74 years) compared to those with normal troponin levels (median age 67 years) and had a greater burden of comorbidities (previous AMI (8 vs. 6%), cancer (18 vs. 15%), heart failure (8 vs. 6%), COPD (10 vs. 8%) and renal disease (5 vs. 3%)) except for a previous DVT, which were more frequently occurring in patients with non-elevated troponin level (15 vs. 19%). Patients with an elevated concentration of troponin had a significantly lower median level of eGFR (68 vs. 83 ml/min) and higher median level of CRP (35 vs. 25 mg/L) at time of PE diagnosis compared to those with normal concentrations of troponin, but both groups showed no difference in level of Hb (Table 1).

30-day all-cause mortality following first-time PE differed between patients with elevated troponin and those with normal level, 11 vs. 3% respectively (Fig. 2) and was confirmed in an adjusted Cox regression model ($HR_{elevated}$ troponin 2.74; 95% CI 1.94–3.86) even after adjustment for age, sex, comorbidities, Hb, eGFR and CRP (Table 2).

Comparing the five groups with increasing troponin concentrations, we found no difference in the distribution of male sex (1st quintile 49%, 2nd quintile 51%, 3rd quintile 54%, 4th quintile 51%, 5th quintile 46%). Median age increased with increasing concentration of troponin from 63 years in the 1st quintile group to 74 years in the 5th quintile group. The same was true for the proportion of patients with ischemic heart disease (1st quintile 11%, 2nd quintile 18%, 3rd quintile 18%, 4th quintile 15%, 5th quintile 12%) and heart failure (1st quintile 4%, 2nd quintile 8%, 3rd quintile 11%, 4th quintile 9%, 5th quintile 7%). Median concentration of eGFR decreased across quintiles (1st quintile 85 ml/min, 2nd quintile 81 ml/min, 3rd quintile 73 ml/min, 4th quintile 67 ml/min, 5th quintile 67 ml/min) whereas CRP increased (1st quintile 23 mg/L, 2nd quintile 24 mg/L, 3rd quintile 32 mg/L, 4th quintile 36 mg/L, 5th quintile 36 mg/L) (Table 3).

All-cause 30-day mortality following first-time PE varied across the quintile groups. No large difference in 30-day mortality was observed between 1st quintile group (1%) and 2nd quintile group (2%). However, 30-day mortality increased significantly across the remaining groups, from 8% in 3rd quintile group, 11% in 4th quintile group and 15% in 5th quintile group (Fig. 3).

A Cox regression model adjusted for age, sex, comorbidities and simultaneous Hb, eGFR and CRP revealed that 30-day mortality still increased across level of troponin, comparing 1st quintile with 2nd quintile (HR 0.84; 95% CI 0.36–1.95), 3rd quintile (HR 3.74; 95% CI 1.94–7.24), 4th quintile (HR 4.67; 95% CI 2.44–8.96) and 5th quintile (HR 6.55; 95% CI 3.46–12.38) respectively (Table 4).

Treating the eight groups with > 50 patients and different upper threshold separately (Fig. 1), we found similar increasing associations between 30-day mortality and level of troponin (data not shown).

From the 20,000 identified patients with PE, 14,361 had non-available data on troponin measurements within − 1/+1 day from admission. Since the size of the missing data population is only partly due to the non-nationwide range of the LABKA database, we performed a sub analysis,

Table 1 Baseline results for patients with a first-time pulmonary embolism between 2013–2018 and elevated and non-elevated troponin levels respectively

	Elevated troponin level, n = 3,278	Non-elevated troponin level, n = 2,361	P-value
Male sex (%)	1,646 (50)	1,190 (50)	0.889
Median age (25th -75th percentile)	74 (65–82)	67 (54–75)	< 0.001
Ischemic heart disease (%)	491 (15)	337 (14)	0.461
Previous acute myocardial infarction (%)	275 (8)	145 (6)	0.002
Cancer (%)	593 (18)	360 (15)	0.005
Heart failure (%)	277 (8)	152 (6)	0.005
Chronic obstructive pulmonary disease (%)	343 (10)	190 (8)	0.002
Renal disease (%)	178 (5)	72 (3)	< 0.001
Deep venous thrombosis (%)	497 (15)	439 (19)	< 0.001
Median haemoglobin (25th -75th percentile)	8.4 (7.5–9.2)	8.5 (7.7–9.1)	0.135
Median estimated glomerular filtration rate (25th -75th percentile)	68 (51–85)	83 (68–90)	< 0.001
Median C-reactive protein (25th -75th percentile)	35 (14–70)	25 (7–62)	< 0.001

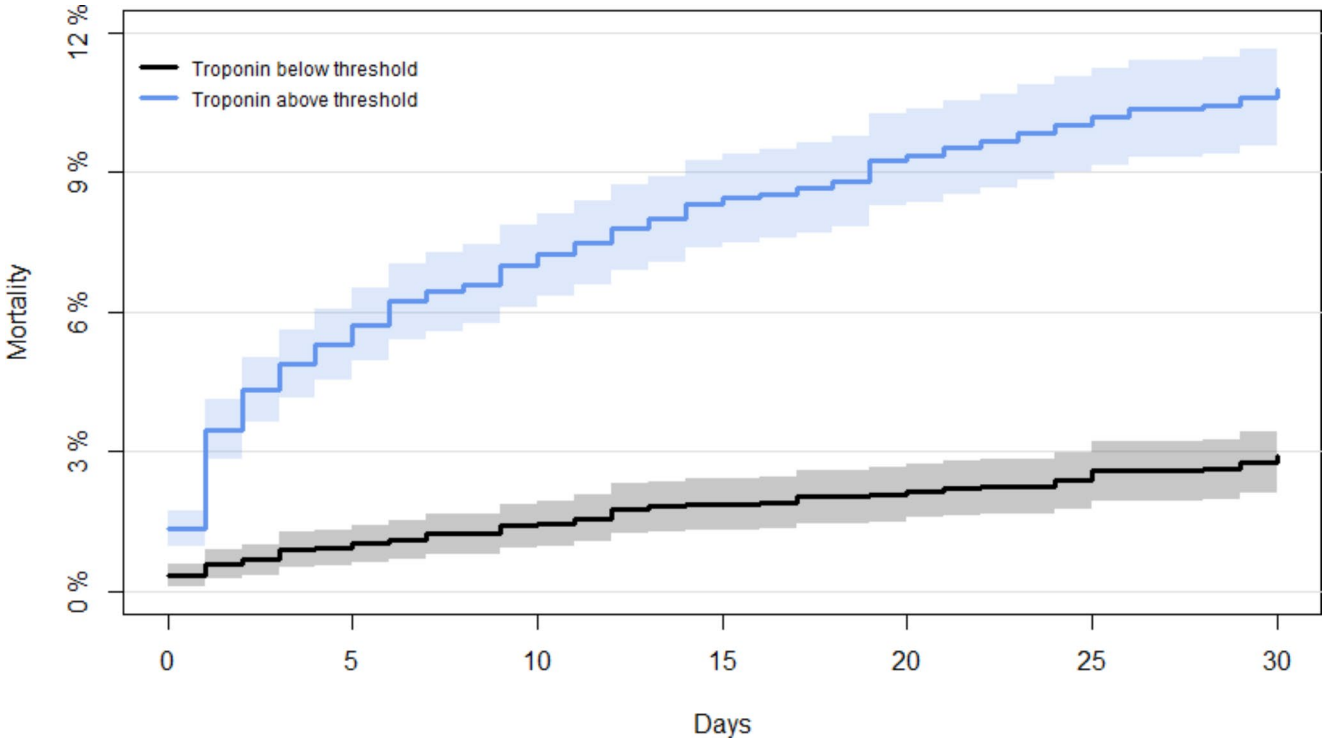

Fig. 2 Cumulative mortality curve 0–30 days from first-time pulmonary embolism diagnosis. 30-day mortality differed significantly depending on troponin level below or above threshold, Log-rank test $p < 0.001$

revealing that age (median age 71 years in both) and sex (50% male in both) did not differ across patients with and without troponin measurements. More cancer patients were represented in the group with missing measurements of troponins (23% vs. 17%). The absolute risk of 30-day mortality was 8% in both patient groups (appendix table).

Discussion

In this study of 5,639 unselected patients with acute PE, increasing troponin levels were associated with an increased 30-day mortality. Troponins were elevated in 58% of the patients studied and our results add, that increasing levels of troponin provides incremental prognostic information, which may be useful in selecting the appropriate therapy for PE patients.

This study agrees with previous findings, that a troponin measurement above threshold at time of PE-diagnosis increases the risk of 30-day mortality considerably [21, 22]. An elevated troponin measurement is associated with dysfunction of the right ventricle and more segmental defects in lung scans [22, 23] and thus represents a clinically important determinant of right ventricular overload. A meta-analysis from 2015 by Bajaj et al. including 16 studies on troponin levels in PE patients, found that overall, 11% of patients with elevated troponin levels and 3% of patients with normal levels died within 30 days [24]. Our results are in accordance with these outcomes. Another meta-analysis by Becattini et al. also concluded that the prognostic value of troponin was consistent among the 20 included studies regardless of the specific assay and relative cut-off point used [8]. The meta-analysis included works on both hemodynamic stable and unselected PE patients, as in our study.

An elevation of troponin concentration above a specific threshold, is thus included in the recommended risk stratification of PE patients to guide the choice of treatment strategy. With tachycardia and low systolic blood pressure resulting from a prognostic unfavourable acute RV failure, it is generally recognized that PE patients with unstable hemodynamics are to be treated with reperfusion treatment without the necessity of troponins to guide the therapeutic decision [1]. In opposition, hemodynamically stable PE patients need further risk assessment before decision on treatment approach. The spectrum of patients includes those with very low risk of death that could be managed in an outpatient clinic with novel oral anticoagulants. On the other side of the spectrum are patients with risk of poor outcomes that needs close monitoring and may benefit from more aggressive treatment, including thrombolytics. We had no data on hemodynamics in our patient population, and thus our results do not exclusively target the group of hemodynamic stable PE patients who needs further risk assessment. However, our study supports previous results, that TnI/

Table 2 Multivariable adjusted Cox proportional hazard model. CI: confidence interval

	Hazard ratio	95% CI	P-value
Troponin > threshold	2.74	[1.94 ; 3.86]	< 0.001
Male sex	1.02	[0.79 ; 1.32]	0.853
Age group			
18–44 years	0.49	[0.19 ; 1.27]	0.142
45–54 years	Ref.	Ref.	Ref.
55–64 years	0.86	[0.46 ; 1.61]	0.632
65–74 years	0.63	[0.32 ; 1.16]	0.138
>75 years	0.86	[0.47 ; 1.55]	0.609
Comorbidity			
Ischemic heart disease	1.02	[0.70 ; 1.48]	0.921
Previous acute myocardial infarction	1.13	[0.70 ; 1.85]	0.613
Cancer	1.88	[1.43 ; 2.46]	< 0.001
Heart failure	1.10	[0.72 ; 1.68]	0.655
Chronic obstructive pulmonary disease	1.54	[1.10 ; 2.14]	0.011
Renal disease	0.81	[0.49 ; 1.33]	0.397
Deep venous thrombosis	0.66	[0.44 ; 0.99]	0.045
Biochemistry			
Haemoglobin	Ref.	Ref.	Ref.
High	1.08	[0.74 ; 1.57]	0.696
Medium	1.95	[1.38 ; 2.74]	< 0.001
Low			
Estimated glomerular filtration rate			
High	Ref.	Ref.	Ref.
Medium	0.95	[0.64 ; 1.41]	0.811
Low	1.88	[1.30 ; 2.71]	< 0.001
C-reactive protein			
High	Ref.	Ref.	Ref.
Medium	0.68	[0.51 ; 0.90]	0.006
Low	0.42	[0.29 ; 0.60]	< 0.001

Table 3 Baseline results for patients with a first-time pulmonary embolism between 2013–2018 across quintiles of troponin measurement

	1st quintile, n = 1,107	2nd quintile, n = 1,107	3rd quintile, n = 1,110	4th quintile, n = 1,111	5th quintile, n = 1,115	P-value
Male sex (%)	545 (49)	563 (51)	595 (54)	567 (51)	517 (46)	0.629
Median age (25th -75th percentile)	63 (50–72)	70 (57–77)	74 (65–82)	74 (65–82)	74 (65–82)	< 0.001
Ischemic heart disease (%)	121 (11)	197 (18)	201 (18)	166 (15)	137 (12)	0.004
Previous acute myocardial infarction (%)	48 (4)	78 (7)	111 (10)	88 (8)	88 (9)	0.125
Cancer (%)	154 (14)	176 (16)	202 (18)	194 (17)	212 (19)	0.431
Heart failure (%)	42 (4)	83 (8)	119 (11)	105 (9)	77 (7)	0.039
Chronic obstructive pulmonary disease (%)	69 (6)	109 (10)	140 (13)	124 (11)	81 (7)	0.066
Renal disease (%)	26 (2)	33 (3)	52 (5)	64 (6)	73 (7)	0.065
Deep venous thrombosis (%)	220 (20)	201 (18)	177 (16)	165 (15)	152 (14)	0.492
Median haemoglobin (25th -75th percentile)	8.5 (7.8–9.1)	8.4 (7.5–9.1)	8.3 (7.5–9.1)	8.4 (7.6–9.1)	8.5 (7.5–9.2)	0.027
Median estimated glomerular filtration rate (25th -75th percentile)	85 (72–90)	81 (63–90)	73 (55–86)	67 (49–82)	67 (48–86)	< 0.001
Median C-reactive protein (25th -75th percentile)	23 (7–61)	24 (7–61)	32 (11–68)	36 (16–75)	36 (16–71)	< 0.001

TnT concentrations, independent of unit and upper reference limit, is an important independent marker of mortality risk in every PE patient [8]. Our baseline table comparing patients with and without registered troponin level at time of PE diagnosis revealed no significant difference in 30-day mortality.

The prognostic value of troponin measurements is considered most valuable when used in combination with echocardiography evaluating right ventricular function [10, 25]. Echocardiographic examination is not immediately available in all acute emergency rooms. Thus, it would be useful if the level of troponin solely could permit an extended early identification of patients at an increased risk

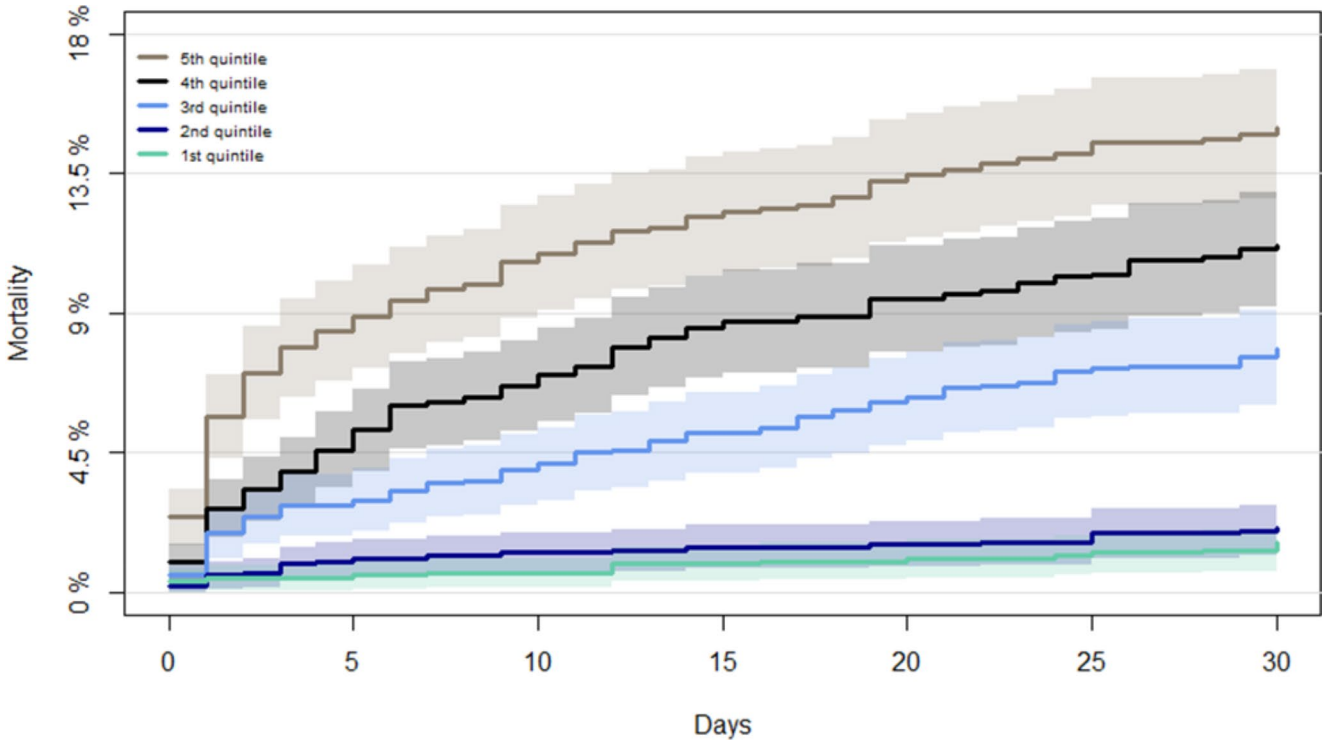

Fig. 3 Cumulative mortality curve 0–30 days from first-time pulmonary embolism diagnosis. 30-day mortality differed significantly across troponin quintiles, Log-rank test $p < 0.001$

of hemodynamic deterioration and death. In patients with unstable coronary artery disease it is known that the risk of cardiac events increases with increasing level of troponin in the first 24 hours [26]. However, in PE patients this possible incremental association between risk of death and increasing level of troponin concentrations is only rarely explored [22, 27]. In our study we found an increase of 30-day mortality with increasing concentration of troponins. Crude risk of death increased continuously from 1% in patients with troponins concentrations in the first quintile to 16% in those with concentrations in the fifth quintile and was confirmed in a multivariable Cox regression. No relevant difference in mortality was observed between first and second quintile group, however, mortality risk increased significantly and steadily across the third to the fifth quintile. This result is in accordance with a study by Konstantinides et al. from 2002, where measurements of TnI and TnT from 106 PE patients were divided into three groups representing low, moderate, and high concentrations. They found that the discrimination between moderate and pronounced elevation of troponin levels could be used to classify patients into an intermediate- and a high-risk group with regard to mortality and major clinical in-hospital events [22]. Another study by La Vecchio et al. including 48 patients with severe PE, concluded that a link between the degree of troponin increase and the severity of the clinical presentation exists. They observed no deaths among patients with normal concentrations, however, in-hospital mortality increased from 5% among those with slightly increased concentrations to 36% among those with still higher concentrations [27]. Lastly, a recent study by Ebner et al. confirmed the prognostic relevance of high-sensitive TnI in 459 normotensive PE patients and found, that patients who suffered an in-hospital adverse outcome had a significantly higher TnI concentration compared with those with a favourable clinical course [28]. Thus, our study including 5,608 PE patients, confirms these findings and suggests that not only a troponin concentration above threshold identifies PE at increased risk of early death, but also the exact level should be considered, when risk stratifying patients prior to a therapeutic decision. Additional clinical trials are needed to determine whether an extension of risk assessment depending on level of troponins are useful in guiding treatments of the spectrum of PE patients and improve prognosis of those in high risk of early mortality.

Strengths and limitations

Due to the thorough registration practice in Denmark, our data cover almost the entire nation and as a result, our study population is one of the largest exploring the association between mortality and troponin concentration in patients with acute PE. In Denmark, the coding of diagnoses of cardiovascular disorders, including codes for PE, has a high

Table 4 Multivariable adjusted Cox proportional hazard model. CI: confidence interval

	Hazard ratio	95% CI	P-value
Level of troponin			
1st quintile	Ref.	Ref.	Ref.
2nd quintile	0.84	[0.36 ; 1.95]	0.687
3rd quintile	3.74	[1.94 ; 7.24]	< 0.001
4th quintile	4.67	[2.44 ; 8.96]	< 0.001
5th quintile	6.55	[3.46 ; 12.38]	< 0.001
Male sex	1.04	[0.81 ; 1.35]	0.739
Age group			
18–44 years	0.50	[0.19 ; 1.30]	0.154
45–54 years	Ref.	Ref.	Ref.
55–64 years	0.78	[0.41 ; 1.47]	0.435
65–74 years	0.57	[0.31 ; 1.05]	0.071
>75 years	0.76	[0.42 ; 1.38]	0.360
Comorbidity			
Ischemic heart disease	1.08	[0.74 ; 1.56]	0.701
Previous acute myocardial infarction	1.10	[0.68 ; 1.79]	0.691
Cancer	1.89	[1.44 ; 2.48]	< 0.001
Heart failure	1.08	[0.71 ; 1.64]	0.726
Chronic obstructive pulmonary disease	1.61	[1.15 ; 2.25]	0.005
Renal disease	0.79	[0.48 ; 1.30]	0.348
Deep venous thrombosis	0.65	[0.43 ; 0.98]	0.038
Biochemistry			
Haemoglobin	Ref.	Ref.	Ref.
High	1.20	[0.82 ; 1.74]	0.342
Medium	2.00	[1.42 ; 2.83]	< 0.001
Low			
Estimated glomerular filtration rate			
High	Ref.	Ref.	Ref.
Medium	0.96	[0.64 ; 1.42]	0.821
Low	1.78	[1.22 ; 2.59]	0.002
C-reactive protein			
High	Ref.	Ref.	Ref.
Medium	0.68	[0.52 ; 0.91]	0.008
Low	0.49	[0.34 ; 0.69]	< 0.001

validity [18, 19] making the register-based design of this study relevant in the discussion of the prognostic influence of troponins.

Due to the retrospective collection of data, our work does not contain information on other important prognostic risk factors, such as hemodynamic status and echocardiographic findings, that also contributes to the risk stratification of PE patients. Thus, our study results are not limited to the hemodynamic stable PE patients and we cannot evaluate whether there is an incremental prognostic value of troponin concentration in combination with echocardiographic findings.

In this study, the registration of expected peak level of troponin may be subject to some uncertainty. However, by choosing a time slot for peak measurement between − 1/+1 day from admission, we assume that we register most relevant peak concentration related to the PE-diagnosis.

Lastly, since different troponin analyses are used across Danish regions, standardization of troponin measurements was not possible in this study and limits the generalization of specific cut-off values. However, the demonstrated association between increasing risk of death and concentration of troponin is generalizable to every PE patient regardless type of troponin measurement used.

Conclusion

The results of this large register-based study confirm the prognostic value of a troponin measurement above threshold at time of diagnosis in patients with acute PE. In addition, we demonstrate an increase in 30-day mortality risk with increasing concentration of troponin. This finding could contribute to further evolvement of risk stratification in PE patients essential in guiding therapeutic decisions but needs to be confirmed in future therapeutic trials.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11239-023-02864-0.

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Declarations of interest None.

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PAPER IV

Dynamics of troponins and 30-day mortality in hospitalized patients with pulmonary embolism. Sonne-Holm E, Kjærgaard J, Bang LE, Køber L, Hassager C, Paulin Beske R, Carlsen J, Winther-Jensen M. Thrombosis Research. 2025 Jan 22;247:109274.

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Dynamics of troponins and 30-day mortality in hospitalized patients with pulmonary embolism

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ABSTRACT

Background: In patients with pulmonary embolism (PE), the impact of repeated troponin I or T (TnI/TnT) measurements remains unclear.
Methods: Using Danish national registries, we identified PE patients (≥18 years) hospitalized between 2013 and 2018 with initial TnI or TnT measurement within −1/+1 day from admission and >1 repeated measurement within three days. Trajectories of TnI and TnT were identified using latent class trajectory modeling. Hazard ratios for 30-day mortality were compared across trajectories via multivariable Cox regression.
Results: Among 1539 patients with TnI measurements and 1323 with TnT measurements, three distinct trajectories were identified. Trajectory I ($n_{TnI} = 286$, $n_{TnT} = 472$) exhibited consistently low TnI/TnT concentrations, trajectory II ($n_{TnI} = 1076$, $n_{TnT} = 724$) demonstrated initial elevated TnI/TnT decreasing within 24 h, and trajectory III ($n_{TnI} = 177$, $n_{TnT} = 127$) was characterized by elevated index TnI/TnT increasing within 10 h. 30-day mortality rates were higher in trajectory II and III compared to I in both the TnI (3 %, 7 % and 18 % across trajectory I to III) and the TnT (1 %, 9 % and 20 % across trajectory I to III) cohort. After adjustment hazard ratio of 30-day mortality for trajectory II vs. I was 7.42 (95 % CI 1.00–54.84, $p = 0.04$, TnI) and 2.93 (95 % CI 1.17–7.33, $p = 0.02$ TnT); and for trajectory III vs. I, 16.42 (95 % CI 2.42–127.29, $p = 0.007$, TnI) and 8.21 (95 % CI 2.78–24.19, $p < 0.001$, TnT).
Conclusion: A steep increase in TnI or TnT concentration within 10 h of PE diagnosis significantly escalates 30-day mortality risk indicating that early serial sampling may enhance risk stratification of PE patients.

1. Introduction

Pulmonary embolism (PE) is a common acute cardiovascular disease with 30-day mortality ranging as high as 15 % [1]. Right ventricular (RV) dysfunction is the critical element decisive for the outcome of the disease [2,3]. An early risk assessment of patients with PE to detect signs of RV dysfunction is thus of utmost importance. Besides echocardiographic findings of RV impairment, measurements of troponin I or T (TnI/TnT) at time of diagnosis are important indicators of RV stress and deoxygenation [4].

In patients with acute coronary syndrome, serial measurements of TnI/TnT are standard practice in order to evaluate the prognosis and treatment strategy [5]. In contrast, when risk stratifying patients with PE, only the initial TnI/TnT measurement upon admission is taken into consideration. TnI/TnT elevation is defined as concentrations above upper threshold depending on the assay used. Elevated TnI/TnT at admission is associated with increased mortality among both unselected and hemodynamic stable patients with PE [6]. The development, progression, and potential clinical impact of repeated TnI/TnT measurements in patients with PE is an under-recognized topic in literature but may be relevant in the discussion of optimal risk assessment. With a novel data analysis technique called latent class trajectory models, patterns or trajectories of TnI/TnT measurements over time within a dataset can be identified [7]. This method has never previously been used on TnI/TnT measurements in patients with PE.

In this register-based study we thus aimed to define different trajectories of repeated TnI and TnT measurements in patients with PE using latent class trajectory modeling; hypothesizing that these different

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TnI and TnT trajectories would be independently associated with 30-day mortality.

2. Methods

In this study data were extracted from national Danish registries. By utilizing patients' unique civil registration numbers, information from multiple registries can be linked, enabling a comprehensive analysis of diverse healthcare-related variables and outcomes. The Danish National Patient register (DNPR) covers all hospital admissions, emergency departments and outpatient clinic contacts in Denmark since 1977. Included in the records are date and time of admission and discharge as well as diagnoses of diseases expressed by the 10th edition of International Classification of Diseases (ICD) coding system [8]. In this study, eligible patients were defined as all patients ≥18 years of age hospitalized with a first-time PE diagnosis between 1st of January 2013 and 31st of December 2018. The ICD-10 codes used to identify PE cases were: I26, I260, I260A, I269 and I269A. The diagnosis of PE could be registered initially at hospital admission or in the emergency department. All hospital diagnoses registered within five years prior to the PE diagnosis was defined as comorbidity (ischemic heart disease (IHD), previous acute myocardial infarction (AMI), cancer, heart failure (HF), diabetes, chronic obstructive pulmonary disease (COPD), renal impairment, hypertension, previous deep vein thrombosis (DVT)). Using the Central Person Register (CPR) we gathered information on all-cause 30-day mortality following the current PE diagnosis. In Danish registries diagnoses of cardiovascular diseases including PE has a high validity, and thus the positive predictive value of a first-time PE diagnosis in the DNPR is 88 % [9,10].

Information on measurements of TnI and TnT during hospitalization was retrieved by linking patients with PE identified in the DNPR to the clinical laboratory information system (LABKA) research database. The database was implemented in 1985 and covers all laboratory test results performed in hospital departments and private clinics in most Danish regions [11]. All performed measurements of TnI and TnT available from one day prior to admission for first-time PE until three days following admission were included. Only patients with a first recording of TnI or TnT −1 to +1 day from admission and with >1 repeated measurement were included in the analysis. All measurements were performed in ng/l, and we included assays with seven different TnI threshold (25, 35, 40, 45, 47, 50, 120 ng/l) and two different TnT threshold (14 and 50 ng/l). Due to large fluctuations in TnI and TnT levels, concentrations were transformed into a 10 % logarithmic value to ensure the running of latent class trajectory models. Patients level of estimated glomerular filtration rate (eGFR) on the day of admission were recorded.

3. Statistical methods

Patients were categorized into either a TnI or TnT cohort, ensuring no overlap between the two groups. To validate the results, separate analyses were conducted for each of these cohorts. Patients were divided into trajectories of their TnI or TnT levels measured −1/+1 day from admission until three days after first measurement using latent class trajectory models [7]. Several trajectory models were assessed using both a linear model, an exponential model and a spline as underlying time. Models with and without random intercept and with both three and four trajectories were evaluated. The assessed number of trajectories relates to the clinical application of four distinct risk groups in PE patients as outlined in the ESC guidelines [1]. Using lowest possible Bayesian information criterion (BIC), plots of trajectories and number of allocated patients to each trajectory, the best fitted model for our data were selected: a spline model with three knots representing quartiles of underlying time (TnI: 0, 4 and 15 h, TnT: 0, 4 and 13 h), a random intercept and three trajectories was preferable in both the TnI and the TnT cohort. A model with a random intercept means a model that follows the shape of the trajectory curve and not the mean of the values in the latent classes. We instructed the function ('nwg = TRUE') to automatically determine the number of within-group parameters based on the complexity of the model and the characteristics of the data. The model categorized patients in each cohort as belonging to one of the three trajectories. Differences in baseline characteristics across the trajectories (age, sex, comorbidities (IHD, previous AMI, cancer, HF, diabetes, COPD, renal disease, hypertension, previous DVT), eGFR and 30-day mortality) were examined using chi-squared test for categorical variables and ANOVA tests for continuous variables. For each trajectory the median and mean of first (TnI/TnT: 0 h), second (TnI: median 7 h, TnT: median 6 h) and third (TnI: median 20 h, TnT: median 21 h) TnI or TnT measurement in ng/l were calculated. The posterior probability of belonging to a trajectory was used as exposure in a Cox regression model adjusted for age, sex, comorbidities, eGFR, and index TnI/TnT below or above upper threshold, using 30-day mortality as an endpoint. eGFR were divided into three levels (low, medium and high) based on tertiles. Results of the Cox model is presented as hazard ratios with 95 % confidence intervals. Posterior probability indicates a patients' estimated probability of belonging to each latent trajectory, based on their unique combination of TnI or TnT concentrations over time. If the model has suggested well separated, predictive latent trajectories, each patient should have a high probability to one trajectory only and low probability elsewhere.

All dataset preparation was performed in SAS 9.4 and analyses were performed in R 3.6.1. Latent class trajectory models were developed using the R-package lcmm [7]. A two-sided *p*-value of <0.05 was considered statistically significant.

4. Ethics

This study was approved by the Danish Data Protection Agency (2007-58-0015, internal reference GEH-2014-015, I-suite: 02733). In Denmark, register studies do not require ethical approval. Data for this study was accessed via an encrypted server hosted by Statistics Denmark with anonymized data, and patients' identities and sensitive information were thereby protected.

5. Results

We identified 20,000 patients ≥18 years of age hospitalized with a first-time PE between 2013 and 2018 in Denmark. Of these, 3185 patients had an available first measurement of TnI performed within −1 to +1 day from admission and 2454 patients had measurements of TnT. The 73 patients with both TnI and TnT measurements were excluded from the TnT cohort. By selecting patients with >1 measurement of TnI or TnT performed within three days from first TnI/TnT measurement, the two final study cohorts counted 1539 patients with relevant TnI measurements and 1323 patients with TnT measurements (Fig. 1).

The first measurement of both TnI and TnT was mainly completed on the day of admission (89 %) and most patients had two serial measurements of TnI or TnT performed (62 %). In total, 3799 measurements of TnI and 3230 measurements of TnT were included in the analyses. Median age of patients in both cohorts was 72 years, and an equal amount of male and female sex was represented. 60 % of patients had an index concentration of TnI above the upper threshold, while 83 % had a TnT concentration exceeding the upper threshold. 112 and 93 patients (both 7 %) died within 30 days from the diagnosis in the TnI and TnT cohort respectively.

Using latent class trajectory modeling in each cohort separately, we were able to identify three distinct trajectories for both TnI (Fig. 2) and TnT (Fig. 3).

All trajectories seem well separated with average posterior probabilities exceeding 0.8 (appendix Table 1), and essentially, consistent troponin dynamics identified across cohorts, despite minor variations in number of patients allocated to each trajectory.

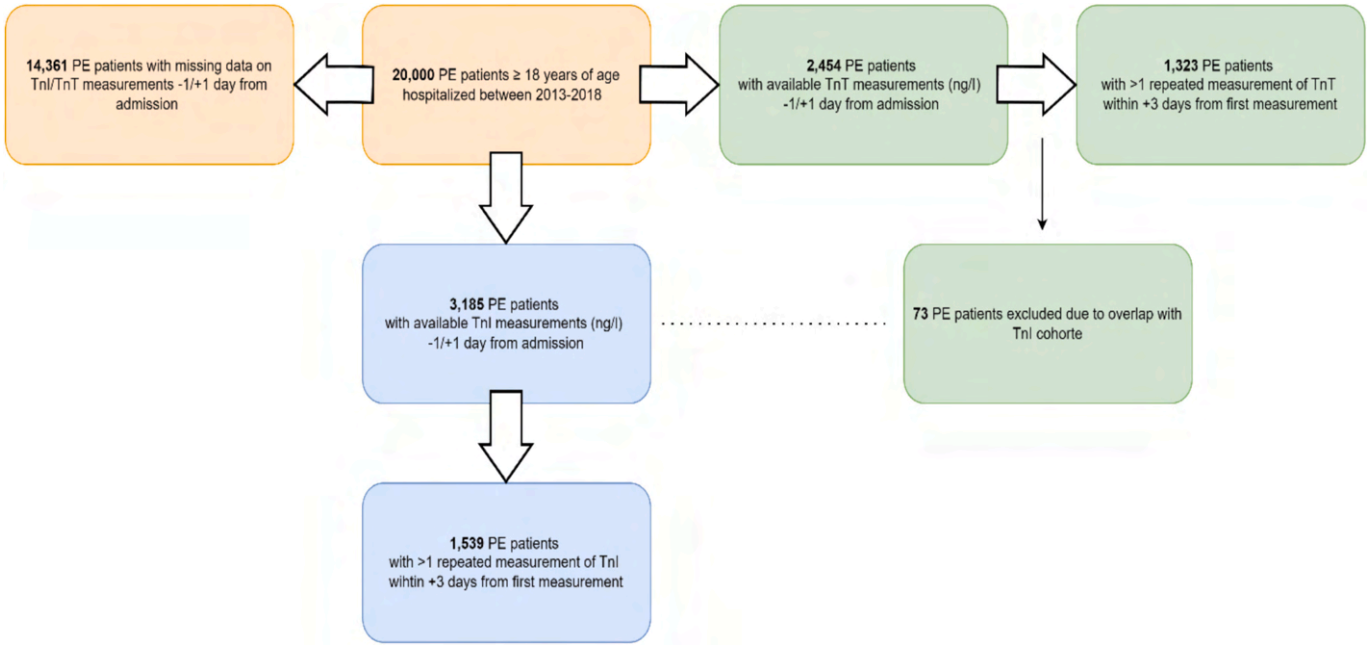

Fig. 1. Flowchart showing data inclusion. PE; pulmonary embolism, TnI; troponin I, TnT; troponin T.

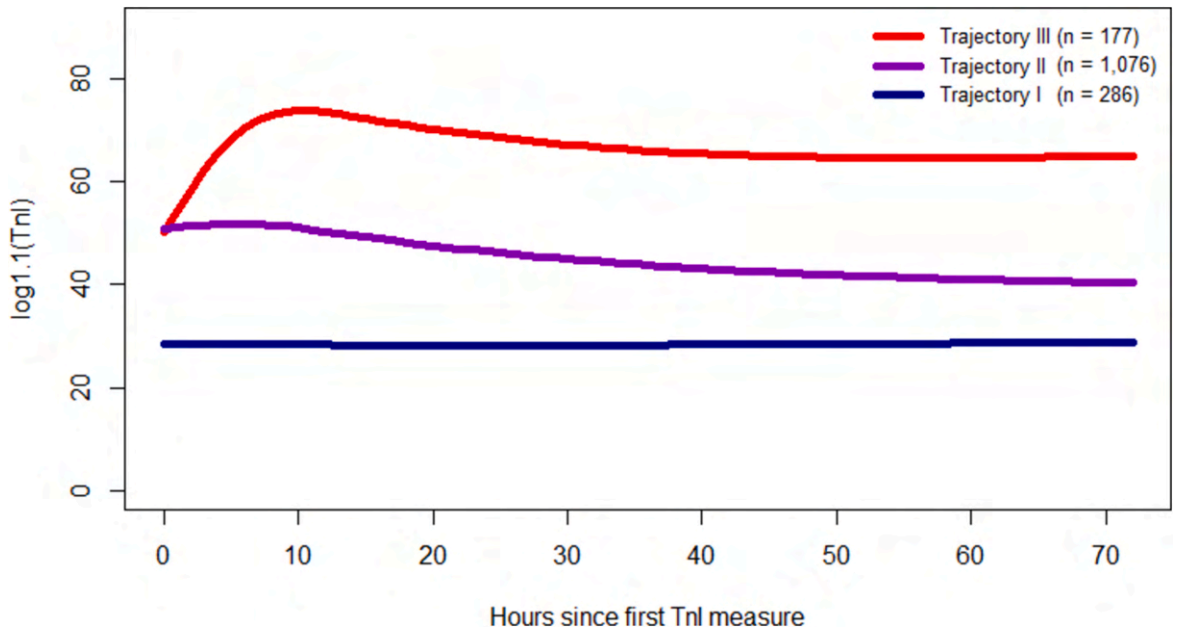

Fig. 2. Identification of three different TnI trajectories I-III using latent class trajectory modeling in hospitalized PE patients. TnI: troponin I.

In both cohorts, trajectory I demonstrates a stable low concentration of TnI (median 15 ng/l) or TnT (median 18 ng/l) throughout the three days of observation ($n_{TnI} = 286$, 18 % and $n_{TnT} = 472$, 36 %). Trajectory II, which accounts for the majority of included patients ($n_{TnI} = 1076$, 70 % and $n_{TnT} = 724$, 55 %), is characterized by an elevated index concentration of TnI (0 h median 140 ng/l) or TnT (0 h median 86 ng/l), a plateau, followed by a steady decrease in TnI (7 h median 119 ng/l, 20 h median 148 ng/l) or TnT level (6 h median 79 ng/l, 21 h median 77 ng/l). Trajectory III ($n_{TnI} = 177$, 12 % and $n_{TnT} = 127$, 10 %) also characterized by an elevated index concentration of TnI/TnT, demonstrates a steep increase in TnI (0 h median 111 ng/l, 7 h median 1065 ng/l) or TnT concentration (0 h median 85 ng/l, 6 h median 342 ng/l) within the first 10 h, followed by a decrease in TnI (20 h median 964 ng/l) or TnT level (21 h median 265 ng/l) within the first 24 h (Table 1).

Information on sex, age, comorbidities, median level of eGFR, and 30-day mortality according to the different TnI and TnT trajectories are provided in Table 2. Sex and comorbidity burden were equally distributed across the three TnI trajectories, however, in the TnT cohort, number of patients with preexisting kidney disease increased significantly across the trajectories. Patient age increased in both the TnI and TnT cohort from 67/70 years in trajectory I to 73/75 years in trajectory III. Median eGFR level decreased across the trajectories from 81/72 ml/min in trajectory I to 62/54 ml/min in trajectory III. Both 30-day and 1-year mortality rates were higher in trajectory II and III compared to I in both the TnI (30-day: 3 %, 7 % and 18 %, 1-year: 11 %, 16 % and 20 % across trajectory I to III) and the TnT cohort (30-day: 1 %, 9 % and 20 %, 1-year: 15 %, 20 % and 21 % across trajectory I to III). Median time to 30-day death in the TnI cohort was ten days for patients in trajectory I

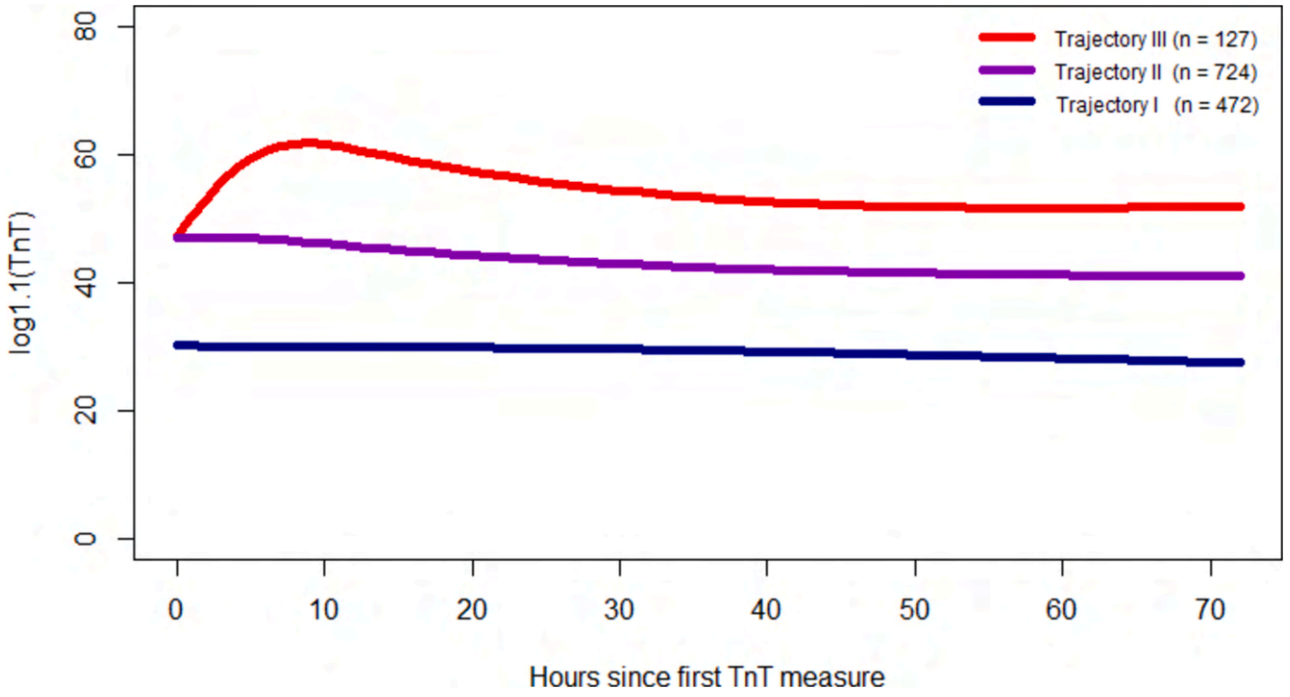

Fig. 3. Identification of three different TnT trajectories I-III using latent class trajectory modeling in hospitalized PE patients. TnT: troponin T.

Table 1
Mean and median concentrations of TnI and TnT (ng/l) at first, second and third measurement in trajectory I-III. TnI: troponin I, TnT: troponin T, SD: standard deviation, IQR: interquartile range.

	TnI			TnT		
	First measurement 0 h (n = 1539)	Second measurement ~ 7 h (n = 1539)	Third measurement ~ 20 h (n = 525)	First measurement 0 h (n = 1323)	Second measurement ~ 6 h (n = 1323)	Third measurement ~ 21 h (n = 405)
Trajectory I						
Mean ng/l (SD)	15 (2)	15 (2)	15 (1)	18 (8)	18 (8)	19 (8)
Median ng/l (IQR)	15 (0)	15 (0)	15 (0)	17 (12)	17 (13)	18 (10)
Trajectory II						
Mean ng/l (SD)	408 (788)	382 (703)	364 (548)	150 (174)	134 (149)	126 (155)
Median ng/l (IQR)	140 (401)	119 (362)	148 (413)	86 (126)	79 (102)	77 (88)
Trajectory III						
Mean ng/l (SD)	591 (2670)	2710 (6025)	3123 (6807)	737 (4886)	1773 (9454)	2142 (11,551)
Median ng/l (IQR)	111 (258)	1065 (2197)	964 (1526)	85 (141)	342 (632)	265 (598)

and three days for patients in both trajectory II and III. In the TnT cohort median time to 30-day death was 14 days in trajectory I, six days in trajectory II to three days in trajectory I.

Hazard ratios of 30-day mortality by TnI and TnT trajectories, age, sex, comorbidities, and eGFR level are provided in Table 3. In the TnI cohort, we found a seven times higher risk of 30-day mortality belonging to trajectory II compared to trajectory I (HR 7.42, 95 % CI 1.00–54.84, $p = 0.04$) and a sixteen times higher risk of 30-day mortality belonging to trajectory III (HR 16.42, 95 % CI 2.42–127.29, $p = 0.007$). In the TnT cohort, we found a significant three times higher risk of 30-day mortality belonging to trajectory II compared to I (HR 2.97, 95 % CI 1.17–7.33, $p = 0.02$) and a significant eight times higher risk of 30-day mortality belonging to trajectory III (HR 8.21, 95 % 2.78–24.19, $p < 0.001$).

6. Discussion

The nationwide data registration practice in Denmark makes large sample sizes available for relevant studies on prognostic influences of troponins in patients with PE. This hypothesis-generating study is thus the first work to identify three distinct TnI and TnT trajectories within two unselected hospitalized cohorts of patients with PE using latent class trajectory models and the first study to investigate the association between these trajectories and the risk of 30-day mortality. We find that a steep increase in TnI or TnT within the first 24 h is associated with a significant increase in the risk of adjusted 30-day mortality compared to patients with PE and a low, stable TnI or TnT concentration. The increased mortality risk associated with the trajectories persists after one year.

Table 2
Patient characteristics according to TnI and TnT trajectories. TnI: troponin I, TnT: troponin T, HF: heart failure, IHD: ischemic heart disease, AMI: acute myocardial infarction, COPD: chronic obstructive pulmonary disease, DVT: deep vein thrombosis, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein.

	TnI			p-Value	TnT			p-Value
	Trajectory I (n = 286)	Trajectory II (n = 1076)	Trajectory III (n = 177)		Trajectory I (n = 472)	Trajectory II (n = 724)	Trajectory III (n = 127)	
Female sex (%)	153 (54)	532 (50)	87 (50)	0.471	227 (48)	376 (52)	66 (52)	0.407
Age years median (25th–75th percentile)	67 (55–76)	73 (63–80)	74 (66–81)	<0.001	70	72	75	<0.001
HF (%)	34 (12)	85 (8)	13 (7)	0.083	40 (9)	69 (10)	12 (9)	0.819
IHD (%)	68 (24)	171 (16)	28 (16)	0.038	89 (19)	116 (16)	18 (14)	0.308
Previous AMI (%)	32 (11)	97 (9)	18 (10)	0.516	43 (9)	65 (9)	10 (8)	0.907
Cancer (%)	34 (12)	174 (16)	32 (18)	0.130	71 (15)	131 (18)	21 (17)	0.385
COPD (%)	22 (8)	93 (9)	23 (13)	0.121	53 (11)	73 (10)	12 (9)	0.761
Renal disease (%)	11 (4)	51 (5)	12 (7)	0.351	14 (3)	51 (7)	11 (9)	0.004
Diabetes (%)	25 (9)	99 (9)	25 (14)	0.102	42 (9)	75 (10)	13 (10)	0.699
Hypertension (%)	79 (28)	332 (31)	61 (35)	0.292	142 (30)	258 (36)	50 (39)	0.057
Previous DVT (%)	46 (16)	175 (16)	30 (17)	0.968	64 (14)	91 (13)	17 (13)	0.875
eGFR ml/min median (25th–75th percentile)	81 (65–90)	69 (52–84)	62 (43–77)	<0.001	72 (56–85)	60 (26–52)	54 (33–68)	<0.001

Table 3
Multivariable adjusted Cox proportional hazards model of 30-day mortality. TnI: troponin I, TnT; troponin T, HF: heart failure, IHD: ischemic heart disease, AMI: acute myocardial infarction, COPD: chronic obstructive pulmonary disease, DVT: deep vein thrombosis, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, CI: confidence interval, HR: hazard ratio.

	TnI		p-Value	TnT		p-Value
	HR	95 % CI		HR	95 % CI	
Trajectory						
I	Ref.	–	–	Ref.	–	–
II	7.42	[1.00; 54.84]	0.04	2.93	[1.17; 7.33]	0.02
III	16.42	[2.42; 127.29]	0.007	8.21	[2.78; 24.19]	<0.001
Female sex	0.89	[0.50; 1.58]	0.68	1.66	[0.85; 3.24]	0.14
Age group						
18–54 years	Ref.	–	–	Ref.	–	–
55–67 years	4.10	[0.53; 31.52]	0.17	0.50	[0.12; 2.01]	0.33
>75 years	5.69	[0.72; 44.83]	0.10	0.92	[0.23; 3.61]	0.90
HF	0.86	[0.31; 2.36]	0.77	0.66	[0.19; 2.29]	0.51
IHD	1.38	[0.66; 2.89]	0.39	1.33	[0.55; 3.22]	0.53
Previous AMI	1.32	[0.54; 3.25]	0.54	2.10	[0.72; 6.15]	0.18
Cancer	2.28	[1.20; 4.33]	0.01	5.01	[2.60; 9.67]	<0.001
Renal disease	1.08	[0.34; 3.36]	0.90	0.20	[0.03; 1.50]	0.12
COPD	1.90	[0.90; 4.00]	0.09	1.60	[0.64; 3.97]	0.31
Diabetes	2.91	[1.41; 6.02]	0.004	1.50	[0.60; 3.75]	0.38
Hypertension	0.61	[0.32; 1.15]	0.13	0.77	[0.39; 1.55]	0.47
Previous DVT	0.78	[0.35; 1.74]	0.54	0.45	[0.11; 1.88]	0.27
eGFR ml/min						
High	Ref.	–	–	Ref.	–	–
Medium	0.79	[0.34; 1.81]	0.58	2.01	[0.67; 6.03]	0.21
Low	1.30	[0.59; 2.89]	0.51	2.30	[0.73; 7.22]	0.15

Elevated concentrations of troponins are found in 30–60 % of all patients with PE [2,12] and have a well-established association with increased risk of early mortality [6]. Though no relevant cut off levels of TnI/TnT has been suggested in ESC guidelines, data shows that the degree of TnI/TnT increase reflects a more severe clinical profile [4,13,14]. The interdependence between troponin concentration and mortality risk probably indicates a more extensive and proximal involvement of the pulmonary vasculature, leading to RV strain and failure [13]. Since an obstructive and hypoxic increase in pulmonary pressure eventually will lead to compromised cardiac output and affected coronary flow in patients with PE, gradual myocardial damage to the RV over time is expected [15]. A delay between onset of symptoms and the release of troponins in patients with PE can thus be assumed and the analysis of repetitive measurements of TnI/TnT seems relevant.

To our knowledge, only very few studies have examined the kinetics of troponins in patients with PE. The first study to present release curves for troponins in patients with PE was in 2002 by Müller-Bardorff et al. The study included only nine patients surviving severe PE. Patients were followed with measurements of TnT concentration from time of admission, every four hour the first 24 h and then daily until discharge. In four out of nine patients, TnT was negative at initial assessment but became positive within 8 h. Increases did not persist beyond 40 h [16]. In 2012 Ferrari et al. studied TnI kinetics in 200 hemodynamic stable patients with PE and found peak level of TnI to be reached after 8 h. Furthermore, they discovered 15 % of patients presenting with a negative TnI measurement at admission to become TnI positive at second assessment, thus concluding a high misclassification rate if PE risk profile is only based on first TnI measurement. Due to the small sample size the study was not able to evaluate any differences in mortality [17]. Based on their findings, both mentioned studies recommended that at least two consecutive measurements of TnT/TnI were obtained with an eight hour interval in order to ensure optimum risk stratification in patients with PE. The studies emphasize the importance of accurate timing in measuring index troponin levels.

Our study confirms this approach. Trajectory III, comprising only 10–12 % of patients, had an elevated index concentration of TnI/TnT and developed a noteworthy surge in concentration within the first 10 h. Unfortunately, we are unable to examine whether differences between trajectory II and III reflects variations in timing of symptom onset or hemodynamic changes. However, the intriguing aspect lies in the delayed surge of TnI/TnT, detectable only through repetitive measurements within the initial 24 h, which seems to provide additive prognostic information beyond the increased index concentration.

In our cohort, peak level of TnI/TnT was measured at second assessment performed after 6–7 h (median). Third assessment performed after 20–21 h (median) already showed a decline in TnI/TnT concentration in all three trajectories. Thus, our data confirms findings from previous studies, that two consecutive measurements with only six–ten hour interval should identify most relevant increases in TnI/TnT

concentrations [16,17].

Recent studies have focused on enhancing risk stratification for PE by using specific cut-off values for index TnI/TnT, however, this approach can be challenging due to the variety of troponin assays used both nationally and internationally, as well as securing the optimal timing of peak measurement, as emphasized by our results. Our findings suggest that prognostic value resides in the dynamics of TnI/TnT. The clinical feasibility of relying on repeated troponin measurements or on specific cut-off values tailored to the assay in use needs further exploration and should be addressed in future studies.

Our study has important limitations. First and foremost, our work does not contain information on other important risk factors included in relevant risk assessment tools such as hemodynamic status and echocardiographic findings. Thus, we are not able to test, whether the approach of repeated measurements adds more prognostic value to the current risk stratification tool as provided by the ESC. However, we exclusively included only hospitalized individuals with serial troponin measurements, potentially representing those clinically most affected by PE. Since TnI/TnT is highly sensitive to even minor myocardial injury, the use of TnI or TnT to detect early signs of RV strain seems especially important in the group of hemodynamically stable patients with PE in high risk of clinical deterioration. Whether inclusion of hemodynamic status affects the prognostic relevance of our finding when simultaneously accounted for, remains to be clarified.

Furthermore, the indication for measuring more than one TnI or TnT concentration is not clear and may be prognostic important but remain unaccounted for in this study as this information is not available. Due to the retrospective design, we are not able to detect any potential impact of differing PE treatments between the trajectories. It should be noted that our data collection extends only through 2018, and since then, treatment strategies for patients with PE have evolved, likely improving patient outcomes. Thus, the mortality risk assessed in this study may not accurately reflect that of today's PE patients.

With different assays of TnI and TnT used across Danish regions, our cohorts include measurements of TnI and TnT in ng/l but varying upper thresholds. Although the identified trajectories are based on a model with a random intercept, thus not accounting for mean trajectory values, we conducted a sensitivity analysis using the percentage increase in TnI or TnT concentrations over time. This analysis yielded results consistent with our main findings (results not shown), addressing potential bias from the use of assays with differing upper thresholds. In Denmark, high-sensitivity troponin assays are the preferred method for cardiac troponin testing in clinical settings. These assays offer greater precision and sensitivity compared to older standard tests, allowing for more accurate detection of myocardial injury, even in patients with lower troponin levels. The role of high-sensitivity troponins has been extensively discussed in recent studies [18–20]. However, in this study, we are unable to differentiate between high-sensitivity and older troponin assays. Given the data collection period of 2013–2018, we assume that mix of both high sensitivity and older assays was used.

The potential bias arising from including patients who died within the first three days of hospitalization, was addressed in a sensitivity analysis by excluding patients who did not survive beyond this initial period. Despite this adjustment, the identified trajectories of TnI and TnT remained consistent, indicating steep troponin rises within the first 24 h are not limited to patients with hemodynamic instability and fatal outcomes. This robustness in trajectory patterns supports the stability of our latent class trajectory model.

Finally, potential assay interference from factors such as macrotroponins, autoantibodies, and rheumatoid factor may impact troponin concentrations and should be considered when interpreting the results [21].

Due to the limitation of our data as mentioned above, this study is only hypothesis-generating and trajectories needs to be confirmed in other relevant cohorts.

7. Conclusion

This nationwide register-based study is the first to identify different trajectories of TnI and TnT measurements in unselected patients with PE. We demonstrate that a steep increase in TnI or TnT concentration within 6 to 10 h is associated with an increase in risk of 30-day mortality compared to PE patients with low, stable concentrations of TnI or TnT. Our results suggest that early serial sampling may enhance risk classification of patients with PE and could be a relevant alternative to the potential use of specific troponin cut-off values. The trajectories and their prognostic relevance should be further explored in future studies.

CRediT authorship contribution statement

Emilie Sonne-Holm: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Jesper Kjærgaard:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Lia E. Bang:** Writing – review & editing, Methodology, Conceptualization. **Lars Køber:** Writing – review & editing, Methodology, Conceptualization. **Emil Fosbøl:** Writing – review & editing, Methodology, Conceptualization. **Christian Hassager:** Writing – review & editing, Methodology, Conceptualization. **Rasmus Paulin Beske:** Writing – review & editing, Methodology, Conceptualization. **Jørn Carlsen:** Writing – review & editing, Methodology, Conceptualization. **Matilde Winther-Jensen:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A

Appendix Table 1
Mean posterior probabilities of trajectory I-III in the TnI and TnT cohort. Probabilities >0.8 represents well-separated, predictive trajectories. TnI; troponin I, TnT; troponin T.

	Probability I		Probability II		Probability III	
	TnI	TnT	TnI	TnT	TnI	TnT
Trajectory I	0.92	0.93	0.0	0.0	0.08	0.07

(*continued on next page*)

Appendix Table 1 (*continued*)

	Probability I		Probability II		Probability III	
	TnI	TnT	TnI	TnT	TnI	TnT
Trajectory II	0.0	0.01	0.92	0.80	0.08	0.19
Trajectory III	0.03	0.03	0.01	0.08	0.96	0.89

Appendix Table 2
Baseline differences between the TnI and TnT cohort. TnI; troponin I, TnT: troponin T, HF: heart failure, IHD: ischemic heart disease, AMI: acute myocardial infarction, COPD: chronic obstructive pulmonary disease, DVT: deep vein thrombosis, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein.

	TnI (n = 1539)	TnT (n = 1323)	p-Value
Female sex (%)	775 (50)	669 (51)	0.94
Age years median (25th–75th percentile)	72 (63–80)	72 (62–81)	0.43
HF (%)	132 (9)	121 (9)	0.64
IHD (%)	267 (17)	223 (17)	0.77
Previous AMI (%)	147 (10)	118 (9)	0.61
Cancer (%)	240 (16)	223 (17)	0.39
COPD (%)	138 (9)	138 (10)	0.21
Renal disease (%)	74 (5)	76 (6)	0.30
Diabetes (%)	149 (10)	130 (10)	0.95
Hypertension (%)	472 (31)	450 (34)	0.06
Previous DVT (%)	251 (16)	172 (13)	0.02
eGFR ml/min median (25th–75th percentile)	68 (50–85)	63 (43–80)	0.31

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PAPER V

Pathophysiology and prognostic value of syncope in patients with intermediate-high risk pulmonary embolism. Sonne-Holm E, Winther-Jensen M, Bang LE, Carlsen J, Jawad S, Sommer Ulriksen P, Kjærgaard J.

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Pathophysiology and prognostic value of syncope in patients with intermediate-high risk pulmonary embolism

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BACKGROUND

Syncope occurs in up to 25% of all patients with acute pulmonary embolism (PE), however, the pathophysiology and prognostic impact in intermediate-high risk PE remains unclear.

METHODS

This study, part of the STRATIFY trial from Copenhagen University Hospital Rigshospitalet, included 210 patients with intermediate-high risk PE. Data on demographics, comorbidities, and clinical parameters were collected upon admission. Patients underwent computed tomography pulmonary angiography (CTPA), transthoracic echocardiography and electrocardiogram at admission. CTPA measurements included right ventricle (RV) and left ventricle (LV) diameter ratio and clot burden using the refined Miller Score (RMS). Patients were grouped by presence of syncope. Chi-square and ANOVA test compared variables between the groups and multivariate logistic regression analysis identified associations with syncope. Survival analysis and multivariate regression analysis examined the association between syncope and in-hospital adverse outcomes (death, rescue thrombolysis).

RESULTS

Of 210 patients, 39 (19 %) experienced syncope. Patients with syncope were younger (mean age 63 vs. 68 years) and more often male (66% vs. 48%). Younger age (OR 0.96, 95% CI 0.93-0.99, p=0.005), lower body mass index (OR 0.92, 95% CI 0.85-0.99, p=0.02) and increased RV/LV ratio (OR 5.24, 95% CI 1.62-17.01, p=0.005) were independently associated with syncope. Increased clot burden was not (OR 1.07, 95% CI 0.96-1.19, p = 0.24). Syncope was associated with a higher risk in-hospital adverse events (OR 9.28, 95% CI 2.04-42.32, p=0.004).

CONCLUSION

Syncope in intermediate-high risk PE patients correlates with increased RV/LV ratio and higher risk of in-hospital adverse events, suggesting its importance in refined risk assessment.

INTRODUCTION

Syncope, characterized by sudden, transient loss of consciousness lasting up to several minutes with spontaneous full recovery[1], is a prevalent symptom in acute pulmonary embolism (PE), affecting up to one fourth of all PE patients[2]. The underlying pathophysiological mechanism is not clearly understood. Hypotheses suggest reduced cerebral perfusion secondary to hemodynamic comprise, arrhythmias, vasovagal reflex triggers, or hypoxemia secondary to ventilation or perfusion abnormalities to play important roles in its pathogenesis[3].

PE patients presenting with syncope appears to be at increased risk of early adverse outcomes[4]. However, most studies investigating both the pathophysiological mechanisms and prognostic implications of syncope have been conducted in PE populations consisting of mixed risk groups confounding the association between syncope, hemodynamic instability, and adverse outcomes[3,5-7]. Consequently, the pathophysiology and prognostic significance of syncope in hemodynamically stable patients remains uncertain.

Recent advancements in optimized treatment methods for hemodynamically stable patients with intermediate-high risk PE[8], have highlighted the need for refined risk assessment strategies to improve clinical outcomes. We hypothesize that syncope may play a significant role in this context and could add to the established risk assessment tools such as the simplified Pulmonary Embolism Severity Index (sPESI) score.

This study aims to investigate the pathophysiological mechanisms and short-term prognostic implications of syncope in intermediate-high risk PE patients and whether presence of syncope adds to the established sPESI score.

METHODS

This study is based on data derived from the clinical randomized trial STRATIFY (“Low dose thrombolysis, ultrasound assisted thrombolysis or heparin for intermediate high risk pulmonary embolism”) emerging from the Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Denmark on patients

with intermediate-high risk PE[9]. Intermediate-high risk PE is defined by European Society of Cardiology guidelines as PE with haemodynamic stability, evidence of right ventricular dysfunction and elevated cardiac biomarkers[8]. Patients with a confirmed diagnosis of intermediate-high risk PE >18 years of age were admitted to a tertiary centre between 6th of June 2019 and 4th of June 2024 and randomised to either 1) standard treatment with heparin, 2) heparin + low dose thrombolysis IV (20 mg Alteplase over 6 hours) or 3) heparin + low dose thrombolysis (20 mg Alteplase over 6 hours) via catheter-based ultrasound assisted thrombolysis (USAT) in a 1:1:1 ratio. In total 210 patients were included in the trial and all patients were eligible for inclusion in this study. Baseline information on demographic characteristics were collected at inclusion in the trial as well as information on clinical features upon admission. Alcohol overuse was defined as >10 standard drinks per week in both male and female patients. Index electrocardiogram (ECG) at admission were analysed for arrythmia, S1Q3T3 pattern, negative T-waves in V1-V3 and complete/incomplete right bundle branch block (RBBB/iRBBB). All patients had a bedside transthoracic echocardiography performed by the cardiologist on-call at time of PE diagnosis, assessing left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE) and the tricuspid regurgitation gradient (TR-gradient). Lastly, an independent experienced radiologist blinded to treatment allocation evaluated the clot burden at the diagnostic CT pulmonary angiography (CTPA) using refined Miller score (RMS), which is validated for patients with intermediate and high-risk PE[10]. The right ventricular (RV) and left ventricular (LV) diameter and RV/LV ratio were measured from the CTPA, and the presence of a saddle embolus was noted. Patients' sPESI score[11] was calculated (age > 80 years = 1 point, history of cancer = 1 point, history of chronic cardiopulmonary disease = 1 point, heart rate ≥ 100 beats per minute = 1 point, systolic blood pressure < 100 mmHg = 1 point, oxygen saturation < 90 % = 1 point).

Patients were divided into two groups based on the presence of either syncope or no syncope as part of initial symptoms leading to hospitalization. Syncope was defined as a sudden, transient loss of consciousness lasting up to several minutes with spontaneous full recovery[1]. Patients with a pre-syncope, defined as the sensation of nearly fainting without actual loss of consciousness[1] was also registered for

subgroup analysis, but remained part of the patient group with no syncope for the main analysis. Need for rescue thrombolysis and/or in-hospital death were recorded and considered prognostic endpoints.

STATISTICAL METHODS

Data were analysed using contingency tables to examine statistical differences between the two patient groups, using chi-square test for categorical variables and ANOVA test for continuous variables. To evaluate the independent effect of relevant predictors of syncope, a multivariate logistic regression analysis was performed including age, sex, body mass index (BMI), arrythmias at index ECG, RMS and RV/LV ratio obtained from the diagnostic CTPA. Kaplan-Meier plot was used to visualise the association between syncope and in-hospital mortality. A multivariate regression analysis, adjusting for study treatment, sPESI-score[11] (0, 1 or ≥2) and sex, was conducted to analyse the association between syncope and a composite endpoint of in-hospital death or conversion to full-dose thrombolysis during hospitalization.
Subgroup analyses were performed comparing patients with pre-syncope with those without syncope/pre-syncope. Statistical significance was set at a p-value of less than 0.05. All analyses were performed in SAS Enterprise 8.3.

RESULTS

Patient characteristics

In this study of 210 patients with intermediate-high risk PE, 39 patients (19 %) presented with syncope as part of initial PE symptoms. Among the patients without syncope, 18 (9 %) additional patients had a pre-syncope. Patients with a syncope was younger men (66 % male, mean age 63 years) compared to patients without a syncope (48 % male sex, mean age 68 years) (p_{sex} = 0.04, p_{age} = 0.02). We found no significant differences in comorbidity burden or other demographic characteristics, such as alcohol consumption or smoking habits, between patients with and without syncope (Table 1). However, a tendency towards an association between lower BMI and syncope was found (29 versus 31, p = 0.09). A subgroup analysis

between patients with pre-syncope and no syncope/pre-syncope revealed no differences in predisposing factors (appendix Table 1).

	Syncope (n = 39)	No syncope (n = 171)	p-value
Female sex (%)	13 (33)	89 (52)	0.04
Age, years (SD)	63 (13)	68 (13)	0.02
BMI (SD)	29 (5)	31 (7)	0.09
Smoking (%)	17 (44)	74 (44)	0.98
Alcohol overuse (%)	3 (8)	4 (2)	0.09
Heart failure (%)	0 (0)	2 (1)	0.49
IHD (%)	0 (0)	9 (5)	0.14
Arrythmia (%)	2 (5)	4 (2)	0.35
Hypertension (%)	16 (41)	72 (42)	0.90
Stroke/TCI (%)	0 (0)	7 (4)	0.19
Diabetes (%)	4 (10)	16 (9)	0.86
Asthma (%)	1 (3)	18 (11)	0.12
COPD (%)	0 (0)	9 (5)	0.14
Renal impair (%)	3 (8)	7 (4)	0.34
Cancer (%)	4 (10)	29 (17)	0.29
Coagulopathy (%)	1 (3)	8 (5)	0.85
Previous DVT (%)	3 (8)	19 (11)	0.53
Previous PE (%)	5 (13)	16 (9)	0.52

Table I. *Predisposing factors in pulmonary embolism patients presenting with and without syncope. SD: standard deviation, BMI: body mass index, IHD: ischemic heart disease, TCI: transitory cerebral ischemia, COPD: chronic obstructive pulmonary disease, DVT: deep vein thrombosis, PE: pulmonary embolism.*

Clinical findings and diagnostic imaging

Table 2 presents differences in clinical findings at admission between patients with and without syncope. Mean heart rate was numerically higher among patients with syncope (110 beats/minute) compared to those without syncope (100 beats/minute), although this difference was not statistically significant (p = 0.12). Systolic blood pressure was within the normal range for all study patients but was significantly lower

in patients with syncope (mean 129 mmHg) compared to those without syncope (mean 137 mmHg) (p = 0.04).

When comparing the respiratory status, no differences was found in oxygen saturation levels (mean 95%). However, there was a tendency towards a higher need of oxygen supplementation in patients with syncope (mean 4 L versus 3 L, p = 0.13) and a lower respiration rate (19 breaths/minute versus 21 breaths/minute, p = 0.05). Arterial blood gas analysis revealed a significantly lower median blood pH in patients with syncope (7.41) compared to those without syncope (7.44) (p = 0.01), however within normal pH range. Hypoxemia and hypocapnia were present in both patient groups, with no significant differences in pO_2 (9.4 kPa in both groups) and pCO_2 values (4.4 versus 4.3 kPa, p = 0.15). No differences were found in levels of relevant biomarkers at admission (lactate, troponin I and T and D-dimér) (Table 2).

The proportion of patients with arrythmias, primarily atrial fibrillation, on index ECG were significantly higher among patients with syncope (10 %) compared to those without syncope (3 %) (p = 0.04). No significant differences were found between the groups in ECG signs indicative of RV strain, including S1Q3T3 pattern, negative T-waves in V1-V3 or RBBB/iRBBB (Table 2).

Findings from index transthoracic echocardiography showed preserved LVEF (approximately 60 %) among all study patients, with a mean TAPSE of 16 mm in both groups, and a mean TR-gradient of 41 mmHg in patients with syncope compared to 44 mmHg in those without (p = 0.28). None of these parameters differed significantly between the groups (Table 2).

Results from the baseline CTPAs readings showed a significantly greater clot burden in patients with syncope compared to those without (mean RMS 21 versus 19, p = 0.04), as well as a significant increase in RV/LV ratio (1.6 versus 1.4, p <0.001). We found no differences in the proportion of saddle emboli among patients with and without syncope (33 % vs 26 %, p = 0.38).

	Syncope (n = 39)	No syncope (n = 171)	p-value
Heart rate, beats/min (SD)	110 (21)	100 (18)	0.12
Systolic pressure, mmHg (SD)	129 (17)	137 (22)	0.04
Saturation (SD)	95 (4)	95 (4)	0.46
Oxygen need, L/min (SD)	4 (5)	3 (4)	0.13
Respiration rate (SD)	19 (3)	21 (4)	0.05
Temperature, ^{o}C (SD)	36.5 (0.5)	36.6 (0.5)	0.25
pH (SD)	7.41 (0.04)	7.44 (0.05)	0.01
pO2, kPa (SD)	9.4 (2.1)	9.4 (3.2)	0.99
pCO2, kPa (SD)	4.4 (0.6)	4.3 (0.6)	0.15
Lactate , mmol/L (SD)	2.2 (1.2)	2.0 (1.5)	0.44
D-dimér, FEU/L (SD)	14 (12)	11 (9)	0.07
TnI, ng/L (SD) - n = 116	726 (681)	685 (995)	0.86
TnT, ng/L (SD) – n = 111	167 (99)	144 (144)	0.48
Arrythmia (%)	4 (10)	5 (3)	0.04
S1Q3T3 (%)	11 (28)	64 (37)	0.28
Neg T V1-V3 (%)	17 (44)	72 (42)	0.87
RBBB/iRBBB (%)	9 (23)	28 (16)	0.32
LVEF, % (SD)	59 (4)	58 (5)	0.37
TAPSE, mm (SD)	16 (3)	16 (4)	0.81
TR-gradient, mmHg (SD)	41 (14)	44 (11)	0.28
Saddle embolus (%)	13 (33)	45 (26)	0.38
Total RMS (SD)	21 (3)	19 (4)	0.04
RV/LV ratio (SD)	1.6 (0.3)	1.4 (0.3)	0.006

Table II. *Clinical findings and hemodynamic data on admission in patients with pulmonary embolism presenting with and without syncope. SD: standard deviation, TnI: troponin I, TnT: troponin T, RBBB/iRBBB: right bundle branch block/intermittent right bundle branch block, LVEF: left ventricular ejection fraction, TAPSE: tricuspid annular plane systolic excursion, TR-gradient: tricuspid regurgitation gradient, RMS: refined Miller score, RV: right ventricle, LV: left ventricle.*

A multivariate logistic regression model including only baseline variables (patient age, sex, BMI, RV/LV ratio, arrythmias on index ECG, total RMS and RV/LV ratio from baseline CTPA) which seemed relevant for the pathophysiological mechanism of syncope was conducted. We found that only younger patient age (OR 0.96, 95% CI 0.93-0.99), lower BMI (OR 0.92, 95% CI 0.85-0.99) and increased RV/LV ratio (OR 5.24, 95% CI 1.62-17.01) were independently associated with syncope, Table 3.

	OR	95% CI	p-value
Age	0.96	0.93-0.99	0.005
Female sex	0.90	0.38-2.12	0.82
BMI	0.92	0.85-0.99	0.02
Arrythmia	3.80	0.47-30.80	0.21
RMS	1.07	0.96-1.19	0.24
RV/LV ratio	5.24	1.62-17.01	0.005

Table III. *Multivariate logistic regression analysis of factors associated with syncope in patients with intermediate-high risk pulmonary embolism. OR: odds ratio, CI: confidence interval, BMI: body mass index, RMS: refined Miller score, RV: right ventricle, LV: left ventricle.*

Our subgroup analysis revealed no differences in clinical findings upon admission between patients with pre-syncope and those without any pre-syncope or syncope (appendix Table 2).

Prognostic importance

In the cohort, five in-hospital deaths were reported; two from in-hospital cardiac arrest, two from intracerebral bleeding and one from multi-organ failure. Two deaths occurred in the syncope group and three in the non-syncope group.

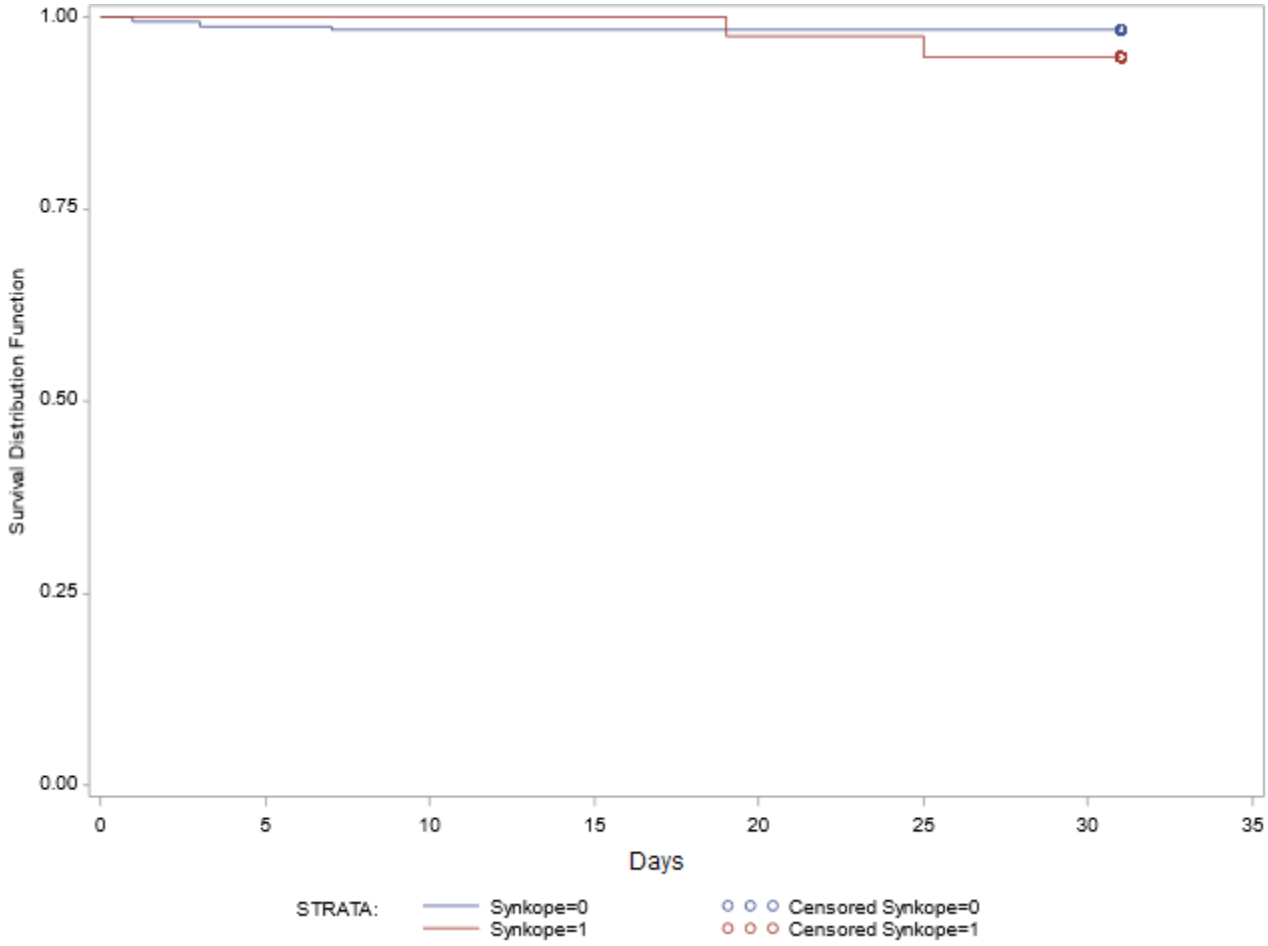

Figure I. *Kaplan-Meier survival curve comparing intermediate-high risk PE patients with and without syncope.*

Rescue thrombolysis was administered in five cases due to clinically worsening, four of whom had presented with syncope ($p < 0.001$). A multivariate regression analysis examined the association between syncope and a composite endpoint of in-hospital death and rescue thrombolysis, adjusting for study treatment, sPESI score and sex. Patients with syncope had an odds ratio of 9.28 (95 % CI: 2.04-42.32, $p = 0.004$) for the composite endpoint compared to those without syncope (Table 4).

A subgroup analysis showed that the composite endpoint did only occur in one patient with pre-syncope and in two patients without any presyncope or syncope.

	OR	95 % CI	p-value
Syncope	9.28	2.04-42.32	0.004
Study treatment			
Heparin (n=69)	Ref.	-	-
Low-dose thrombolysis IV (n=70)	2.06	0.18-8.20	0.85
USAT (n=71)	1.20	0.28-15.15	0.48
sPESI score			
0 (n=71)	Ref.	-	-
1 (n=95)	2.03	0.33-12.65	0.45
≥2 (n=44)	4.43	0.55-35.65	0.16
Female sex	0.15	0.02-1.32	0.09

Table IV. *Multivariate regression analysis of composite endpoint (death during hospitalization + conversion to rescue thrombolysis during hospitalization). OR: odds ratio, CI: confidence interval, IV: intravenous, USAT: ultrasound assisted catheter directed thrombolysis, sPESI: simplified Pulmonary Embolism Severity Index.*

DISCUSSION

This study, based on data derived from a clinical randomized trial of 210 patients with intermediate-high risk PE, identifies syncope as an early symptom in approximately one fifth of patients. Younger patient age, lower BMI, and an increased RV/LV ratio on diagnostic CTPA were associated with syncope. After adjusting for study treatment, sPESI score and sex, syncope was found to significantly increase the risk of in-hospital death and the need for rescue thrombolysis.

Patients with intermediate-high risk PE constitutes approximately 15 % of all PE cases and are characterized by stable hemodynamic measurements despite signs of RV strain[8]. Since previous studies on syncope have mainly been performed in mixed PE populations, it has been suggested that the prognostic influence of syncope is confounded by patients' hemodynamic status[4]. To our knowledge, no previous studies on syncope have been limited to include only normotensive intermediate-high risk PE patients. We found approximately 20 % of the patient cohort to present with syncope as part of initial symptoms, which is in accordance with previous literature[2,4,7].

Results of our study suggests that the presence of syncope at time of presentation in patients with intermediate-high risk PE is independently associated with increased RV/LV ratio when compared to patients without syncope. It is well known that an occlusion of the pulmonary vascular bed of >30-50 %

increases pulmonary pressure, resulting in acute RV dilation and subsequent reduction in cardiac output affecting cerebral perfusion[12]. In this cohort of intermediate-high risk patients, clot burden was in general severe, but were significantly higher among those with syncope. Previous studies have stated that clot burden and RV/LV ratio are only moderately correlated, as RV dilatation is also influenced by patients cardiac and respiratory reserve[12,13]. This could explain our finding of an independent association between lower BMI and syncope, highlighting that less physiological reserve increases the vulnerability to sudden hemodynamic changes. Median values of systolic blood pressures were within normal range in the two groups, however, our results indicated a trend towards lower index blood pressure in patients with syncope compared to those without. There was a tendency towards increased heart rate among patients with syncope, supporting the theory of affected cardiac output due to RV strain despite blood pressure within normal range at time of admission. In addition, we found a significant association between syncope and arrythmias (primarily atrial fibrillation) at index ECG implying that arrythmias also plays a vital role in the link between RV impairment and syncope. Another plausible pathophysiological mechanism behind syncope in intermediate-high risk PE patients could be the Bezold-Jarisch reflex. This reflex is triggered by sudden, central occlusion of the pulmonary bed, leading to an abrupt decline in cardiac output, vasodilatation and subsequent neurocardiogenic syncope[14,15]. Regardless of the underlying mechanism, our results suggest that syncope in intermediate-high risk PE patients represents those with the highest level of RV strain.

Previous studies have emphasized the significance of older age and comorbidities in contributing to syncope risk among hemodynamically stable PE patients[16]. Our study does not support these findings. In contrast, we observed a previously unaddressed trend where younger patients showed a higher susceptibility to syncope. This raises the question of whether younger age is associated with a limited pulmonary collateral arterial supply or reduced LV resilience against increased RV pressure, potentially escalating the risk of syncope.

The prognostic influence of syncope at PE presentation have been discussed in several previous studies, with conflicting results[2,7,17-22]. It has been suggested that haemodynamic instability rather than syncope itself, is the main predictor of early adverse outcomes[4]. However, the prognostic value of syncope is incorporated in the modified FAST score (H-FABP (or high-sensitivity troponin T), Syncope, Tachycardia score)[23,24], which is a validated tool for simple and easy risk assessment of hemodynamic stable PE patients [21]. The model has proved to be effective in identifying those patients with symptoms and clinical findings indicating more severe PE with a high risk of in-hospital adverse outcomes[25]. To date the score has not been tested as a guide for early therapeutic decisions in randomized controlled trials. In this study of hemodynamic stable intermediate-high risk PE patients, we found no significant association between syncope and in-hospital death, which we believe is due to our relatively small sample size and limited event-rate. However, patients with syncope had an almost eight-fold higher risk of a composite endpoint of rescue thrombolysis and/or in-hospital death even after adjustment for sPESI score, indicating that syncope represents patients with the most unstable hemodynamic. The prognostic influence of syncope is thus beyond the risk estimated by sPESI score in patients already categorized as intermediate-high risk. Since it is well known that an increased RV/LV ratio measured from CTPA in patients with PE is associated with short-term mortality[13,26,27], our results imply that syncope, as an indicator of severe RV strain, is an important predictor of high risk of adverse in-hospital outcomes.

Our subgroup analyses comparing patients with pre-syncope to those without syncope or pre-syncope showed no differences in predisposing factors, clinical findings upon admission, or in-hospital adverse outcomes. This underscores the importance of distinguishing between syncope and pre-syncope when incorporating this information into risk assessment.

Whether the presence of syncope should be used to guide future treatment strategies in intermediate-high risk patients to improve patient outcomes needs confirmation in future prospective management trials.

LIMITATIONS

This study has several limitations. First, we were unable to report any hemodynamic measurements and ECG findings in the exact moment of syncope which was mainly occurring prior to hospital admission, which limits the ability to definitively conclude on pathophysiological mechanism underlying syncope. However, this study is the first to focus exclusively on syncope in intermediate-high risk PE patients, and further to provide data on clot burden and RV strain derived from diagnostic CTPAs and their association with syncope.

Secondly, the reporting of syncope in our cohort is primarily relied on witnessed episodes of loss of consciousness, which introduces some uncertainty regarding the accuracy of symptom reporting. Finally, our study cohort was relatively small, with few syncope cases and fatal outcomes, which restricts our ability to draw robust conclusions about the pathophysiological mechanism and prognostic significance of syncope in this patient population. Results from the multivariate and Cox regression analyses should thus be interpreted with caution.

CONCLUSION

This study, based on data from a clinical trial, demonstrates that syncope in patients with intermediate-high risk PE correlates with increased RV strain, and is associated with increased risk of adverse in-hospital outcomes. The prognostic impact of syncope extends beyond the established sPESI score, highlighting its significance in intermediate-high risk PE patients and emphasizing the need for closer monitoring and potential advanced treatment strategies for this subgroup of patients. Future prospective management trials should determine whether the presence of syncope should be integrated into refined risk assessment of patients with intermediate-high risk PE to ensure optimal treatment strategies.

AUTHOR CONTRIBUTIONS

ESH: Conceptualization, Methodology, Software, Formal analysis and Writing – original draft preparation. JK and MWJ: Supervision, Conceptualization, Methodology and Formal analysis. LEB, JC: Conceptualization, Methodology, Writing – reviewing and editing. PSU, SJ: Methodology, Writing – reviewing and editing. All authors approved the final version of the manuscript.

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	Pre-syncope (n = 18)	No syncope or pre-syncope (n = 153)	p-value
Female sex (%)	11 (61)	78 (51)	0.42
Age, years (SD)	71 (12)	68 (13)	0.37
BMI (SD)	32 (6)	31 (7)	0.77
Smoking (%)	5 (29)	69 (45)	0.21
Alcohol overuse (%)	0 (0)	4 (3)	0.49
Heart failure (%)	0 (0)	2(1)	0.62
IHD (%)	1 (6)	8 (5)	0.95
Arrythmia (%)	1 (6)	3 (2)	0.34
Hypertension (%)	6 (33)	66 (43)	0.43
Stroke/TCI (%)	0 (0)	7 (5)	0.35
Diabetes (%)	2 (11)	14 (9)	0.79
Asthma (%)	3 (17)	15 (10)	0.37
COPD (%)	2 (11)	7 (5)	0.24
Renal impair (%)	2 (11)	5 (3)	0.11
Cancer (%)	3 (17)	26 (17)	0.97
Coagulopathy (%)	2 (11)	7 (5)	0.29
Previous DVT (%)	2 (11)	17 (11)	1.00
Previous PE (%)	2 (11)	14 (9)	0.79

Appendix table I. *Predisposing factors in pulmonary embolism patients presenting with pre-syncope and without pre-syncope/syncope. SD: standard deviation, BMI: body mass index, IHD: ischemic heart disease, TCI: transitory cerebral ischemia, COPD: chronic obstructive pulmonary disease, DVT: deep vein thrombosis, PE: pulmonary embolism.*

	Pre-syncope (n = 18)	**No syncope or pre-syncope** (n = 153)	**p-value**
Heart rate, beats/min (SD)	99 (21)	101 (17)	0.65
Systolic pressure, mmHg (SD)	131 (25)	137 (22)	0.21
Saturation, % (SD)	94 (5)	95 (4)	0.48
Oxygen need, L/min (SD)	0.7 (1.5)	2.9 (4.4)	0.03
Respiration rate, /min (SD)	20 (4)	21 (4)	0.42
Temperature, ^{o}C (SD)	36.6 (0.5)	36.6 (0.5)	0.92
pH (SD)	7.42 (0.05)	7.44 (0.05)	0.13
pO2, kPa (SD)	8.6 (1.4)	9.4 (3.3)	0.37
pCO2, kPa (SD)	4.2 (0.8)	4.3 (0.6)	0.85
Lactate, mmol/L (SD)	2.6 (2.4)	1.9 (1.3)	0.10
D-dimér, FEU/L (SD)	10 (6)	11 (9)	0.72
TnI, ng/L (SD) - n = 95	581 (624)	694 (1024)	0.76
TnT, ng/L (SD) – n = 90	111 (88)	148 (150)	0.42
Arrythmia (%)	1 (6)	4 (3)	0.48
Atrial fibrillation	1	3	
Other	0	1	
S1Q3T3 (%)	7 (39)	57 (37)	0.89
Neg T V1-V3 (%)	9 (50)	63 (41)	0.47
RBBB/iRBBB (%)	3 (17)	25 (16)	0.97
LVEF, % (SD)	58 (4)	58 (5)	0.81
TAPSE, mm (SD)	18 (5)	16 (4)	0.09
TR-gradient, mmHg (SD)	46 (14)	44 (11)	0.39
Saddle embolus (%)	4 (22)	41 (27)	0.68
Total RMS (SD)	20 (6)	19 (4)	0.16
RV/LV ratio (SD)	1.5 (0.4)	1.4 (0.3)	0.27

Appendix table II. *Clinical findings and hemodynamic data on admission in patients with pulmonary embolism presenting with pre-syncope and those without any pre-syncope/syncope. SD: standard deviation, TnI: troponin I, TnT: troponin T, RBBB/iRBBB: right bundle branch block/intermittent right bundle branch block, LVEF: left ventricular ejection fraction, TAPSE: tricuspid annular plane systolic excursion, TR-gradient: tricuspid regurgitation gradient, RMS: refined Miller score, RV: right ventricle, LV: left ventricle.*