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Cystic fibrosis and its impact on prognosis in pulmonary embolism

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ABSTRACT

Background: Pulmonary embolism (PE) and cystic fibrosis (CF) are both diseases that impact the cardiovascular-pulmonary system. While CF is a rare heterogeneous monogenetic autosomal-recessive inherited multisystem-disease that reduces life-expectancy, PE is a common emergency event with also high morbidity and mortality. We aimed to investigate the impact of CF on prognosis of PE patients.
Methods: The German nationwide inpatient sample was used for this study. All patient-cases of patients with PE in Germany 2005–2020 were included and stratified for CF.
Results: Overall, 1,373,084 patient-cases of PE patients (median age 72.0 years, 53.0 % females) in Germany were included in our study 2005–2020. Among these, 126 patients (0.01 %) were coded with CF.
PE patients with CF were younger (33.0 [24.0–43.0] vs. 72.0 [60.0–80.0] years, $P < 0.001$) displaying a lower prevalence of arterial hypertension, hyperlipidemia and lower comorbidity-burden (Charlson comorbidity index: 2.0 [1.0–4.0] vs. 4.0 [3.0–7.0], $P < 0.001$) compared to those without CF. In contrast, diabetes mellitus was more frequent in PE patients with CF (49.2 % vs. 18.7 %, $P < 0.001$).
After adjustment for age, sex and comorbidities, CF was associated with higher case-fatality (OR 2.451 [95 % CI 1.542–3.896], $P < 0.001$), pneumonia (OR 1.518 [95 % CI 1.059–2.176], $P = 0.023$) and necessity regarding transfusion of blood constituents (OR 3.702 [95 % CI 2.540–5.396], $P < 0.001$).
Conclusions: PE patients with CF were younger at the time of PE event and accompanied by typical comorbidities such as diabetes mellitus and renal disease compared to PE patients without CF. CF was associated with higher complication rates comprising pneumonia, bleeding events and 2.5-fold increased case-fatality.

1. Introduction

Cystic fibrosis (CF) is a heterogeneous monogenetic autosomal recessive inherited multisystem-disease that shortens life of the affected patients [1–4]. More than 80,000 people are afflicted by CF worldwide [2,5].

Mutations and deficiencies in the CF transmembrane conductase regulator protein (CFTR) are responsible for development of a complex multi-organ disease leading predominantly to impaired mucus hydration and clearance. This condition promotes comprising progressive respiratory deterioration, chronic bacterial infections of the air-ways and sinus, maldigestions with exocrine pancreatic insufficiency and hepatobiliary impairment, infertility in males, and sweating with abnormal sweat composition [1–6]. Management strategies, include augmentation of muccociliary clearance and aggressive treatment of infections, which have gradually improved life expectancy of individuals affected by CF. [5] In addition, restoration of CFTR function via new small molecule modulator drugs is transforming the disease for many patients [5,7,8]. Due to the progress in treatment strategies during the last three decades, the long-term prognosis of patients with CF has

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enormously improved [1,8].

However, individuals with CF confronted with an increased risk of venous thromboembolism (VTE) due to chronic inflammation, use of central venous catheters, as well as acquired thrombophilia [5,9,10]. VTE with its two manifestations pulmonary embolism (PE) and deep vein thrombosis is accompanied by high morbidity and mortality [11–16]. Since PE represents pulmonary disease-manifestation with a significant and relevant impact on the cardiovascular system caused by embolus material blocking the pulmonary artery bed, it is of interest whether CF as disease with focus on the lungs, but also affecting the cardiovascular system, might influence cardiac deterioration caused by PE and the prognosis of acute PE [12–14,16–23]. Therefore, we aimed to investigate the impact of CF on prognosis of PE patients.

2. Methods

The year 2004 was the starting date for all German hospitals to transfer their coded patient-data of hospitalizations focusing on diagnoses, (coexisting) conditions/comorbidities, surgeries, interventions, treatments and procedures to the Institute for the Hospital Remuneration System and the Federal Statistical Office of Germany (Statistisches Bundesamt) to receive their corresponding remuneration for the provided and rendered services [13]. For this reason, patients' diagnoses are coded according to ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification), while diagnostic, surgical and interventional procedures have to be coded according to OPS-codes in order to get the remuneration (Operationen- und Prozedurenschlüssel) [30,47].

The coding-information on all hospitalization-data from the inpatient cases, which is gathered by the Federal Statistical Office of Germany (Statistisches Bundesamt), will be included in the German nationwide inpatient sample (diagnosis related groups [DRG] statistic), which can be analysed and is the basis of the analysis of this present study [13].

Our study analyses were computed by the Research Data Center (RDC) of the Federal Statistical Office and the Statistical Offices of the federal states (in Wiesbaden, Germany) on our behalf (based on our made-up and generated SPSS syntaxes, delivered to the RDC).

For the present analysis, we selected all inpatients hospitalized with PE (ICD code I26) (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2020, own calculations) and stratified these hospitalizations of PE patients according of the presence of CF (ICD code E84). Since remuneration is the primary cause of coding the diagnoses, all diagnoses are coded, which are related to patient-costs during hospitalizations. Thus CF was coded if it was newly diagnosed during hospitalization or was a well-known diagnosis in the treated patient.

2.1. Study endpoints and in-hospital adverse events

The primary study endpoint was death of any cause during the hospital stay (in-hospital death). In addition, the adverse in-hospital events stroke (ischemic or haemorrhagic) (ICD codes I61-I64), acute kidney injury (ICD code N17), pneumonia (ICD-codes J12-J18), as well as serious bleeding events such as intracerebral bleeding (ICD code I61), and necessity of transfusion of blood components (OPS code 8-800) were included as further outcome parameters in the present study. It is well known that the airways of patients with CF are susceptible to infection inducing an intense inflammatory response even in those patients with only modest pulmonary disease [24]. Mucus retention in the lungs favors recurrent and persistent bacterial infections of the lungs and is followed by development of structural lung damage (bronchiectasis) [25,26]. However, data regarding prevalence of pneumonia with or without parapneumonic effusions are inconsistent [27]; thus, we included pneumonia as another outcome of our study to close this gap of knowledge.

2.2. Definitions

The definition of obesity was oriented towards the recommendation of the WHO (World Health Organization) determined by a body mass index $\geq$30 kg/m^2. Stroke comprised both stroke entities: ischemic as well as haemorrhagic stroke. Hemodynamically unstable PE was defined as PE patients with shock or cardio-pulmonary resuscitation (CPR). Thrombophilia comprised anti-thrombin deficiency, protein C and S deficiency, prothrombin gene mutation, factor V Leiden mutation and other thrombophilia including anti-phospholipid (anti-cardiolipin) syndrome.

2.3. Ethical aspects and study oversight

Since our study did not include a direct access by us (as the investigators) to individual data of patients, approval by an ethics committee and informed consent were not required, in compliance with German law. There was no commercial influence on the interpretation of the data.

2.4. Statistics

We compared hospitalization data of PE patients who also had CF to those of PE patients without CF. Descriptive statistics for this comparison of both groups (with and without CF) were provided with median and interquartile range (IQR), or absolute numbers and corresponding percentages and the continuous variables were compared with the help of Wilcoxon-Whitney *U* test, while the categorical variables were compared with Fisher's exact or chi^2 test, as appropriate.

Logistic regression models were used to investigate associations between CF and I) case-fatality as well as II) the investigated adverse in-hospital events. Results are presented as odds ratios (OR) and 95 % confidence intervals (CI). To ensure and provide that the results of these logistic regressions are not biased by important comorbidities, conditions and further factors and therefore, to guarantee a wide independence, the multivariable logistic regressions were calculated with the following adjustment: age, sex, obesity, cancer, heart failure, essential arterial hypertension, hyperlipidemia, acute and chronic kidney disease, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, and atrial fibrillation/flutter.

Temporal trends in the annual total numbers and proportion of PE patients with CF among all PE patients were analysed and illustrated.

We used the software of SPSS® (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) for the computerised data analysis. *P* values $<$0.05 (two-sided) were accounted to be statistically significant.

3. Results

Overall, 1,373,084 patient-cases of patients with PE (median age 72.0 years, 53.0 % females) were registered in Germany between the years 2005 and 2020 and included in our study. Among these, 126 patients (0.01 %) were coded with CF. The annual total numbers of PE patients with CF and the proportion of PE with CF related to all PE patients each year did not change over time (Fig. 1A). In contrast, we detected a large peak of PE patients with CF in 3rd decade of life with decreasing numbers of PE patients with CF in higher age-decades (Fig. 1B).

PE patients with CF were significantly younger than those PE patients without CF (33.0 [24.0–43.0] vs. 72.0 [60.0–80.0] years, $P < 0.001$). Only 7.1 % of the PE patients with CF were 70 years or older. The in-hospital stay of PE patients with CF was distinctly longer than that of those without CF (16.0 [7.0–32.3] vs. 9.0 [5.0–16.0], $P < 0.001$) (Table 1). While the cardiovascular risk factors essential arterial hypertension and hyperlipidemia were less prevalent in PE patients with CF probably driven by younger age, diabetes mellitus was substantially

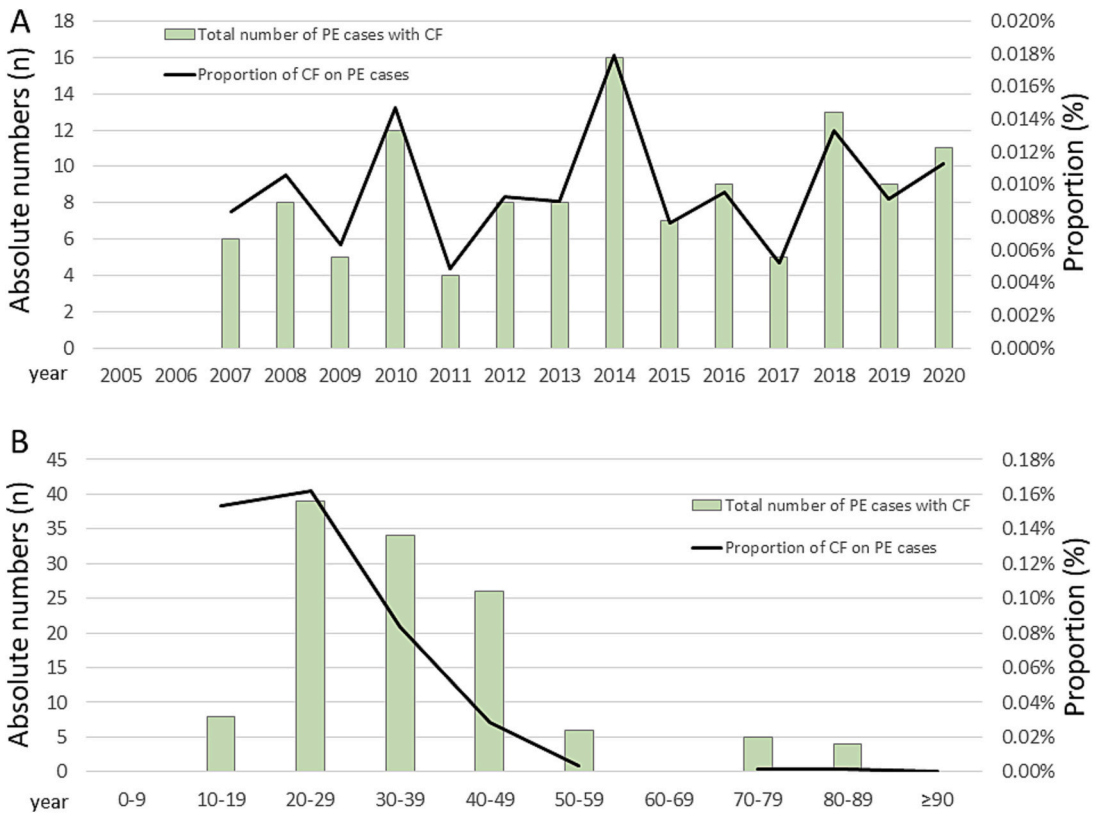

Fig. 1. Time trends in PE patients with cystic fibrosis (CF).
Panel A: Annual time trend regarding absolute numbers of PE patients with CF and proportion of PE patients with CF related to all PE patients 2005–2020.
|Panel B: Age-dependent time trend regarding absolute numbers of PE patients with CF and proportion of PE patients with CF related to all PE patients in the different age-decades of life.
In the years 2005 and 2006 the absolute and relative numbers of PE patients with CF were not provided by the RDC due to reasons of data protection.

more frequently detected in PE patients with CF (49.2 % vs. 18.7 %, $P < 0.001$). Regarding the classical risk factors for venous thromboembolism, cancer was more common in PE patients without CF, whereas surgery and thrombophilia were more prevalent in PE patients with CF. Interestingly, deep venous thrombosis and/or thrombophlebitis were less often detected in PE patients with CF (15.1 % vs. 35.6 %, $P < 0.001$) (Table 1).

The Charlson comorbidity index mirrors a higher comorbidity burden of PE patients without CF vs. those with CF (4.0 [3.0–7.0] vs. 2.0 [1.0–4.0], $P < 0.001$) most probably due to older age. Notably, the prevalence of acute and chronic kidney disease was higher in PE patients with CF, whereas frequency of heart failure and chronic obstructive pulmonary disease were similar between both groups (Table 1).

When focusing on the risk stratification markers of PE, PE patients with CF were more often afflicted by hemodynamic instability (14.3 % vs. 9.0 %, $P = 0.037$) and tachycardia, but were less often coded with right ventricular dysfunction (Table 1). However, despite PE patients with CF were more often afflicted by hemodynamic compromise, the standard reperfusion treatment of systemic thrombolysis was not more frequently administered in PE patients with CF than without CF (2.4 % vs. 4.2 %, $P = 0.498$).

PE patients with CF had a slightly, not significantly elevated case-fatality (19.0 % vs. 15.3 %, $P = 0.264$) in comparison to PE patients without CF, - which has to be considered in the light of the younger age of CF patients, who were in median 39 years younger than PE patients without CF (Table 1). CF was accompanied by higher risk of pneumonia (40.5 % vs. 24.1 %, $P < 0.001$) and acute kidney injury (15.9 % vs. 6.6 %, $P < 0.001$) in PE patients. Regarding bleeding events, PE patients with CF had a higher necessity of transfusion of blood constituents (37.3 % vs. 11.6 %, $P < 0.001$) compared to those without CF (Table 1).

The logistic regression models revealed that CF was independently related to higher case-fatality (OR 2.451 [95 % CI 1.542–3.896], $P < 0.001$) after adjustment for age, sex and comorbidities (Table 2). In addition, CF was independently associated with pneumonia (OR 1.518 [95 % CI 1.059–2.176], $P = 0.023$). In contrast, CF was not independently related to acute kidney injury ($P = 0.608$), right ventricular dysfunction ($P = 0.103$) and hemodynamic compromise ($P = 0.422$). However, the independent association between CF and lower usage of systemic thrombolysis (OR 0.287 [95 % CI 0.091–0.905], $P = 0.033$) might underline an underuse of this standard reperfusion treatment in PE patients with CF, which may be driven by the fear for major bleeding events since CF was associated with higher necessity regarding transfusion of blood constituents (OR 3.702 [95 % CI 2.540–5.396], $P < 0.001$) (Table 2). Lastly, the detection of deep venous thrombosis and/or thrombophlebitis was substantially lower in PE patients with CF than in those without CF (OR 0.284 [95 % CI 0.174–0.464], $P < 0.001$) (Table 2).

Regarding subgroup analysis, we detected that CF was an independent driver of in-hospital case-fatality especially in PE patients with pneumonia (OR 3.597 [95 % CI 1.852–6.988], $P < 0.001$), whereas in PE patients without pneumonia (OR 1.768 [95 % CI 0.910–3.432], $P = 0.093$) CF was not independently associated with in-hospital case-fatality. In PE patients with sepsis, CF was not an additional powerful trigger of hemodynamic instability (OR 0.256 [OR 0.026–2.507], $P = 0.242$) and in-hospital case-fatality (OR 0.663 [95 % CI 0.068–6.444], $P = 0.723$).

When focussing on the 817,796 patients, who were admitted due to PE (main diagnosis of PE), CF was diagnosed in only 23 patients, which indicates that PE might occur more often in CF patients than in those without CF. Length of in-hospital stay of patients admitted due to PE

Table 1
Patients' characteristics, medical history, presentation and outcomes of the included 1,373,084 patients with pulmonary embolism (PE) stratified according the presence of additional cystic fibrosis (CF). *P* values <0.05 were accounted to be statistically significant.

Parameters	PE patients without CF (*n* = 1,372,958; 99.99 %)	PE patients with CF (*n* = 126; 0.01 %)	*P*-value
Age	72.0 (60.0–80.0)	33.0 (24.0–43.0)	**<0.001**
Age ≥70 years	767,898 (55.9 %)	9 (7.1 %)	**<0.001**
Female sex	727,412 (53.0 %)	72 (57.1 %)	0.349
In-hospital stay (days)	9.0 (5.0–16.0)	16.0 (7.0–32.3)	**<0.001**
Traditional cardiovascular risk factors			
Essential arterial hypertension	602,718 (43.9 %)	12 (9.5 %)	**<0.001**
Diabetes mellitus	256,167 (18.7 %)	62 (49.2 %)	**<0.001**
Hyperlipidaemia	172,137 (12.5 %)	3 (2.4 %)	**0.001**
Classical risk factors for venous thromboembolism and proportion of DVT			
Cancer	279,144 (20.3 %)	13 (10.3 %)	**0.005**
Any surgery	711,778 (51.8 %)	77 (61.1 %)	**0.037**
Thrombophilia	16,064 (1.2 %)	6 (4.8 %)	**0.004**
Deep venous thrombosis and/or thrombophlebitis	489,000 (35.6 %)	19 (15.1 %)	**<0.001**
Comorbidities			
Charlson comorbidity index	4.0 (3.0–7.0)	2.0 (1.0–4.0)	**<0.001**
Heart failure	300,758 (21.9 %)	24 (19.0 %)	0.438
Atrial fibrillation/flutter	207,041 (15.1 %)	4 (3.2 %)	**<0.001**
Chronic obstructive pulmonary disease	138,380 (10.1 %)	17 (13.5 %)	0.203
Acute and chronic kidney disease	294,419 (21.4 %)	37 (29.4 %)	**0.030**
Risk stratification parameters of PE			
Hemodynamic instability	123,153 (9.0 %)	18 (14.3 %)	**0.037**
Shock	56,631 (4.1 %)	10 (7.9 %)	**0.041**
Cardio-pulmonary resuscitation	89,121 (6.5 %)	9 (7.1 %)	0.717
Right ventricular dysfunction	381,220 (27.8 %)	25 (19.8 %)	**0.047**
Tachycardia	40,906 (3.0 %)	10 (7.9 %)	**0.005**
Adverse events during hospitalization			
In-hospital death	210,530 (15.3 %)	24 (19.0 %)	0.264
Systemic thrombolysis	57,172 (4.2 %)	3 (2.4 %)	0.498
Surgical embolectomy	2007 (0.15 %)	3 (2.4 %)	**0.001**
Pneumonia	330,768 (24.1 %)	51 (40.5 %)	**<0.001**
Sepsis	19,859 (1.4 %)	4 (3.1 %)	0.113
Acute kidney injury	90,334 (6.6 %)	20 (15.9 %)	**<0.001**
Stroke (ischaemic or haemorrhagic)	40,576 (3.0 %)	3 (2.4 %)	1.000
Intracerebral bleeding	8565 (0.6 %)	0 (0.0 %)	**1.000**
Transfusion of blood constituents	159,599 (11.6 %)	47 (37.3 %)	**<0.001**

with and without CF does not differ significantly (8.0 [5.0–12.0] vs. 7.0 [4.0–18.0], $P = 0.944$) between the groups.

4. Discussion

Venous thromboembolism (VTE) comprising both deep vein thrombosis and PE affects approximately 10 million people every year worldwide and are accompanied by high morbidity and mortality [11–16,28]. The PE-related mortality is closely related to patient's hemodynamic status, cardiac deteriorations as well as comorbidities [12–14,16–23]. In this context, the impact of patient's comorbidities on survival during the acute phase of PE is mostly underrated [29–33]. Patients' comorbidity burden affects the patients' capacities to encounter the strain, stress and complications due to PE to avoid right

Table 2
Impact of cystic fibrosis (CF) on different outcomes and adverse in-hospital events (univariable and multivariable logistic regression model). *P* values <0.05 were accounted to be statistically significant.

	Univariable regression model		Multivariable regression model[a]	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value
In-hospital death	1.299 (0.833–2.027)	0.249	2.451 (1.542–3.896)	**<0.001**
Pneumonia	2.143 (1.501–3.058)	**<0.001**	1.518 (1.059–2.176)	**0.023**
Sepsis	2.222 (0.821–6.015)	0.116	0.737 (0.268–2.032)	0.556
Acute kidney injury	2.679 (1.661–4.320)	**<0.001**	0.837 (0.423–1.654)	0.608
Stroke (ischaemic or haemorrhagic)	0.801 (0.255–2.518)	0.704	1.005 (0.319–3.166)	0.993
Hemodynamic instability	1.691 (1.027–2.786)	**0.039**	1.232 (0.740–2.049)	0.422
Right ventricular dysfunction	0.644 (0.416–0.998)	**0.049**	0.691 (0.444–1.077)	0.103
Deep venous thrombosis and/or thrombophlebitis	0.321 (0.197–0.523)	**<0.001**	0.284 (0.174–0.464)	**<0.001**
Systemic thrombolysis	0.561 (0.179–1.765)	0.323	0.287 (0.091–0.905)	**0.033**
Surgical embolectomy	16.661 (5.296–52.415)	**<0.001**	4.139 (1.286–13.318)	**0.017**
Transfusion of blood constituents	4.523 (3.152–6.490)	**<0.001**	3.702 (2.540–5.396)	**<0.001**

[a] Adjusted for age, sex, obesity, cancer, heart failure, essential arterial hypertension, hyperlipidemia, acute and chronic kidney disease, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, and atrial fibrillation/flutter.

heart failure and in-hospital death [29,34–37]. Of course, the effect of comorbidities on prognosis varies widely and results not least from the interaction and interplay of different comorbidities [29]. In particular, cardiovascular as well as pulmonary diseases seem to negatively influence the capacities to encounter the deterioration of PE and aggravate prognosis [38,39]. This was shown for coronary artery disease [39] and heart failure [40], as well as for acute and chronic lung disease including chronic obstructive pulmonary disease [38] and pneumonia caused by COVID-19 [41]. Data for the rather rare disease CF (with approximately 80,000 affected people worldwide) and its impact on prognosis of PE are sparse [2,5]. Since PE represents a cardiovascular as well as pulmonary disease-manifestation, we hypothesized that CF as multisystem-disease with focus on the lungs might have a direct influence on cardiac deterioration during PE and might impact the prognosis of acute PE substantially [1–4,12–14,16–23]. It seems very unlikely that PE patients with CF will be treated ambulatory without admission to a hospital. Since CF is a chronic lung disease and PE patients with chronic cardiopulmonary diseases are classified as sPESI of 1 point or more depending on the other parameters which are assessed for risk stratification, these patients were classified as high risk patients according the sPESI and were not intended for early discharge of the hospitals or a complete ambulatory management [42–44]. However, data regarding outpatient treatment of pulmonary embolism (PE) is scarce [45].

In this large nationwide-inpatient sample from Germany with more than 1.3 million included hospitalizations of PE patients spanning the years 2005–2020, only a small minority (9.2 per 100,000 hospitalizations of PE patients) was coded with CF. However, if we put the small number of 126 patients during the 16 years observational period in correlation to the 80,000 patients worldwide, the number of included patient-cases is not so small as it seems to be. Approximately 0.01 % of the world population lives in Germany. If we calculate the 0.01 % proportion of the 80,000 CF patients worldwide, we would expect 800 patients with CF in Germany (if CF would be similarly distributed worldwide). Among these, 8 hospitalizations with PE and CF were

counted annually, which corresponds to a high 1 % incidence rate of PE in patients with CF. As expected and in accordance with the established knowledge that CF shortens life of the affected patients (despite the treatment progress in CF) [1–4], PE patients with CF were in our study in median nearby 40 years younger than those PE patients without CF. Although risk for PE increases substantially with age [13,19,46–48], only 7.1 % of the PE patients with CF were 70 years and older at the PE event. Therefore, this finding of lower median age does not surprise mirroring the shorter life expectancy of CF patients [1–4]. According to the distinctly younger age of PE patients with CF, typical cardiovascular risk-factors with age-dependent prevalence such as arterial hypertension and hyperlipidemia were (as expected) less often detected in patients with CF than without [49]. In line, we identified a higher comorbidity burden in PE patients without than with CF mirrored by the Charlson comorbidity index most probably due to older age. In contrast, diabetes mellitus was substantially more frequent (more than 30 % higher prevalence) in PE patients with CF. It is well established that diabetes mellitus requiring insulin is the leading complication and comorbidity in patients with CF. [50,51] Notably, the reported frequency of almost half of the PE patients with CF suffering from diabetes mellitus is higher than the reported prevalence of 5–30 % of CF patients in other studies [50,51]. In this context, the understanding regarding the nature of diabetes mellitus in CF is crucial, since diabetes mellitus is associated with an increased nutritional failure, worse pulmonary disease and earlier death in these affected patients [50,51]. Additionally and in part consecutively to higher prevalence of diabetes mellitus, the prevalence of acute and chronic kidney disease was higher in PE patients with CF in comparison to those without CF. [52,53] In this context, studies have shown that patients with CF presented with impaired renal function with increased serum Cystatin C and decreased eGFR values compared to controls [53].

It is well known that patients with CF are afflicted by acquired thrombophilia triggered by inflammation, or deficiencies of different anticoagulant proteins due to vitamin K deficiency and/or liver dysfunction [9], which was also confirmed in our study.

However, lung complications are the major cause of morbidity and mortality in CF patients [1–6,54]. Since the lung complications in CF patients are predominatly caused by infections, CF is associated with increased and intensified inflammation prcesses, but these inflammatory defense mechanisms in CF are less effective or ineffective to defeat and clear the pathogens [1–6,54]. Mucus retention in the lungs favors recurrent and persistent bacterial infections followed by development of structural lung damage, especially bronchiectasis [25,26]. The airways of CF patients are susceptible to infection inducing an intense inflammatory response even in those patients with only modest pulmonary disease [24]. Data regarding prevalence of pneumonia with or without parapneumonic effusions are inconsistent [27]. Our study detected a substantially higher rate of pneumonia in PE patients with CF. More than 40 % of the PE patients with CF developed a pneumonia. The pneumonia rate was substantially higher than in literature [27]. In addition, it has to be mentioned that persistent high-intensity inflammation results in structural damage of the airways and impaired lung function in CF patients potentially followed by respiratory failure and death [54].

Notably, deep venous thrombosis and/or thrombophlebitis were less often detected in PE patients with CF, which might be driven by higher inflammation levels in CF patients resulting in higher incidence rates of isolated PE without deep vein thrombosis. For PE without underlying deep venous thrombosis (isolated PE), data from previously published studies suggest an important role of co-morbidities such as cancer [55], atrial fibrillation [56,57], myocardial infarction [56] and HF [56,57] in the pathogenesis of thrombus formation. CF as lung and inflammatory disease might be one additional comorbidity contributing to isolated PE.

Our study demonstrated that CF was independently associated with a 2.5-fold increased case-fatality after adjustment for age, sex and comorbidities. This finding underlines the crucial impact of CF on prognosis of PE patients. In contrast to our hypothesis that CF might make patients more susceptible to cardiac changes and alterations due to PE, CF was not independently related to higher risk of development of right ventricular dysfunction. However, CF was accompanied by increased risk for hemodynamic instability and tachycardia, which might underline the effect of CF as an important comorbidity regarding prognosis in PE with reduced capacities to resist the stress of PE besides cardiac adaptations [29,54]. It is important, that our analysis revealed that the hemodynamic compromise was not primarily a result of an underlying sepsis.

Remarkably, although PE patients with CF were more often afflicted by hemodynamic compromise, the standard reperfusion treatment of systemic thrombolysis was less commonly administered in PE patients with CF, which might be driven by the fear regarding major bleeding events since CF was afflicted by crucially higher necessity regarding transfusion of blood constituents. In this context it is well known that individuals with CF are associated with higher bleeding rates (e.g. hemoptysis). This bleeding risk increases with higher age in CF patients in the context of higher life expectancy, which is achieved through better therapy options in recent years [1,8,58].

We detected a longer in-hospital stay of PE patients with CF in comparison to those without CF. This difference was no longer seen, if we focussed only on hospitalizations of patients admitted due to PE. The finding seems to be triggered by the younger age of the PE patients with CF. The younger age has a larger effect in patients admitted due to PE although CF is afflicted by higher complication rate than in admissions due to complications of CF with pneumonia and developing PE for example.

However, due to the imbalanced group sizes of hospitalizations of PE patients with and without CF, the associations of CF with increased complications in PE have to be evaluated with caution, since these imbalanced analysis are more prone to BIAS, since deteriorations in the smaller group of hospitalizations with CF have a larger weight compared with deteriorations in the larger group. Nevertheless, the primary aim of the study was to present for the first time data derived from a very large epidemiological data set and analyse and illustrate the impact of CF on outcomes in PE. Since CF is a rare disease smaller data sets would not be able to indicate significant differences between PE patients with and without CF. Keeping this limitation in mind, our study reveals clear evidence that CF in association with inflammation influences the outcomes of PE patients significantly and negatively. However, the generalizability of the results appears restricted.

4.1. Limitations

The present study has some limitations that merit consideration: Firstly, due to the nature of ICD- and OPS-code-based study-analysis of hospitalized patients of the German nationwide-inpatient sample, under-reporting as well as under-coding are possible. Secondly, data on most concomitant medication or laboratory markers are not available. Thirdly, the data of the German nationwide sample comprises the hospitalization duration and no follow-up evaluation after discharge from the hospital. Fourthly, due to the data structure of the German Nationwide Inpatient Statistics and confidential reasons, we could only analyse patient-cases and were not able to exclude that patient may be include in the study twice. Nevertheless, it is unlikely that a significant number of patients with CF have twice or more PE events and be twice or more often included in the study and distort statistical analysis. Fifthly, we were not able to differentiate between patients with single PE or recurrent PE events. Sixtly, due to the imbalanced group sizes of hospitalizations of PE patients with and without CF, the analysis are more prone by BIAS, since deteriorations in the smaller group of hospitalizations with CF have a larger weight compared with the larger group. Seventhly, the cause of death is not available in the German nationwide inpatient statistics. Eighthly, due to the data structure, data about results of echocardiography were not available in detail. However, the German

nationwide inpatient statistics provided data about the presence of RVD. Lastly, the sample size of PE patients with CF was small and this group exhibited a much younger age profile, which may impact the reliability of the reported effect estimates and confidence intervals.

5. Conclusions

PE patients with CF suffered from PE events in younger age and CF was accompanied by typical comorbidities such as diabetes mellitus and renal disease.

Additionally, CF was linked to higher complication rates, including an increased prevalence of pneumonia and bleeding events. Importantly, CF was independently associated with a 2.5-fold increase in case fatality.

CRediT authorship contribution statement

Karsten Keller: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Volker H. Schmitt:** Writing – review & editing. **Visvakanth Sivanathan:** Writing – review & editing. **Omar Hahad:** Writing – review & editing. **Thomas Münzel:** Writing – review & editing. **Philipp Lurz:** Writing – review & editing. **Christine Espinola-Klein:** Writing – review & editing. **Stefano Barco:** Writing – review & editing. **Stavros Konstantinides:** Writing – review & editing. **Lukas Hobohm:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

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