COVID-19 infection and its impact on case fatality in patients with pulmonary embolism

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Abstract

Background Although a high prevalence of pulmonary embolism (PE) has been reported in association with coronavirus disease 2019 (COVID-19) in critically ill patients, nationwide data on the outcome of hospitalised patients with COVID-19 and PE are still limited. Thus, we investigated seasonal trends and predictors of in-hospital death in patients with COVID-19 and PE in Germany.

Methods We used a German nationwide inpatient sample to analyse data on hospitalisations among COVID-19 patients with and without PE during 2020, and to detect changes in PE prevalence and case fatality in comparison with 2019.

Results We analysed 176 137 COVID-19 hospitalisations in 2020; PE was recorded in 1.9% (n=3362) of discharge certificates. Almost one-third of patients with COVID-19 and PE died during the in-hospital course (28.7%) compared with COVID-19 patients without PE (17.7%). Between 2019 and 2020, numbers of PE-related hospitalisations were largely unchanged (98 485 *versus* 97 718), whereas the case fatality rate of PE increased slightly in 2020 (from 12.7% to 13.1%; p<0.001). Differences in case fatality were found between PE patients with and without COVID-19 in 2020 (28.7% *versus* 12.5%; p<0.001), corresponding to a 3.1-fold increased risk of PE-related death (OR 3.16, 95% CI 2.91–3.42; p<0.001) in the presence of COVID-19.

Conclusions In Germany, the prevalence of PE events during hospitalisations was similar in 2019 and 2020. However, the fatality rate among patients with both COVID-19 and PE was substantially higher than that in those with only one of these diseases, suggesting a life-threatening additive prognostic impact of the COVID-19–PE combination.

Introduction

The first patient cases of pneumonia caused by a previously unknown virus were identified in China by the end of 2019 [1, 2]. The fast spread of infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) resulted in a global pandemic [1]. Since the beginning of the pandemic, deaths related to COVID-19 surpassed 6 million people worldwide and more than 120 000 in Germany as of March 2022 [3]. Most often, COVID-19 patients present with respiratory

symptoms but may also suffer from chest pain and haemoptysis. These symptoms largely overlap with the typical symptoms observed in the clinical presentation of patients with acute pulmonary embolism (PE). In this context, thrombotic and thromboembolic complications such as PE have been described as frequent and relevant complications of COVID-19 infection across several countries in 2020 [4–7]. From a pathophysiological point of view, it is still a matter of debate whether venous thromboembolism (VTE), *in situ* immunothrombosis or both may cause contrast-filling defects in computed tomography pulmonary angiography (CTPA) when PE is diagnosed [8, 9]. COVID-19-associated local and systemic inflammation in combination with traditional predisposing factors for VTE such as immobilisation, hypovolaemia as well as endothelial damage are assumed to provoke VTE and/or immunothrombosis in patients with severe COVID-19 infection. However, if acute PE is confirmed, regardless of COVID-19 status, treatment should follow the general risk-adapted guidelines for the management of acute PE [10]. Studies have suggested that the incidence and fatality rates of patients with COVID-19 and PE vary among countries, and seem to be considerably higher compared with PE patients without COVID-19 [11–14]. Unselected data of nationwide studies of hospitalised patients with COVID-19 and PE are missing in Germany. The aim of this analysis was to provide comprehensive and precise information on patient characteristics, regional and seasonal differences, and outcomes of hospitalised patients with COVID-19 and PE in Germany in 2020, and to compare changes of PE prevalence and case fatality between 2019 and 2020.

Methods

Data source

Statistical analyses were performed on our behalf by the Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany). Aggregated statistics were provided from RDC on the basis of our SPSS codes (SPSS Statistics for Windows version 20.0; IBM, Armonk, NY, USA), which we had supplied to the RDC (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, Diagnosis-Related Groups (DRG) Statistic 2019–2020, own calculations) [15, 16].

With this data analysis of the German nationwide inpatient sample, we aimed to analyse temporal trends of all hospitalised patients with a confirmed COVID-19 diagnosis (International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code U07.1) and an additional diagnosis of PE (ICD-10 code I26) during the observational period between 1 January 2020 and 31 December 2020 and identify independent predictors of in-hospital death. To allow a comparison of PE prevalence between 2020 and previous years, all patients with the diagnosis of PE in 2019 and 2020 were analysed for this additional comparison.

Study oversight and support

Since our study did not comprise direct access by the investigators to individual patient data but only access to summarised results provided by the RDC, approval by an ethics committee as well as patients' informed consent were not required, in accordance with German law [15, 16].

Coding of diagnoses, procedures and definitions

Diagnosis- and procedure-related remuneration was introduced in Germany in 2004. Coding according the German DRG system, with coding of patient data on diagnoses, coexisting conditions, surgeries as well as on procedures/interventions and transferring these codes to the Institute for the Hospital Remuneration System, is mandatory for German hospitals to get their remuneration. Patients' diagnoses are coded according to ICD-10, German Modification (ICD-10-GM). In parallel, surgical, diagnostical and interventional procedures were coded according to OPS (Operationen- und Prozedurenschlüssel) codes.

To obtain data regarding coexisting conditions and complications, we used the available diagnostic and procedural codes for acute and chronic conditions (OPS and ICD-10-GM codes), which are presented with related ICD and OPS coding in supplementary table S1.

Statistical analysis

Differences in patient characteristics between the groups of hospitalised COVID-19-patients with PE *versus* without PE and patients who died during the in-hospital course and those who were discharged alive were calculated with the Wilcoxon–Whitney U-test for continuous variables and Fisher's exact or the Chi-squared test for categorical variables, as appropriate. Temporal trends regarding hospitalisations of COVID-19 and PE, and in-hospital mortality over time, were estimated by means of linear regression analyses. Logistic regression models were calculated to investigate associations between patients' characteristics as well as adverse events, on one hand, and 1) need for mechanical ventilation or 2) in-hospital death, on the other. In order to test the (in)dependence of the findings on confounding parameters, multivariate regression models were adjusted for age, sex, cancer, heart failure, coronary artery

disease, peripheral artery disease, COPD, essential arterial hypertension, hyperlipidaemia, renal insufficiency (glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}), diabetes mellitus and atrial fibrillation/flutter. Tested variables were not adjusted on their own. The results were presented as odds ratios and 95% confidence intervals. All statistical analyses were performed with SPSS Statistics for Windows version 20.0; p-values <0.05 (two-sided) were considered to be statistically significant.

Results

COVID-19 patients with and without PE: baseline characteristics

In total, 176 137 cases with confirmed COVID-19 infection were hospitalised in Germany during 2020. The majority were male (n=92 188 (52.3%)) and aged ⩾70 years (n=94 329 (53.6%)). In total, 31 607 (17.9%) patients with COVID-19 died.

A minority of patients with COVID-19 had an additional diagnosis of PE (n=3362 (1.9%)). The proportion of PE in patients with COVID-19 infection did not change significantly on a monthly basis during 2020, with the highest numbers in spring and winter (figure 1a). Regarding age distribution, PE proportion increased with age, revealing a peak in the fifth to seventh decades of life (figure 1b). Similar to the baseline characteristics, the majority of patients with COVID-19 and PE were male (n=2062 (61.3%)) and more than half of them were aged ⩾70 years (n=1717 (51.1%)). Cardiovascular risk factors and comorbidities such as obesity (299 (8.9%) versus 9084 (5.3%); p<0.001), malignancies (217 (6.5%) versus 8784 (5.1%); p<0.001) and chronic renal insufficiency (1119 (33.3%) versus 47 822 (27.7%); p<0.001) were more prevalent in patients with COVID-19 and PE compared with patients with COVID-19 without
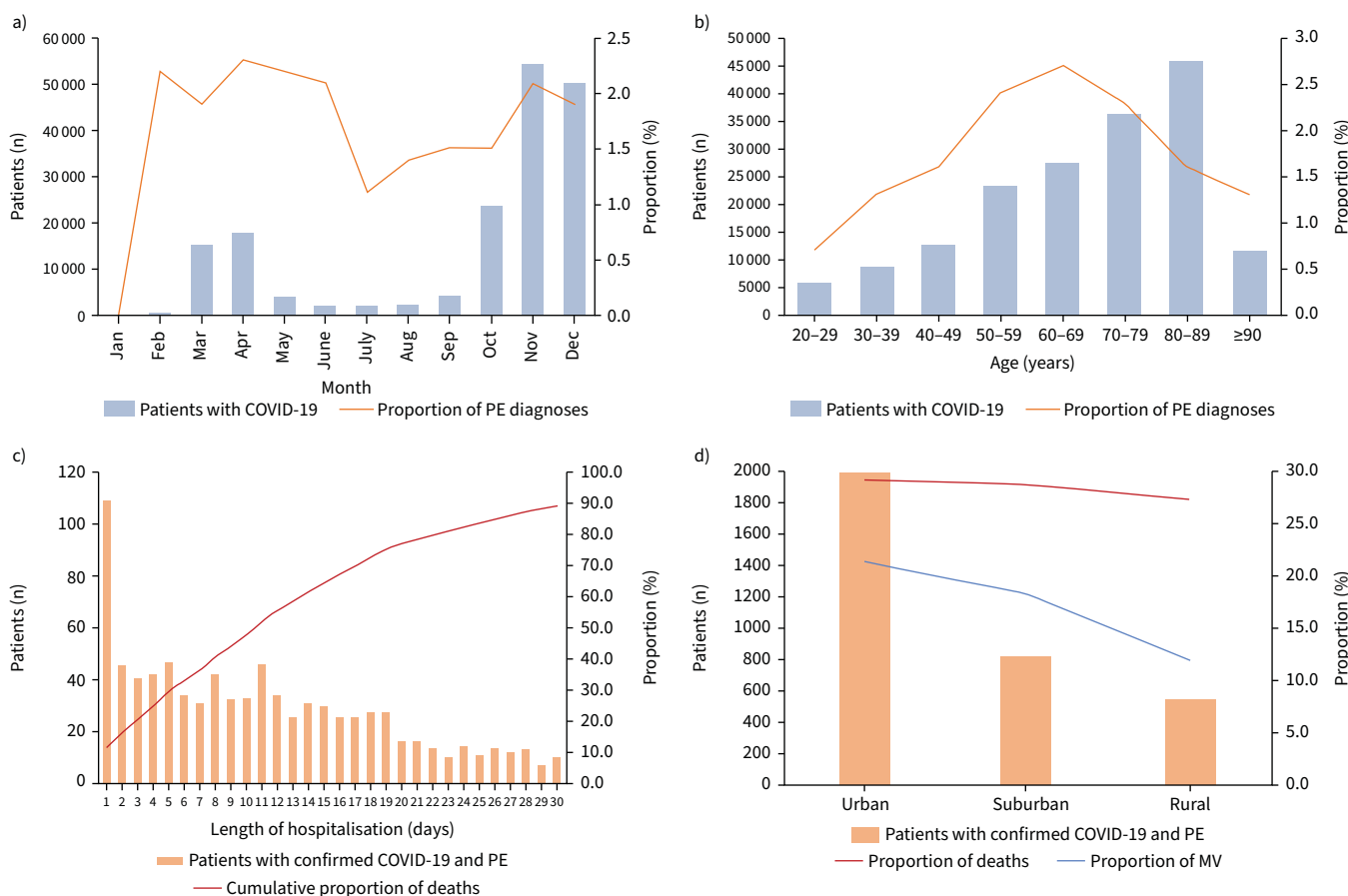

FIGURE 1 Temporal and regional trends regarding hospitalised patients with COVID-19 infection and pulmonary embolism (PE) in 2020. a) Temporal trends regarding total numbers of hospitalised patients with COVID-19 and proportion of PE stratified by months. b) Age (decade)-dependent total numbers of hospitalised patients with COVID-19 and proportion of PE. c) Time trends regarding total numbers of hospitalised patients with COVID-19 and PE and cumulative proportion of deaths stratified by hospitalisation days. d) Regional trends regarding total numbers of hospitalised patients with COVID-19 and PE, proportion of deaths and proportion of mechanical ventilation (MV).

PE (table 1). A multivariate regression analysis revealed that male sex (OR 1.35, 95% CI 1.10–1.49; p>0.001), obesity (OR 1.88, 95% CI 1.66–2.12; p<0.001) and cancer (OR 1.25, 95% 1.09–1.44; p<0.001) were independently associated with an increased risk for diagnosis of PE in patients with COVID-19.

Of the total population hospitalised in relation to the diagnosis of COVID-19, 60.7% (n=106 913) exhibited pneumonia and 6.6% (n=11 594) exhibited acute respiratory distress syndrome (ARDS).

TABLE 1 Characteristics, medical history, presentation and in-hospital adverse events (AEs) of the 176 137 hospitalised patients with confirmed COVID-19 infection in Germany in 2020 stratified for the presence of pulmonary embolism (PE)		
	COVID-19 infection without PE	COVID-19 infection with PE	p-value
Patients	172 775 (98.1)	3362 (1.9)	
Age (years)	71.0 (55.0–82.0)	70.0 (59.0–80.0)	0.219
Age ⩾70 years	92 612 (53.6)	1717 (51.1)	0.004*
Female	82 649 (47.8)	1300 (38.7)	<0.001*
In-hospital stay (days)	8.0 (4.0–14.0)	12.0 (6.0–21.0)	<0.001*
VTE risk factors			
Obesity	9084 (5.3)	299 (8.9)	<0.001*
Diabetes mellitus	44 371 (25.7)	861 (25.6)	0.935
Thrombophilia	398 (0.2)	44 (1.3)	<0.001*
Surgery	46 597 (27.0)	1398 (41.6)	<0.001*
Cancer	8784 (5.1)	217 (6.5)	<0.001*
Comorbidities			
Coronary artery disease	25 199 (14.6)	375 (11.2)	<0.001*
Peripheral artery disease	5554 (3.2)	86 (2.6)	<0.001*
Atrial fibrillation/flutter	33 595 (19.4)	565 (16.8)	<0.001*
COPD	11 953 (6.9)	201 (6.0)	0.035*
Chronic renal insufficiency[#]	47 822 (27.7)	344 (10.2)	<0.001*
Essential arterial hypertension	80 906 (46.8)	1574 (46.8)	1.000
Charlson Comorbidity Index	4.1 (2.0–6.0)	4.5 (2.0–6.0)	<0.001*
Respiratory manifestations of COVID-19			
Pneumonia	104 078 (60.2)	2835 (84.3)	<0.001*
ARDS	10 834 (6.3)	760 (22.6)	<0.001*
Mild ARDS	513 (0.3)	16 (0.5)	<0.001*
Moderate ARDS	2603 (1.5)	161 (4.8)	<0.001*
Severe ARDS	7337 (4.2)	575 (17.1)	<0.001*
Treatment			
Intensive care unit	25 728 (14.9)	1325 (39.4)	<0.001*
Mechanical ventilation	11 504 (6.7)	638 (19.0)	<0.001*
ECMO	1283 (0.7)	153 (4.6)	<0.001*
Dialysis	5271 (3.1)	304 (9.0)	<0.001*
Systemic thrombolysis	285 (0.2)	173 (5.1)	<0.001*
Surgical embolectomy	0	7 (0.2)	<0.001*
AEs during hospitalisation			
Transfusion of blood constituents	13 249 (7.7)	625 (18.6)	<0.001*
Deep vein thrombosis	1275 (075)	508 (15.1)	<0.001*
Acute kidney failure	21 296 (12.3)	779 (23.2)	<0.001*
Severe liver disease	3961 (2.3)	178 (5.3)	<0.001*
Myocarditis	217 (0.1)	9 (0.3)	0.044*
Stroke (ischaemic or haemorrhagic)	3068 (1.8)	128 (3.8)	<0.001*
Intracerebral bleeding	535 (0.3)	41 (1.2)	<0.001*
Gastrointestinal bleeding	2869 (1.7)	79 (2.3)	0.003*
Right ventricular dysfunction	0	706 (21.0)	<0.001*
Shock	5933 (3.4)	453 (13.5)	<0.001*
Cardiopulmonary resuscitation	2584 (1.5)	275 (8.2)	<0.001*
Case fatality	30 643 (17.7)	964 (28.7)	<0.001*

Data are presented as n (%) or median (range), unless otherwise stated. VTE: venous thromboembolism; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation. [#]: glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}. *: statistically significant (p<0.05).

Regarding the development of pneumonia between COVID-19 patients with *versus* without PE, the unadjusted risk ratio was 1.4 and, in the same comparison regarding the development of ARDS, the unadjusted risk ratio was 3.6. More than one-third of patients with COVID-19 and PE had to be treated in an intensive care unit (ICU). Regarding parameters indicating the severity of PE, right ventricular dysfunction was present in 706 (21.0%) patients, shock in 453 (13.5%) patients and cardiopulmonary resuscitation was provided in 275 (8.2%) patients with COVID-19 and PE (table 1).

COVID-19 patients with PE: regional differences and predictors of case fatality

In total, 964 (28.7%) patients with COVID-19 and PE died as opposed to patients without PE, with a case fatality rate of 17.7% (n=30 643) (table 1). More than one-third of deaths (36.2%) of patients with COVID-19 and PE occurred during the first 7 days of hospitalisation and >60% during the first 14 days (figure 1c). The case fatality rate increased substantially with patient age, with a peak in the ninth decade of life (supplementary figure S1a). In this context, elderly patients in the eighth (n=613 (74.7%)) and ninth (n=528 (70.9%)) decades of life underwent diagnostic work-up with CTPA less frequently than patients in the fifth (n=166 (82.2%)) or sixth (n=438 (78.9%)) decades (supplementary figure S1b).

Some regional differences in admissions and treatment approaches were evident in Germany. Most patients with confirmed COVID-19 and with PE were treated in hospitals in urban areas (59.1% (n=1989)), with a comparable case fatality (29.1% (n=579)) compared with hospitals in suburban (28.6% (n=234)) or rural areas (27.2% (n=151)). There was a considerably higher rate of mechanical ventilation in urban and suburban areas *versus* rural areas (21.3% (n=424) *versus* 18.2% (n=149) *versus* 11.9% (n=66)) (figure 1d).

Nonsurvivors were older, more often had comorbidities such as obesity, diabetes mellitus and coronary artery disease, and had ∼30% higher prevalence of ARDS (table 2). Parameters of PE-related severity such as right ventricular dysfunction, shock as well as cardiopulmonary resuscitation were more often presented in deceased patients. Consequently, nonsurvivors were more often treated in an ICU, and they more frequently necessitated extracorporeal membrane oxygenation (ECMO), mechanical ventilation and haemodialysis. Several independent predictors of in-hospital case fatality were detected in a multivariate logistic regression model. Briefly, age ⩾70 years, right ventricular dysfunction, dialysis, ECMO, ARDS, intracerebral bleeding, shock and cardiopulmonary resuscitation had a strong association with increased case fatality (table 3).

Diagnosis of PE: comparison of the pre-COVID-19 and COVID-19 era

The number of hospitalisations for PE was slightly higher in 2019 (n=98 485) than in 2020 (n=97 718) (figure 2a and b), whereas the case fatality of patients with PE was lower in 2019 compared with 2020 (12.7% *versus* 13.1%). The difference in case fatality rates between the two years was most pronounced in the months of November and December (11.7% and 13.4%, respectively, in 2019, increasing to 13.9% and 15.5%, respectively, in 2020), being in association with the second wave of COVID-19 at the end of 2020. These results are supported by the multivariate regression analysis, which showed a slightly higher risk of case fatality for patients hospitalised with the diagnosis of PE in 2020 compared with 2019 (OR 1.03, 95% CI 1.01–1.06; p=0.018). Parameters indicating severe disease such as right ventricular dysfunction, shock, cardiopulmonary resuscitation, systemic thrombolysis, intracranial bleeding and mechanical ventilation were distributed equally in both years.

Considering 2020 singularly, PE patients with and without COVID-19 infection demonstrated substantial differences (supplementary table S1). With regard to adverse outcomes, patients with co-prevalence of PE and COVID-19 infection had a higher case fatality rate compared with patients with PE without COVID-19 infection (28.7% *versus* 12.5%; p<0.001) (figure 3a and supplementary table S1). In a univariate regression model, COVID-19 infection was associated with a 2.8-fold increased risk of case fatality in patients with PE (OR 2.81, 95% CI 1.66–2.12; p<0.001). When adjusting for several parameters, COVID-19 infection was still associated with a 3.1-fold increased risk of case fatality in patients with PE in the multivariate regression model (OR 3.16, 95% CI 2.91–3.42; p<0.001) (supplementary table S3). In this context, patients with PE and COVID-19 more often had right ventricular dysfunction, shock and cardiopulmonary resuscitation (figure 3a). Additionally, patients with PE and concomitant COVID-19 infection exhibited increased frequency of treatment in the ICU, mechanical ventilation and systemic thrombolysis (figure 3b and supplementary table S1).

Discussion

The aim of the present study was to examine patient characteristics, regional and seasonal differences, and outcomes of hospitalised patients with COVID-19 and PE in German hospitals during 2020. Additionally, PE adverse outcomes were compared with 2019 in order to assess the impact of COVID-19 on the in-hospital course of patients with PE. The main results of the study can be summarised as follows: 1) in

TABLE 2 Characteristics, medical history, presentation and in-hospital adverse events (AEs) of the 3362 hospitalised patients with confirmed COVID-19 infection and concomitant pulmonary embolism (PE) in Germany in 2020 stratified for the presence of in-hospital mortality

	Survivors	Nonsurvivors	p-value
Patients	2398 (71.3)	964 (28.7)	
Age (years)	67.0 (57.0–79.0)	75.0 (65.0–82.0)	0.001*
Age ⩾70 years	1097 (45.7)	620 (64.3)	<0.001*
Female	971 (40.5)	329 (34.1)	0.001*
In-hospital stay (days)	12.0 (7.0–22.0)	11.0 (5.0–19.0)	0.001*
VTE risk factors			
Obesity	197 (8.2)	102 (10.6)	0.032*
Diabetes mellitus	544 (22.7)	317 (32.9)	<0.001*
Thrombophilia	27 (1.1)	17 (1.8)	0.178
Surgery	849 (35.4)	549 (57.0)	<0.001*
Cancer	135 (5.6)	82 (8.5)	0.003*
Comorbidities			
Coronary artery disease	233 (9.7)	142 (14.7)	<0.001*
Peripheral artery disease	43 (1.8)	43 (4.5)	<0.001*
Atrial fibrillation/flutter	293 (12.2)	272 (28.2)	<0.001*
COPD	121 (5.0)	80 (8.3)	0.001*
Chronic renal insufficiency[#]	202 (8.4)	142 (14.7)	<0.001*
Essential arterial hypertension	1125 (46.9)	449 (46.6)	0.879
Charlson Comorbidity Index	4 (2.0–5.0)	6.0 (4.0–8.0)	<0.001*
Respiratory manifestations of COVID-19			
Pneumonia	1988 (82.9)	847 (87.9)	<0.001*
ARDS	354 (14.8)	406 (42.1)	<0.001*
Mild ARDS	Censored	Censored	0.052
Moderate ARDS	96 (4.0)	65 (6.7)	0.001*
Severe ARDS	239 (10.0)	336 (34.9)	<0.001*
Treatment			
Intensive care unit	760 (31.7)	565 (58.6)	<0.001*
Mechanical ventilation	352 (14.7)	286 (29.7)	<0.001*
ECMO	50 (2.1)	121 (12.6)	<0.001*
Dialysis	90 (3.8)	214 (22.4)	<0.001*
Systemic thrombolysis	53 (2.2)	120 (12.4)	<0.001*
Surgical embolectomy	Censored	Censored	1.000
AEs during hospitalisation			
Transfusion of blood constituents	277 (11.6)	348 (36.1)	<0.001*
Deep vein thrombosis	411 (17.1)	97 (10.1)	<0.001*
Acute kidney failure	318 (13.3)	461 (47.8)	<0.001*
Severe liver disease	57 (2.4)	121 (12.6)	<0.001*
Stroke (ischaemic or haemorrhagic)	52 (2.2)	76 (7.9)	<0.001*
Intracerebral bleeding	13 (0.5)	28 (2.9)	<0.001*
Gastrointestinal bleeding	42 (1.8)	37 (3.8)	0.001*
Right ventricular dysfunction	379 (15.8)	327 (33.9)	<0.001*
Shock	131 (5.5)	322 (33.4)	<0.001*
Cardiopulmonary resuscitation	40 (1.7)	235 (24.4)	<0.001*

Data are presented as n (%) or median (range), unless otherwise stated. VTE: venous thromboembolism; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; [#]: glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}. *: statistically significant (p<0.05).

COVID-19 patients, the prevalence of PE was 1.9% and did not change over the months of 2020; 2) male sex, obesity and cancer were independently associated with an increased risk for PE in patients with COVID-19 infection; 3) case fatality was considerably higher (28.7%) in patients with COVID-19 and PE as opposed to COVID-19 patients without PE (17.7%); 4) COVID-19 patients with PE suffered especially from ARDS compared with COVID-19 patients without PE, and were more often treated on the ICU with a higher rate of mechanical ventilation, dialysis and ECMO; 5) the numbers of hospitalisations for PE were largely unchanged between 2019 and 2020, while the case fatality rate was slightly higher in 2020 in accordance with peak numbers of the COVID-19 pandemic; 6) PE patients with COVID-19 infection more often demonstrated right ventricular dysfunction, shock, cardiopulmonary resuscitation and case fatality

TABLE 3 Associations of baseline characteristics, comorbidities and adverse events (AEs) with in-hospital mortality in patients with pulmonary embolism and confirmed COVID-19 infection (n=3362; 964 died during in-hospital stay (28.7%)): univariable and multivariable logistic regression models

	Univariate		Multivariate[#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age ⩾70 years	2.137 (1.832–2.494)	<0.001*	2.039 (1.760–2.490)	<0.001*
Female	0.761 (0.651–0.890)	0.001*	0.594 (0.499–0.707)	<0.001*
Obesity	1.322 (1.028–1.700)	0.030*	1.633 (1.238–2.156)	0.001*
Comorbidities				
Coronary artery disease	1.605 (1.284–2.007)	<0.001*	0.929 (0.720–1.198)	0.570
Cancer	1.558 (1.172–2.073)	0.002*	1.541 (1.140–2.083)	0.005*
Peripheral artery disease	2.557 (1.664–3.929)	<0.001*	1.465 (0.918–2.340)	0.110
Heart failure	2.501 (2.100–2.978)	<0.001*	1.840 (1.522–2.224)	<0.001*
COPD	1.703 (1.271–2.283)	<0.001*	1.278 (0.932–1.751)	0.128
Arterial hypertension	0.859 (0.849–1.146)	0.859	0.811 (0.688–0.957)	0.013*
Renal insufficiency	1.878 (1.493–2.362)	<0.001*	1.147 (0.886–1.484)	0.297
Diabetes mellitus	1.670 (1.416–1.969)	<0.001*	1.420 (1.185–1.704)	<0.001*
Atrial fibrillation	2.824 (2.345–3.401)	<0.001*	1.994 (1.634–2.432)	<0.001*
Charlson Comorbidity Index	1.370 (1.327–1.414)	<0.001*	1.210 (1.207–1.225)	<0.001*
Clinical presentation				
Right ventricular dysfunction	2.735 (2.301–3.250)	<0.001*	2.575 (2.129–3.115)	<0.001*
NYHA FC III	1.400 (1.281–1.529)	<0.001*	0.946 (0.832–1.077)	0.403
NYHA FC IV	3.342 (2.473–4.516)	<0.001*	1.593 (1.112–2.282)	0.011*
Serious AEs through hospitalisation				
Stroke	3.861 (2.691–5.540)	<0.001*	3.444 (2.340–5.069)	<0.001*
Dialysis	7.317 (5.644–9.487)	<0.001*	7.994 (5.995–10.659)	<0.001*
Acute renal failure	5.995 (5.043–7.126)	<0.001*	5.785 (4.779–7.002)	<0.001*
ARDS	4.201 (3.543–4.982)	<0.001*	5.721 (4.666–7.016)	<0.001*
Mild ARDS	0.165 (0.022–1.251)	0.081	0.149 (0.019–1.195)	0.073
Moderate ARDS	1.734 (1.254–2.397)	0.001*	1.701 (1.195–2.420)	0.003*
Severe ARDS	4.833 (4.004–5.834)	<0.001*	6.448 (5.179–8.027)	<0.001*
MSCOVID	20.383 (6.123–67.850)	<0.001*	24.273 (7.039–83.696)	<0.001*
Post-COVID	0.620 (0.207–1.860)	0.394	0.999 (0.325–3.066)	0.998
Severe liver disease	5.895 (4.261–8.155)	<0.001*	5.658 (3.982–8.039)	<0.001*
ECMO	6.740 (4.803–9.458)	<0.001*	10.334 (7.107–15.027)	<0.001*
Pneumonia	1.493 (1.197–1.862)	<0.001*	1.698 (1.339–2.115)	<0.001*
Deep venous thrombosis	0.541 (0.428–0.684)	<0.001*	0.550 (0.429–0.706)	<0.001*
Intracerebral bleeding	5.488 (2.831–10.641)	<0.001*	5.531 (2.708–11.297)	<0.001*
Gastrointestinal bleeding	2.239 (1.430–3.506)	<0.001*	1.885 (1.170–3.039)	0.009*
Admission to ICU	3.052 (2.615–3.561)	<0.001*	3.887 (3.238–4.666)	<0.001*
Mechanical ventilation	2.452 (2.051–2.931)	<0.001*	2.618 (2.142–3.199)	<0.001*
Transfusion of erythrocytes	4.326 (3.608–5.187)	<0.001*	4.365 (3.570–5.338)	<0.001*
Shock	8.680 (6.957–10.829)	<0.001*	10.658 (8.310–13.671)	<0.001*
Cardiopulmonary resuscitation	19.003 (13.453–26.842)	<0.001*	23.561 (16.286–34.085)	<0.001*

NYHA FC: New York Heart Association Functional Class; ARDS: acute respiratory distress syndrome; MSCOVID: multisystem inflammatory syndrome COVID-19; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit. [#]: adjusted for age, sex, cancer, coronary artery disease, heart failure, COPD, arterial hypertension, renal insufficiency, diabetes mellitus, atrial fibrillation, peripheral arterial disease and hyperlipidaemia. *: statistically significant at least in the multivariate regression model (p<0.05).

(28.7% *versus* 12.5%) in contrast to PE patients without COVID-19; and 7) COVID-19 infection was associated with a 3.1-fold increased risk of case fatality in patients with PE.

Several studies estimated the proportion of patients diagnosed with PE among those hospitalised with COVID-19 infection, but the rates varied widely between 0.5% and 61.5% across all risk categories [12, 17–19]. A recent meta-analysis included 23 177 patients of 66 studies and estimated a 7.8% (95% CI 6.2–9.4%) overall prevalence of COVID-19-related PE [20]. Our analysis demonstrated a proportion of 1.9%, which corresponds to an in-hospital incidence rate of 2.9 per 100 000 infections per year. The prevalence of PE diagnosis increased with age and the peak occurred between the fifth and seventh decades of life; this peak occurred at considerably older ages compared with previously published PE studies from the
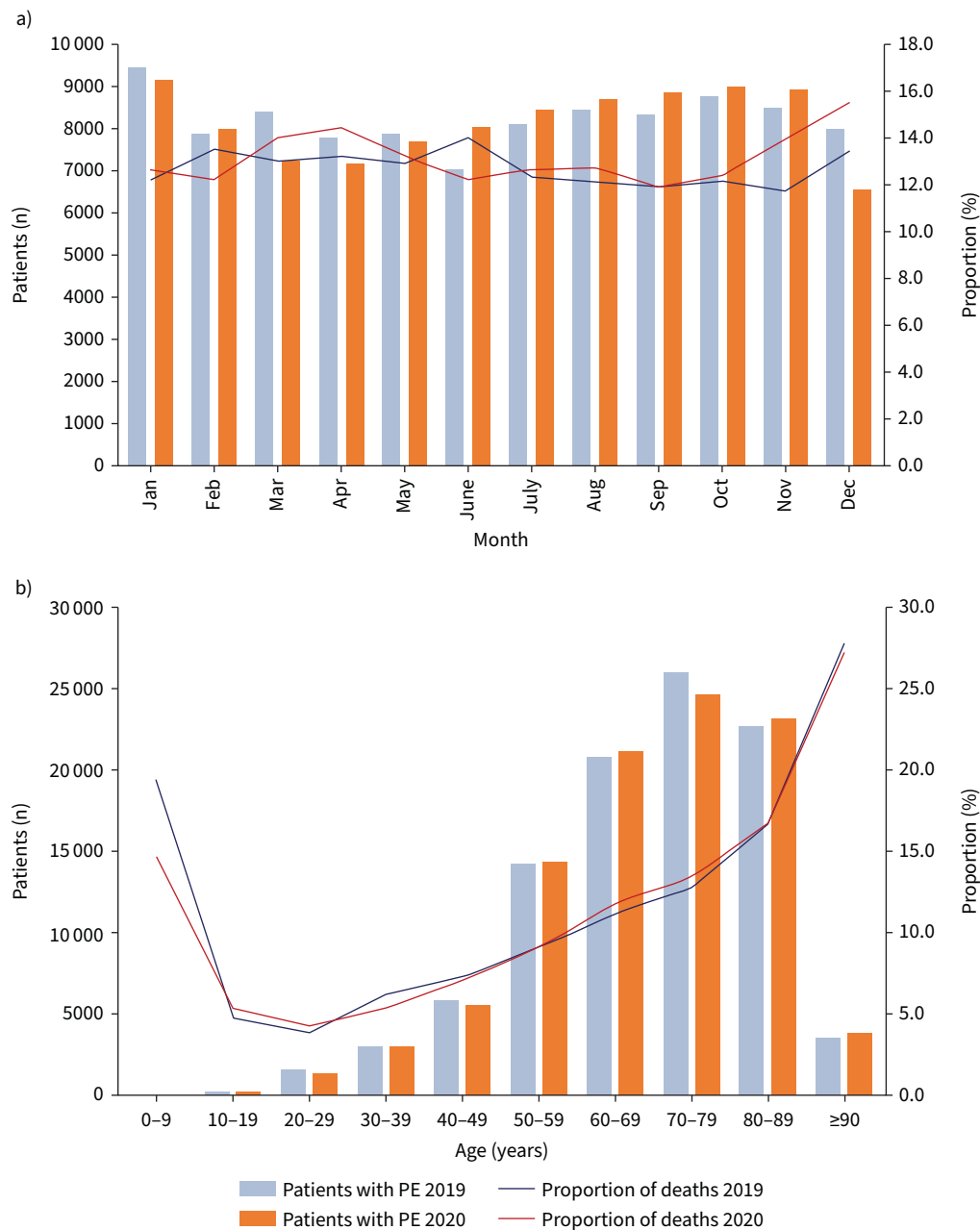
FIGURE 2 Changes in temporal trends in pulmonary embolism (PE) diagnosis regarding the pre-COVID era in 2019 and the COVID era in 2020. a) Temporal trends regarding total numbers of hospitalised patients with PE in 2019 compared with 2020 with respective proportions of deaths stratified for months. b) Age (decade)-dependent total numbers of hospitalised patients with PE in 2019 compared with 2020 with respective proportion rates of deaths.

USA, Canada and Europe [21, 22]. In the literature, autopsy reports in particular have proposed the hypothesis of pulmonary microvascular immunothrombosis, according to findings of thrombosis in the small vessels and capillaries of the lung [19, 23]. It has to be kept in mind that detection of PE in COVID-19 patients strongly depends on the use of CTPA [24–28]. Indeed, specific recommendations on the appropriate use of CTPA in the diagnostic pathway of PE in COVID-19 are still lacking [29]. Our results showed age-dependent differences regarding the use of CTPA in COVID-19 patients, with less frequent use in the elderly, which may have contributed to underdiagnosis of PE in this age group (supplementary figure S1).
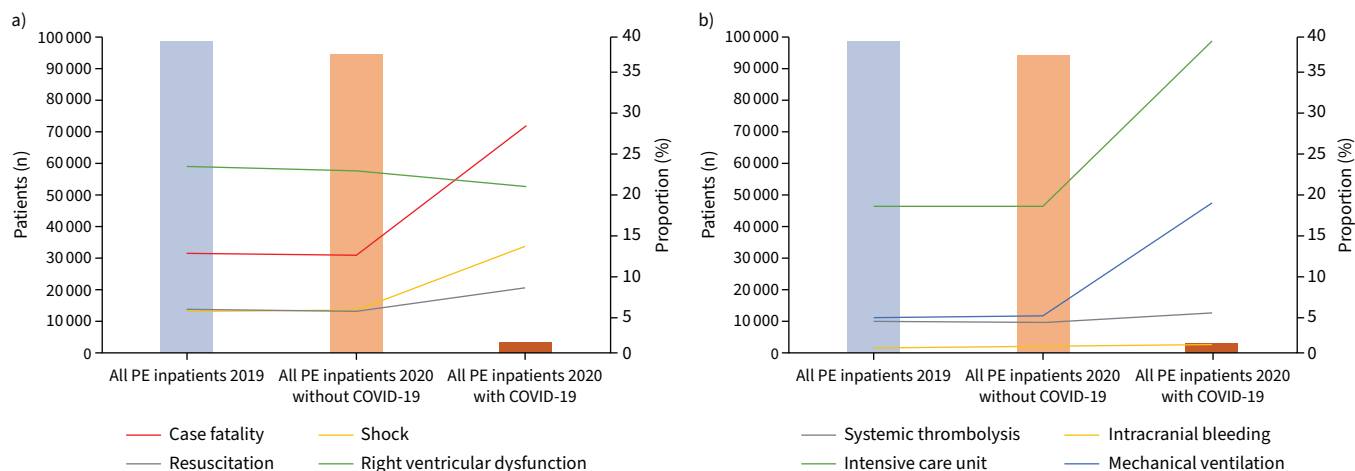
FIGURE 3 Total numbers of hospitalised patients with pulmonary embolism (PE) with respective parameters indicating severe in-hospital course stratified for 2019 and 2020 as well as for COVID-19 infection. Further parameters are presented in supplementary table S1.

Several studies investigated whether the risk factors for PE in patients with COVID-19 differ from those for PE without COVID-19 infection [7, 13]. A recent meta-analysis found that among others, male sex and obesity represent risk factors for PE in COVID-19 as opposed to age and common comorbidities with no association regarding PE occurrence [30]. Our data support these previous results by finding that PE occurrence in COVID-19 infection is associated with risk factors such as male sex, obesity and cancer, but interestingly not age.

The prevalence of PE was higher in COVID-19 patients in the ICU than in those hospitalised in general wards [31, 32]. A recent meta-analysis has shown that PE is significantly associated in COVID-19 patients with mechanical ventilation and ICU admission [33]. In our analysis, results demonstrated that more than one-third (39.4%) of patients with COVID-19 and PE were treated in the ICU as opposed to 14.9% of COVID-19 patients without PE. The frequent coexistence of COVID-19 and PE in critically ill patients may reflect the high burden of thromboembolic complications in those patients. It can also be assumed that in COVID-19 patients who die early after admission or who cannot be transported to the radiology department for contrast CT angiography due to instability or limited resources during a wave of the pandemic, PE might be underdiagnosed as the cause of death. As expected, the manifestation of the respiratory infection was a strong predictor of in-hospital case fatality in our cohort, since pneumonia and ARDS were both independently associated with an unfavourable course of illness. In particular, COVID-19 patients with multisystem inflammatory syndrome (MSCOVID) had a 24-fold increased risk for in-hospital mortality, indicating that a cytokine storm could further trigger the coagulation cascade and predispose to immunothrombosis [34]. In this context, transfer of the sickest patients to larger tertiary hospitals in urban areas for escalation of intensive treatment (including mechanical ventilation) may explain the higher case fatality rate compared with the suburban and rural medical supply.

Several studies reported a substantial increase in the number of all-cause and cardiovascular mortalities during the COVID-19 pandemic [35, 36]. COVID-19 itself was the main cause of death or a concomitant cause in 90% of excess deaths [6]. In this context, numbers of PE-related deaths also increased during the pandemic in several countries [6, 37, 38]. Our findings from Germany revealed no increase in the prevalence of PE between 2019 and 2020, but we did observe a slightly higher case fatality for PE in 2020 with seasonal characteristics following the pandemic waves; this is opposed to reports from Italy and France, but in line with nationwide data from Denmark [6, 37, 39]. However, considering PE patients with COVID-19 infection, case fatality was dramatically increased compared with PE patients without COVID-19 infection. Comparable results were found in Denmark, but were in contrast to findings from Spain, which found no difference between the groups [18]. Those differences might be explained by the larger, unselected dataset of nationwide data in Denmark and in our study [37]. In general, the higher rate of case fatality in PE patients with COVID-19 has to be considered in the context of the haemodynamic effect of systemic inflammation. Those systemic effects are also reflected in our results, by showing a higher rate of shock, need for cardiopulmonary resuscitation and mechanical ventilation in PE patients with COVID-19 compared with patients without COVID-19. Overall, COVID-19 was associated with a 3.1-fold

increased risk for an adverse outcome in patients with PE, which underlines the importance to pay particular attention for this special patient population and to establish optimal antithrombotic strategies that may minimise the risk of thromboembolic events in COVID-19 patients.

Although this study includes data collected on a national level, with almost 200 000 adult patients of all ages hospitalised with PE and more than 180 000 hospitalised with COVID-19, we recognise that it has several limitations. First, as our results are based on administrative and retrospective data, we cannot exclude misclassification or inconsistencies. Additionally, this analysis of the German nationwide inpatient sample was not pre-specified; therefore, our findings can only be considered to be hypothesis generating. Second, patients with confirmed COVID-19 infection who died out of hospital or were diagnosed post-mortem were not included in the nationwide inpatient sample. Third, the nationwide inpatient sample does not report long-term outcomes after discharge from hospital. Fourth, changes in treatment recommendations such as prophylactic or even therapeutic doses as well as anti-inflammatory regimens were not considered in this analysis due to missing codes in the nationwide sample.

Our findings demonstrated a considerable impact of COVID-19 infection on adverse outcomes of patients with PE in 2020, which should guide our attention to this special population with regard to antithrombotic prevention and diagnostic strategies. However, a roughly constant but high case fatality in patients hospitalised with PE was found in both 2019 and 2020.

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