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

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Title:

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

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Case-fatality in COVID-19 and pulmonary embolism

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

Abstract

Background

Although a high prevalence of pulmonary embolism (PE) has been reported in association with coronavirus disease (COVID)-19 in critically ill patients, nationwide data on the outcome of hospitalised patients with COVID-19 and PE is 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 the 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 to 2019.

Results

We analysed 176,137 COVID-19 hospitalisations in 2020; PE was recorded in 1.9% (n=3,362) of discharge certificates. Almost one third of patients with COVID-19 and PE died during the in-hospital course (28.7%) compared to COVID-19 patients without PE (17.7%). Between 2019 and 2020, numbers of PE-related hospitalisations were largely unchanged (98,485 vs. 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% vs. 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-PE combination.

Key words: COVID-19, pulmonary embolism, mortality, intensive care unit

Introduction

First patient-cases of pneumonia caused by a previously unknown virus were identified in China by the end of 2019 [1, 2]. The fast spreading of infections with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the 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 a frequent and relevant complication 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), or 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 rate of patients with COVID-19 and PE vary amongst countries and seem to be considerably higher compared to 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 hospital-

ised patients with COVID-19 and PE in Germany 2020 and to compare changes of PE prevalence and case-fatality between the years 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 basis of our SPSS codes (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: 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, DRG Statistics 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 (ICD-code U07.1) and an additional diagnosis of PE (ICD-code I26) during the observational period between Jan 1st and December 31st, 2020 and identify independent predictors in-hospital death. To allow a comparison of PE prevalence between 2020 and former 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 an 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

In the year 2004, diagnosis- and procedure-related remuneration was introduced in Germany. Coding according the German Diagnosis Related Groups (G-DRG) system with coding of patient data on diagnoses, coexisting conditions, and on 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 the International Statistical Classification of Diseases and Related Health Problems, 10th revision, with German modification (ICD-10-GM). In parallel, surgical, diagnostical and interventional procedures were coded according to OPS codes (Operationen- und Prozedurenschlüssel).

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 **Table S1** of the **Supplementary Appendix**.

Statistical analysis

Differences in patient characteristics between the groups of hospitalised COVID-19-patients with PE vs. without PE and patients, who deceased during in-hospital course, and those, who were discharged alive were calculated with Wilcoxon-Whitney U test for continuous variables and Fisher's exact or chi² 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 i) need for MV or ii) in-hospital death on the other. In order to test the (in)dependence of the findings on confounding parameters, the multivariate regression models were adjusted for age,

sex, cancer, heart failure, coronary artery disease, peripheral artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, hyperlipidaemia, renal insufficiency (glomerular filtration rate [GFR] <60 ml/min/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 (OR) and 95% CI. All statistical analyses were carried out with the use of SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA); 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 the year 2020. The majority were men (n=92,188; 52.3%) and aged 70 years or older (n=94,329; 53.6%). In total, 31,607 (17.9%) patients with COVID-19 died.

The minority of patients with COVID-19 had an additional diagnosis of PE (n=3,362; 1.9%). The proportion of PE in patients with COVID-19-infection did not change significantly on a monthly base during 2020 with highest numbers in spring and winter (**Figure 1A**). Regarding age distribution, PE proportion increased with age revealing a peak in the 5^{th} to 7^{th} life-decade (**Figure 1B**). Similar to the baseline characteristics, the majority of patients with COVID-19 and PE were of male sex (n=2,062; 61.3%) and more than half of them aged 70 years or older (n=1,717; 51.1%). Cardiovascular risk factors and comorbidities as obesity (299 [8.9%] vs. 9,084 [5.3%], p<0.001), malignancies (217 [6.5%] vs. 8,784 [5.1%], p<0.001) or chronic renal insufficiency (1,119 [33.3%] vs. 47,822 [27.7%], p<0.001) were more prevalent in patients with COVID-19 and PE compared to patients with COVID-19 without PE (**Table 1**). A multivariate regression analysis revealed that male sex, obesity and cancer were independently associated with an increased risk for diagnosis of PE in patients with COVID-19 infection (OR 1.35, 95%CI 1.10-1.49, P>0.001, OR 1.88, 95%CI 1.66-2.12, p<0.001 and OR 1.25, 95% 1.09-1.44, p<0.001).

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) the acute respiratory distress syndrome (ARDS). Regarding the development of pneumonia between COVID-19 patients with vs. 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 a COVID-19 infection 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 cardio-pulmonary 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 opposed to patients without PE with a case-fatality rate of 17.7% (n=30,643). More than one-third of death (36.2%) of patients with COVID-19 and PE occurred during the first 7 days of hospitalisation and more than 60% during the first 14 days (**Figure 1C**). The case-fatality rate increased substantially with the patients' age, with a peak in the 9th decade of life (**Figure S1, Panel A**). In this context, elderly patients in the 8th (n=613, 74.7%) and 9th (n=528, 70.9%) decade of their life underwent diagnostic work-up with computed tomography pulmonary angiography (CTA) less frequently than patients in the 5th (n=166, 82.2%) or 6th (n=438, 78.9%) decade (**Figure S1, Panel B**).

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=1,989) with a comparable case-fatality (29.1%; n=579) compared to hospitals in suburban (28.6%; n=234) or rural areas (27.2%; n=151), a considerable higher rate of mechanical ventilation in urban and suburban areas vs. rural areas (21.3% [n=424] vs. 18.2% [n=149] vs. 11.9% [n=66]) (**Figure 1D**).

Non-survivors were older, had more often comorbidities as obesity, diabetes mellitus, and coronary artery disease and had approximately 30% higher prevalence of ARDS (**Table 2**). Parameters of PE-related severity as right ventricular dysfunction, shock as well as cardio-pulmonary resuscitation were more often presented in de-

ceased patients. Consequently, non-survivors were more often treated in an intensive care unit, 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 cardio-pulmonary 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 **2B**), whereas the case fatality of patients with PE was lower in 2019 compared to 2020 (12.7% vs 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 to 2019 (OR 1.03, 95%CI 1.01-1.06, p=0.018). Parameters indicating severe disease as right ventricular dysfunction, shock, cardiopulmonary resuscitation, systemic thrombolysis, intracranial bleeding and mechanical ventilation, were distributed equally in both years.

Considering the year 2020 singularly, PE patients with and without COVID-19 infection demonstrated substantial differences (**Table S1**). With regard to adverse outcomes, patients with co-prevalence of PE and COVD-19 infection had a higher case-fatality rate in comparison to patients with PE without COVID-19 infection (28.7% vs. 12.5%, P<0.001) (**Figure 3A, Table S1**). In a univariate regression model, a 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) (**Table S3**). In this context, patients with PE and COVID-19 had more often 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, 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 pulmonary embolism (PE) in German hospitals during the year 2020. Additionally, PE adverse outcomes were compared to 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: (i) in COVID-19 patients, the prevalence of PE was 1.9% and did not change over the months of the year 2020; (ii) male sex, obesity and cancer were independently associated with an increased risk for PE in patients with COVID-19 infection; (iii) case fatality was considerably higher (28.7%) in patients with COVID-19 and PE opposed to COVID-19 patients without PE (17.7%); (iv) COVID-19 patients with PE suffered especially from ARDS compared to COVID-19 without PE and were more often treated on ICU with a higher rate of MV, dialysis and ECMO; (v) 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; (vi) PE patients with COVID-19 infection demonstrated more often right-ventricular dysfunction, shock, cardiopulmonary resuscitation and case-fatality (28.7% vs. 13.1%) in contrast to PE without COVID-19; and (vii) 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 vary 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% to 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 prevealence of PE diagnosis increased with age and the peak occurred between the 5th and the 7th decade; this peak occurred in considerably older ages in comparison to previously published PE studies from the United States, Canada and Europe [21, 22]. In the literature, especially autopsy reports 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 (**Figure S1**).

Several studies investigated whether the risk factors for PE in patients with COVID-19 may differ from one for PE without COVID-19 infection [7, 13]. A recent meta-analysis found that amongst others, male sex and obesity represent risk factors for PE in COVID-19 opposed to age and common comorbidities with no association regarding PE occurrence [30]. Our data supports 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 the patient's age.

The prevalence of PE was higher in COVID-19 patients on ICU than in those hospitalised in general wards [31, 32]. A recent meta-analysis have 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 co-existence of COVID-19 and PE in criti-

cally 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 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. Especially COVID-19 patients with multisystem inflammatory syndrome 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, the 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 to suburban and rural medical supply.

Several studies reported a substantial increase in the number of all-cause and cardiovascular mortality during the COVID-19 pandemic [35, 36]. COVID-19 itself was the main cause of death or a concomitant cause in 8 to 9 out of 10 excess deaths [6]. In this context, also numbers of PE-related deaths 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 of PE in 2020 with seasonal characteristics following the pandemic waves; this is opposing to reports of Italy or 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 in comparison to 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 larger, unselected data set of nationwide data in Denmark and in our study [37]. In general, the higher rate of case-fatality in PE patients with COVID-19 have 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 of cardio-pulmonary resuscitation and mechanical ventilation in PE patients with COVID-19 compared to 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 underline 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 prespecified; 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 German nationwide inpatient sample. Third, the German nationwide inpatient sample does not report long-term outcomes after the discharge from hospital. Fourth, changes in treatment recommendations as prophylactic or even therapeutic doses as well 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 years, 2019 and 2020.

Conflicts of interest

LH received lecture/consultant fees from MSD and Actelion, outside the submitted work. InSa reports reports lecture/ consultant fees from Hamilton Medical and Novalung, outside the submitted work. SB received lecture/consultant fees from Bayer HealthCare, Concept Medical, BTG Pharmaceuticals, INARI, Boston Scientific, and LeoPharma; institutional grants from Boston Scientific, Bentley, Bayer HealthCare, INARI, Medtronic, Concept Medical, Bard, and Sanofi; and economical support for travel/congress costs from Daiichi Sankyo, BTG Pharmaceuticals, and Bayer HealthCare, outside the submitted work. IF reports no conflict of interests. UF reports no conflict of interests. SKoe reports no conflict of interests. TG reports having received consultancy and lecture honoraria from Abbott Vascular and Boston Scientific. CEK reports having from Amarin Germany, Amgen GmbH, Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, MSD Sharp & Dohme, Novartis Pharma, Pfizer Pharma GmbH, Sanofi-Aventis GmbH. TM reports no conflict of interests. TM is PI of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany. SK reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol Myers Squibb/Pfizer. KK reports no conflict of interests.

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Figure 1. Temporal and regional trends regarding hospitalised patients with COVID-19-infection and PE in 2020

Panel A – Temporal trends regarding total numbers of hospitalised patients with COVID-19-infection (grey bars) and proportion rate of PE (orange line) stratified for months

Panel B – Decade dependent total numbers of hospitalised patients with COVID-19-infection (grey bars) and proportion rate of PE (orange line)

Panel C – Time trends regarding total numbers of hospitalised patients with COVID-19-infection and PE (orange bars) and cumulative proportion of death (dark red line) stratified for hospitalisation days.

Panel D – Regional trends regarding total numbers of hospitalised patients with COVID-19-infection and PE (orange bars), proportion of death (dark red line) and mechanical ventilation (blue line).

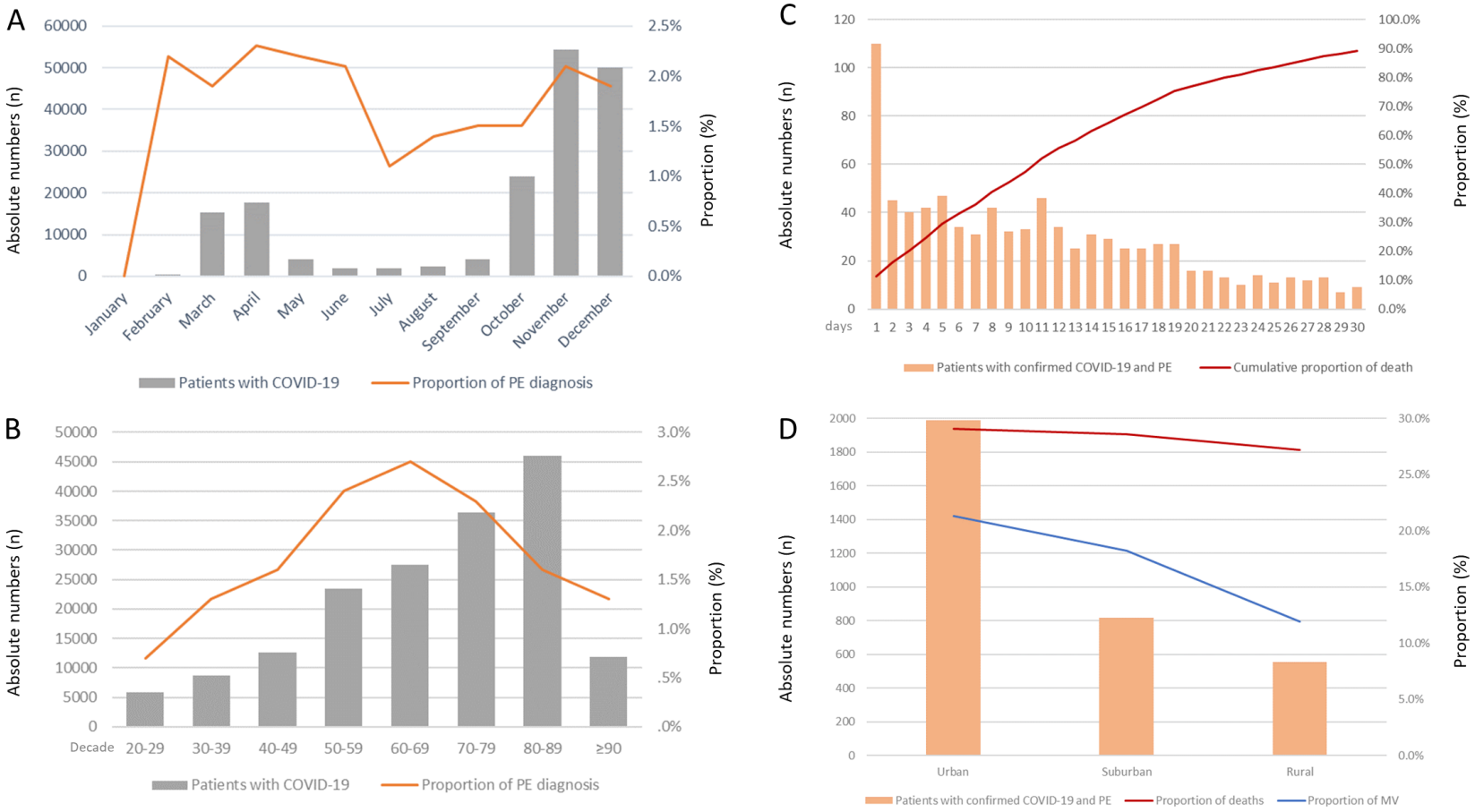

Figure 2. Changes of temporal trends in PE diagnosis regarding the pre-COVID era in 2019 and the COVID era in 2020

Panel A – Temporal trends regarding total numbers of hospitalised patients with PE in 2019 (blue bars) compared to 2020 (orange bars) with respective proportion rate of death (blue line for 2019 and red line for 2020) stratified for months

Panel B – Decade dependent regarding total numbers of hospitalised patients with PE in 2019 (blue bars) compared to 2020 (orange bars) with respective proportion rate of death (blue line for 2019 and red line for 2020)

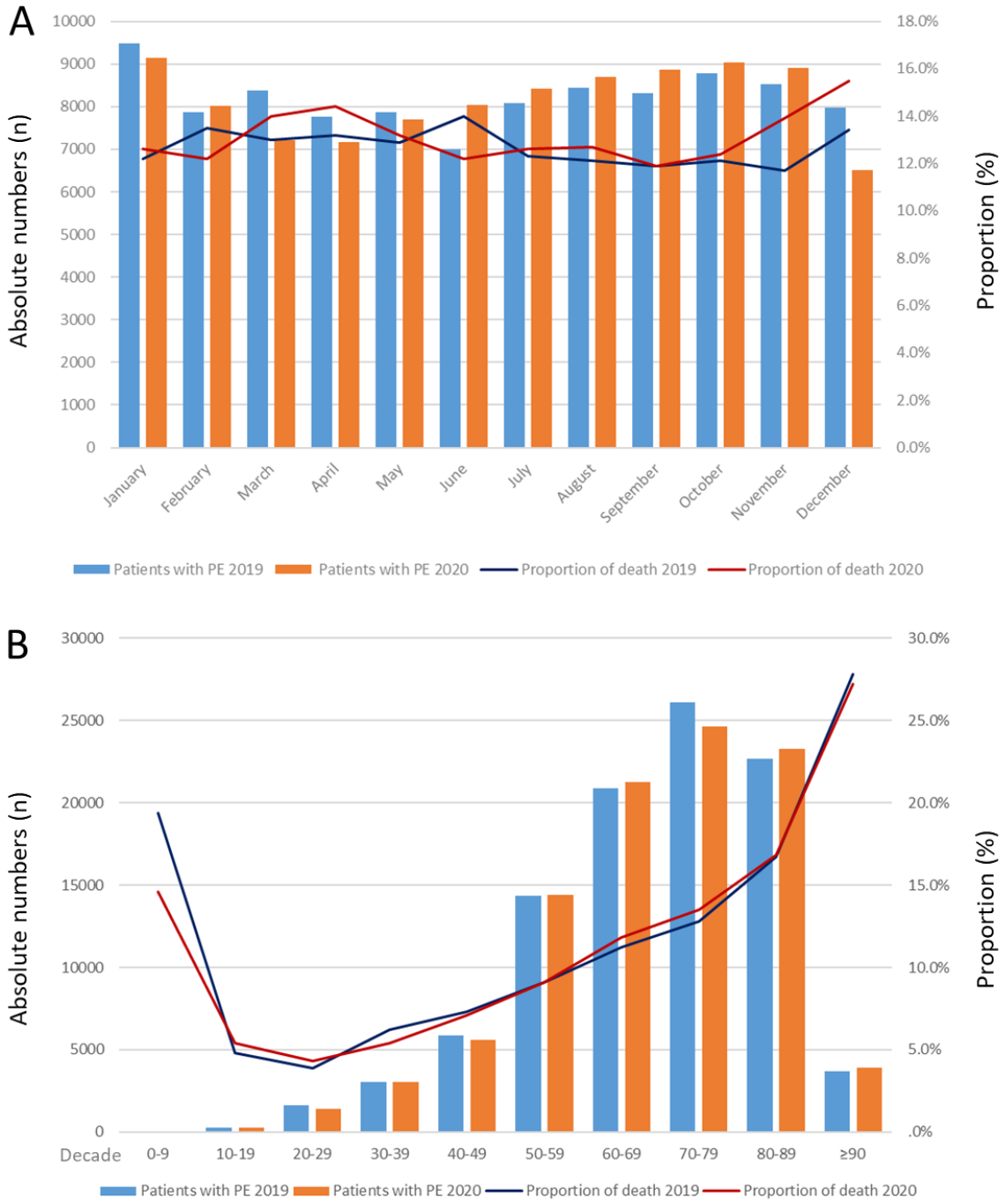

Figure 3. Total numbers of hospitalised patients with PE with respective parameters indicating severe in-hospital course stratified for 2019 and 2020 as well as for COVID-19 infection. Further parameters are presented in Table S1.

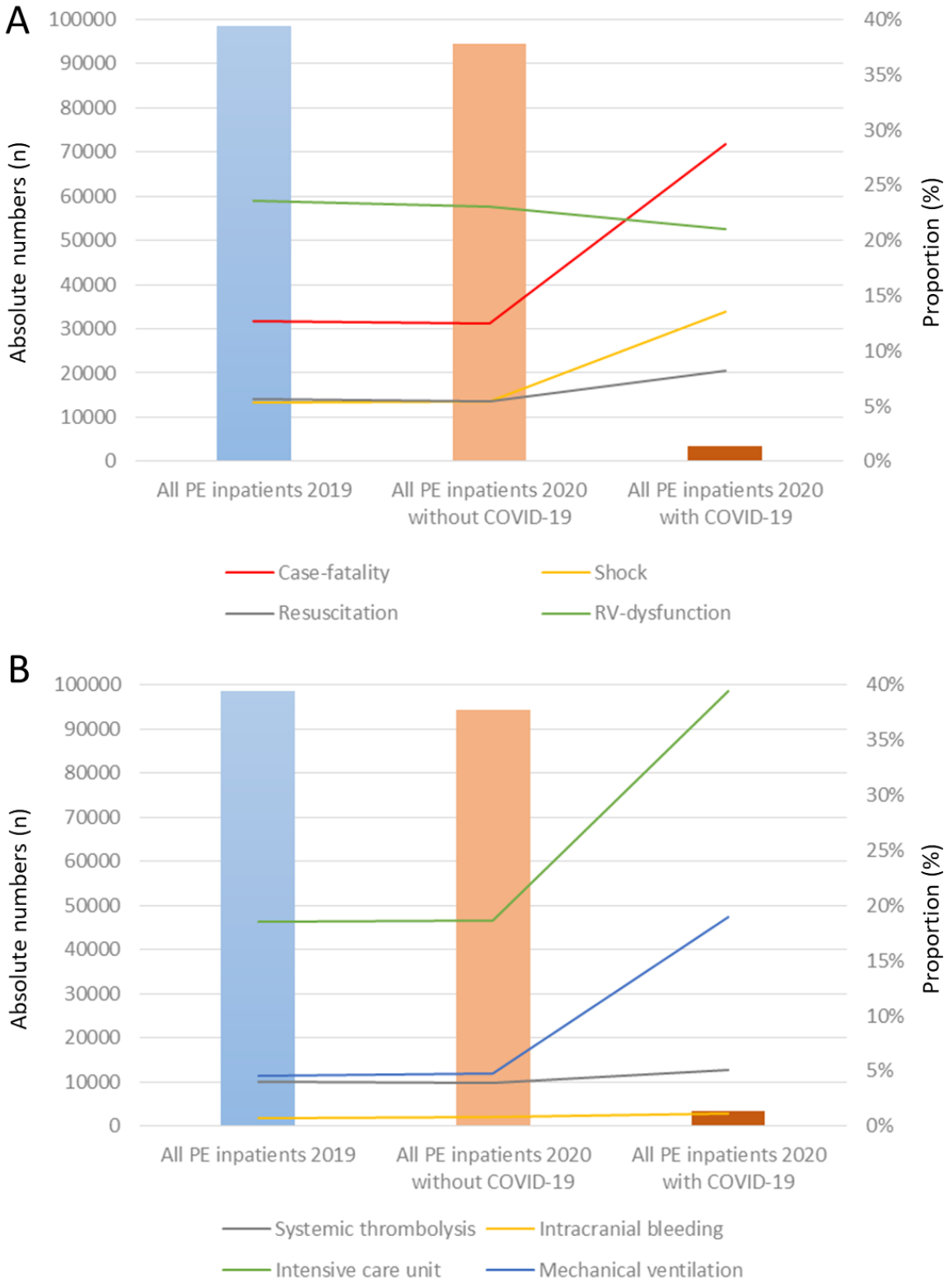

Table 1: Patients' characteristics, medical history, presentation and adverse in-hospital events of the 176,137 hospitalised patients with confirmed COVID-19 infection in Germany in the year 2020 stratified for the presence of pulmonary embolism (PE).

Parameters	COVID-19 infection without PE (n= 172,775; 98.1%)	COVID-19 infection with PE (n= 3,362; 1.9%)	P-value
Age	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 sex	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**
Chronic obstructive pulmonary disease	11,953 (6.9%)	201 (6.0%)	**0.035**
Chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m²)	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**
Acute respiratory distress syndrome	10,834 (6.3%)	760 (22.6%)	**<0.001**

ARDS mild	513 (0.3%)	16 (0.5%)	**<0.001**
ARDS moderate	2603 (1.5%)	161 (4.8%)	**<0.001**
ARDS severe	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**
Extracorporeal membrane oxygenation	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**
Adverse events 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**
Gastro-intestinal 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**
Cardio-pulmonary resuscitation	2584 (1.5%)	275 (8.2%)	**<0.001**
Case-fatality	30,643 (17.7%)	964 (28.7%)	**<0.001**

Abbreviations: ARDS= Acute respiratory distress syndrome

Table 2: Patients' characteristics, medical history, presentation and adverse in-hospital events of the 3,362 hospitalised patients with confirmed COVID-19 infection and concomitant pulmonary embolism (PE) in Germany in the year 2020 stratified for the presence of in-hospital mortality.

Parameters	Survivors (n= 2,398; 71.3%)	Non-survivors (n= 964; 28.7%)	P-value
Age	67.0 (57.0 / 79.0)	75.0 (65.0 / 82.0)	**0.001**
Age ≥70 years	1,097 (45.7%)	620 (64.3%)	**<0.001**
Female sex	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**
Chronic obstructive pulmonary disease	121 (5.0%)	80 (8.3%)	**0.001**
Chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m²)	202 (8.4%)	142 (14.7%)	**<0.001**
Essential arterial hypertension	1,125 (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	1,988 (82.9%)	847 (87.9%)	**<0.001**
Acute respiratory distress syndrome	354 (14.8%)	406 (42.1%)	**<0.001**

ARDS mild	censored	censored	0.052
ARDS moderate	96 (4.0%)	65 (6.7%)	**0.001**
ARDS severe	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**
Extracorporeal membrane oxygenation	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**
Adverse events 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**
Gastro-intestinal 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**
Cardio-pulmonary resuscitation	40 (1.7%)	235 (24.4%)	**<0.001**

Abbreviations: ARDS= Acute respiratory distress syndrome

Table 3: Associations of baseline characterisics, comorbidities and adverse events with in-hospital mortality in patients with pulmonary embolism and confirmed COVID-19 infection (univariable and multivariable logistic regression models).

	All in-hospital PE patients with COVID-19 infection (n=3,362; 964 died during in-hospital stay [28.7%])			
	Univariate		**Multivariate** (adjusted for age, sex, cancer, coronary artery disease, heart failure, COPD, arterial hypertension, renal insufficiency, diabetes mellitus, atrial fibrillation, pAVK and Hyperlipidemia)	
Parameters	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age ≥ 70	**2.137 (1.832-2.494)**	**<0.001**	**2.039 (1.760-2.490)**	**<0.001**
Female Sex	**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**
PAD	**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 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 III	**1.400 (1.281-1.529)**	**<0.001**	0.946 (0.832-1.077)	0.403
NYHA IV	**3.342 (2.473-4.516)**	**<0.001**	**1.593 (1.112-2.282)**	**0.011**
Serious adverse events 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**
ARDS mild	0.165 (0.022-1.251)	0.081	0.149 (0.019-1.195)	0.073
ARDS moderate	**1.734 (1.254-2.397)**	**0.001**	**1.701 (1.195-2.420)**	**0.003**
ARDS severe	**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**
Gastro-intestinal 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**
Cardio-Pulmonary Resuscitation	**19.003 (13.453-26.842)**	**<0.001**	**23.561 (16.286-34.085)**	**<0.001**

Abbreviations: NYHA= New York Heart Association; CI= Confidence interval; COPD= Chronic obstructive pulmonary disease; ECMO= extracorporeal membrane oxygenation; ICU= intensive care unit; MSCOVID= Multisystem Inflammatory Syndrome COVID; OR= Odds ratio; PAD= peripheral artery disease

Values in bold indicate that the difference is statistically significance at least in the multivariate regression model ($p<0.05$).

Supplementary

Supplementary results

Table S1: Presentation and adverse in-hospital events of hospitalized patients with pulmonary embolism (PE) in Germany in stratified for the year of hospitalization and the COVID-19 infection status.

Parameters	Hospitalized patients with PE 2019 (n=98,485)	Hospitalized patients with PE 2020 without COVID-19 (n=94,356)	Hospitalized patients with PE 2020 with COVID-19 (n=3,362)
Case-fatality rate	12,470 (12.7%)	11,795 (12.5%)	964 (28.7%)
Resuscitation	5,564 (5.6%)	5,115 (5.4%)	275 (8.2%)
Shock	5,214 (5.3%)	5,115 (5.4%)	453 (13.5%)
Systemic thrombolysis	3,917 (4.0%)	3,810 (3.9%)	173 (5.1%)
RV-dysfunction	23,205 (23.6%)	21,947 (23.1%)	706 (21.0%)
Treatment on ICU	18,241 (18.5%)	17,527 (18.6%)	1,325 (39.4%)
Mechanical ventilation	4,569 (4.6%)	4,532 (4.8%)	638 (19.0%)
ARDS	786 (0.8%)	747 (0.8%)	760 (22.6%)
Pneumonia	26,115 (26.5%)	25,664 (27.2%)	2,835 (84.3%)
ECMO	551 (0.6%)	429 (0.5%)	153 (4.6%)
CT-Angiography	64,503 (65.5%)	64,021 (67.9%)	2,517 (74.9%)
Renal insufficiency	12,413 (12.6%)	11,589 (12.3%)	344 (10.2%)

Abbreviations: ARDS, Acute respiratory distress syndrome; CT= Computed tomography; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit;

Table S2: Associations of patients' characteristics, comorbidities and adverse events with pulmonary embolism in patients with confirmed COVID-19 infection (univariable and multivariable logistic regression models).

	All in-hospital patients with COVID-19 infection (n=176,137; 3362 patients had diagnosis of PE [1.9%])			
	Univariate		**Multivariate** (adjusted for age, sex, cancer, coronary artery disease, heart failure, COPD, arterial hypertension, renal insufficiency, diabetes mellitus, atrial fibrillation, pAVK and hyperlipidemia)	
Parameters	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age ≥ 70	**0.903 (0.844-0.967)**	**0.004**	1.029 (0.952-1.112)	0.468
Male Sex	**1.208 (1.115-1.376)**	**<0.001**	**1.349 (1.205-1.497)**	**<0.001**
Obesity	**1.759 (1.559-1.985)**	**<0.001**	**1.875 (1.657-2.121)**	**<0.001**
Comorbidities				
Coronary artery disease	**0.735 (0.660-0.819)**	**<0.001**	**0.683 (0.608-0.767)**	**<0.001**
Cancer	**1.288 (1.121-1.481)**	**<0.001**	**1.254 (1.090-1.442)**	**0.002**
PAD	**0.790 (0.637-0.981)**	**0.033**	0.838 (0.672-1-044)	0.116
COPD	**0.856 (0.741-0.988)**	**0.033**	0.815 (0.704-0.944)	0.006
Arterial hypertension	**1.000 (0.934-1.070)**	**0.991**	0.997 (0.926-1.073)	0.997
Renal insufficiency	**0.615 (0.549-0.688)**	**<0.001**	**0.553 (0.491-0.623)**	**<0.001**
Diabetes mellitus	0.996 (0.921-1.077)	0.925	0.989 (0.910-1.074)	0.790
Atrial fibrillation	**0.837 (0.764-0.917)**	**<0.001**	**0.736 (0.666-0.812)**	**<0.001**
Charlson Index	**1.042 (1.030-1.054)**	**<0.001**	**1.095 (1.041-1.104)**	**<0.001**

Abbreviations: CI= Confidence interval; COPD= Chronic obstructive pulmonary disease; OR= Odds ratio; PAD= peripheral artery disease

Values in bold indicate that the difference is statistically significance at least in the multivariate regression model ($p<0.05$).

Table S3: Associations of COVID-19 with in-hospital mortality in patients with pulmonary embolism in 2020 (univariable and multivariable logistic regression models).

	All in-hospital patients with pulmonary embolism in 2020 (n=97,718; 12,759 patients died [13.1%])			
	Univariate		**Multivariate** (adjusted for age, sex, cancer, coronary artery disease, heart failure, COPD, arterial hypertension, renal insufficiency, diabetes mellitus, atrial fibrillation, pAVK and Hyperlipidemia)	
Parameters	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
COVID-19	**2.814 (2.605-3.040)**	**<0.001**	**3.155 (2.910-3.420)**	**<0.001**

Abbreviations: CI= Confidence interval, OR= Odds ratio;

Values in bold indicate that the difference is statistically significance at least in the multivariate regression model ($p<0.05$).

Figure S1:

Panel A - Proportion of deaths (red line) in COVID-19 patients with PE (blue bars) stratified for age-decades of life

Panel B - Proportion of computed tomography pulmonary angiography (green line) in COVID-19 patients with PE (blue bars) stratified for age-decades of life

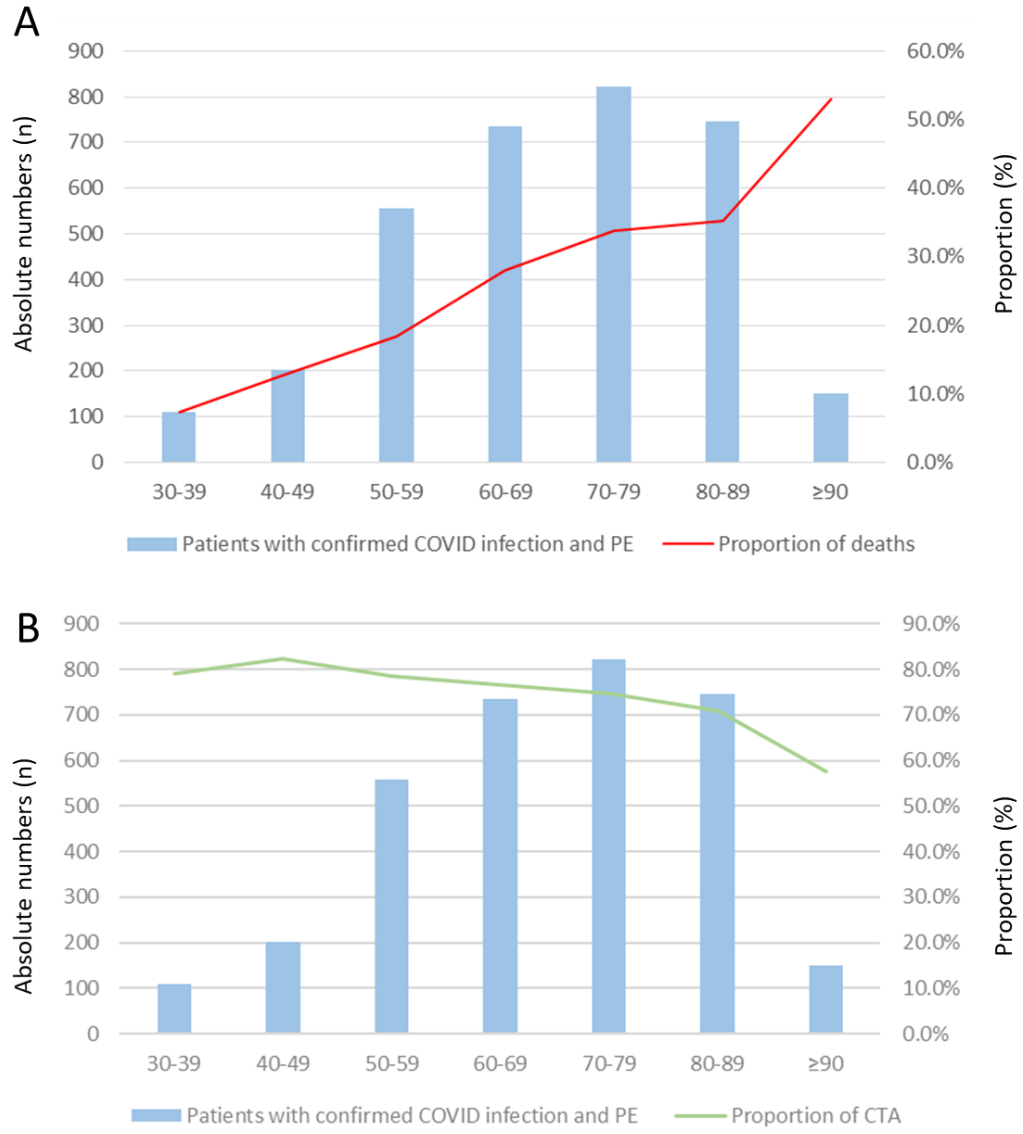

Figure S2: Proportion of PE (blue line) in COVID-19 patients undergoing surgeries (orange bars) stratified for different kind of surgeries.