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ORIGINAL ARTICLE

Association between pulmonary embolism and COVID-19 disease.

Martin Števík[1], Kamil Zeleňák[1], Anton Dzian[2], Beáta Drobná Saniová[3], Zuzana Trabalková[1], Daniel Lozan[1], Marián Grendár[4], Ján Sýkora[1], Martin Vorčák[1], Marek Malík[2], Lukas Meyer[5], Jens Fiehler[1], Veronika Vajdová[1]

1 Clinic of Radiology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin University Hospital, Kollárova 2, 036 59, Martin, Slovakia.
2 Department of Thoracic Surgery, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin University Hospital, Kollárova 2, 036 59, Martin, Slovakia.
3 Department of Anesthesiology and Intensive Medicine, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin University Hospital, Kollárova 2, 036 59, Martin, Slovakia.
4 Biomedical Centre Martin – BioMed Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Malá hora 4, 036 01, Martin, Slovakia.
5 Diagnostic and Interventional Neuroradiology, University Medical Centre Hamburg-Eppendorf, 20251, Hamburg, Germany.

Correspondence to: Martin Števík, MUDr, PhD.
Clinic of Radiology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin University Hospital, Kollárova 2, 036 59, Martin, Slovakia
TEL: 00421434203361, E-MAIL: martin.stevik@unm.sk,
ORCID: 0000-0002-6824-5915

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Abstract

OBJECTIVES: The current retrospective study focused on evaluation of the relationship between pulmonary embolism during COVID-19 pandemic and demographic, presenting symptoms, comorbidities and laboratory results in patients who underwent CT angiography of the pulmonary arteries.
METHODS: The study enrolled all adult patients with suspected acute pulmonary embolism (PE) who underwent computed tomography pulmonary angiography (CTPA) between March 1, 2020, and April 30, 2022, during the SARS-CoV-2 pandemic. 1698 CTPAs were reviewed and various data were collected. Based on examination results, patients were divided into 4 groups: a group with positive PE and a group with negative PE for both COVID-19 and non-COVID-19 patients.
RESULTS: When comparing different predictors of COVID-19 patients and non-COVID-19 patients we noticed lower probability of PE in female gender (OR 0.77, 95% CI: 0.60–1.00, $p = 0.052$) and in chronic obstructive pulmonary disease (COPD) patients (OR 0.6, 95% CI: 0.38–0.90, $p = 0.017$). Higher probability of PE was in cases of older age (OR 1.02, 95% CI: 1.01–1.02, $p < 0.001$), increased heart rate (OR 1.01, 95% CI: 1.01–1.02, $p < 0.001$) and increased D-dimer levels (OR 1.03, 95% CI: 1.02–1.04, $p < 0.001$).
CONCLUSION: Considering predictors of PE there was a significantly lower risk of PE in the female gender and COPD, and a higher risk with increasing age, heart rate, and D-dimer levels.

Abbreviations:

AUC	- area under the receiver operating characteristic
BMI	- body mass index
CHD	- coronary heart disease
CI	- confidence interval
COPD	- chronic obstructive pulmonary disease
COVID-19	- coronavirus disease 2019
CRP	- c-reactive protein
CT	- computed tomography
CTPA	- computed tomography pulmonary angiography
HU	- Hounsfield units
ICU	- intensive care unit
IQR	- interquartile range
OR	- odds ratio
PCR	- polymerase chain reaction
PE	- pulmonary embolism
PTE	- pulmonary thromboembolism
ROC	- receiver operating characteristic
SARS-CoV-2	- severe acute respiratory syndrome coronavirus 2

INTRODUCTION

In December 2019 a new type of coronavirus (severe acute respiratory syndrome coronavirus-2 – SARS-CoV-2) was isolated (Elmokadem *et al.* 2022). This novel coronavirus disease-2019 (COVID-19) spread very rapidly affecting the entire world and causing a global pandemic (Rea *et al.* 2021). An extenuating effort of researchers and clinicians led to improvements in diagnostic and therapeutic strategies. However, two years after the beginning of the COVID-19 pandemic, it remains a frequent cause of morbidity and death internationally and is still a challenge for the medical community. The spectrum of thromboembolic complications of COVID-19 is broad and ranges in severity from asymptomatic to organ dysfunction resulting in death (Stals *et al.* 2021). The main targets of SARS-CoV-2 infection are pulmonary epithelial cells, lymphocytes, and vascular endothelium, especially in the elderly. There is evidence that the SARS-CoV-2 virus may invade the endothelial cells directly. Endothelial damage leading to cell injury comes with an inflammation-driven activation of the coagulation cascade, resulting in an increased thrombotic risk (Ho *et al.* 2021). In particular, there is a high release of inflammatory mediators, increased levels of factor VIII, von Willebrand factor, fibrinogen, and local fibrinolysis with increased D-dimer and increased viscosity (Alaithan *et al.* 2021). That leads to thrombosis, which can be a defense mechanism that compartmentalizes infection and prevents further dissemination (Masselli *et al.* 2021; Raj *et al.* 2021; Tankere *et al.* 2021).

Literature evidence suggests that COVID-19 is a systemic disease and it may affect almost all human organs. COVID-19 predominantly causes respiratory symptoms. These findings are remarkably similar to that of pulmonary thromboembolism (PTE). Signs and symptoms of pulmonary embolism (PE) are for instance shortness of breath, coughing, and chest pain; they are nonspecific and show overlap with mimicking conditions, including other respiratory tract infections, like COVID-19 which results in diagnostic challenges (Rea *et al.* 2021; Stals *et al.* 2021). Symptoms of pulmonary embolism are an important cause of emergency department visits. Thus, the incidence of PE varies widely in the literature, and therefore the uncertainty about which patients should be imaged remains. D-dimer levels are often elevated in the absence of thrombosis (Korevaar *et al.* 2021). Hence, it is currently not recommended to use D-dimer levels to diagnose PTE associated with COVID-19 or decide which patients should undergo imaging to diagnose PE. However, similarly to non-COVID-19 patients, normal D-dimer values can effectively rule out PTE in the context of low pretest probability (Stals *et al.* 2021; Metra *et al.* 2021; Trunz *et al.* 2021). The current modality of choice for PE imaging is multidetector computed tomography pulmonary angiography. CTPA examination in patients with COVID-19 is mostly based on the empirical evaluation of patients by clinicians. The common indications are unexplained respiratory deterioration, a rapid increase in D-dimer, or clinical symptoms of PE (Karolyi *et al.* 2021). Clinical findings and D-dimer tests help to triage patients with suspected PE and reduce the number of unnecessary CT scans in this population. These represent a low PE judgment rate with high heterogeneity between studies in COVID-19 (positive CTPA: 8–44%) compared with the classic PE judgment using Wells or the revised Geneva prediction rule (confirmed PE expected to be 0–10% in the low-probability category and 65% in the high-probability category) (Cui *et al.* 2021; Fauvel *et al.* 2021). Also, this rate may be overestimated because of the cautious screening strategy of suspected PE adopted to reduce cross-infection (Ooi *et al.* 2020).

The primary goal of the present study was to evaluate baseline characteristics, risk factors, comorbidities, and laboratory values in patients who underwent CT angiography of the pulmonary arteries during the current pandemic.

MATERIAL AND METHODS

Study design and setting

This was a single-center retrospective study conducted at University Hospital in Martin, Jessenius Faculty of Medicine in Martin, Comenius University, Slovakia. This study enrolled all consecutive adult patients with suspected acute pulmonary embolism who underwent CT angiography of the pulmonary arteries during the SARS-CoV-2 pandemic between March 1, 2020, and April 30, 2022. The radiology picture archive and communication system (TomoCon, Tatramed, Bratislava, Slovak republic) was queried by a radiologist using the search terms "CT pulmonary angiography" to identify CT pulmonary angiography. The hospital electronic medical record (MEDEA, Bratislava, Slovak republic) for these patients was reviewed to identify clinical and laboratory data. All patients included in

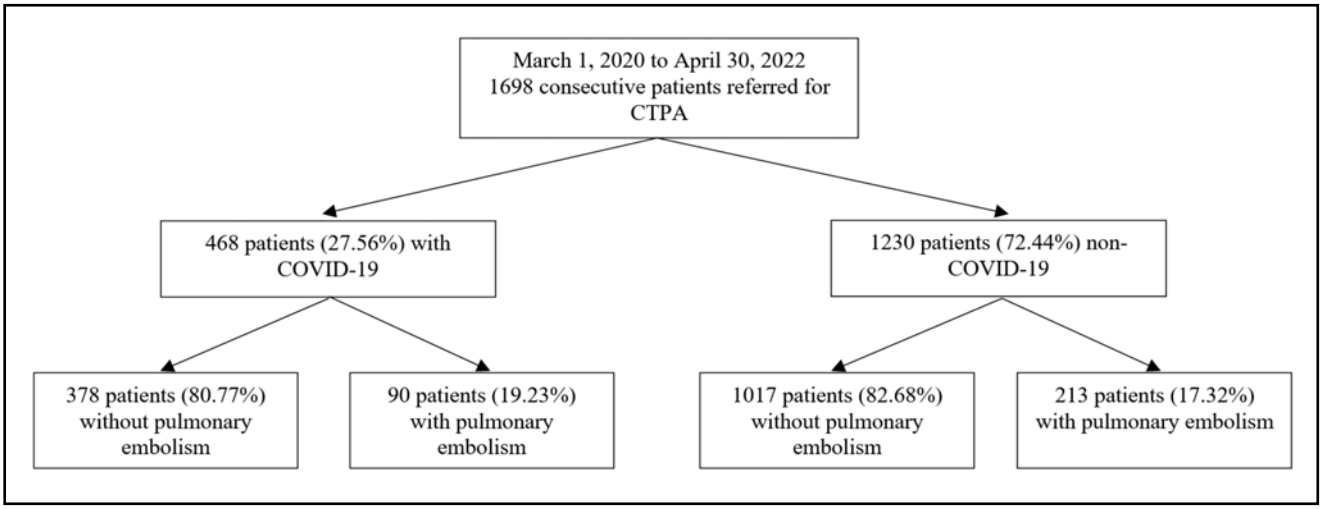

Fig. 1. Flow chart
Abbreviations: COVID-19 – coronavirus disease 2019, CTPA – computed tomography pulmonary angiography

the study were 18 years of age or older. We excluded patients with no data about the clinical condition and unavailable laboratory results. Those with technically inadequate CT studies and outside of the region patients were excluded as well. Two cohorts are detailed below.

A: Patients with COVID-19: those with positive polymerase chain reaction (PCR) tests or with high index of clinical and radiological suspicion, consistent symptoms (respiratory symptoms, fever, dry cough, dyspnoea, myalgia) and lung parenchyma lesions characteristic for COVID-19 infection on a CTPA. Although COVID-19 is diagnosed by PCR test, in addition to patients with positive PCR results (patients with confirmed COVID-19), those with signs and symptoms as well as chest CT findings typical for COVID-19 who had negative PCR results or did not undergo PCR testing were included in the COVID-19 group. This was because the sensitivity of PCR is relatively low, with a reported rate of false negatives up to 30%.

B: Non-COVID-19 patients: those with negative PCR test or without high index of clinical and radiological suspicion.

Data collection and study variables

The patients' clinical and laboratory data were extracted from our local hospital's electronic database. Demographic data such as age and gender were recorded for these patients. Presenting symptoms before CTPA were assessed. The clinical and laboratory data included the following: the main complaints at the time of CTPA scanning (fever, cough, dyspnoea, hemoptysis, D-dimer positivity, chest pain), the laboratory results including D-dimer level, c-reactive protein (CRP) level, the leukocyte count and the lymphocyte count. All laboratory results included must be within 72 hours around the time of CTPA. Data included clinical symptoms, heart rate, saturation of O_2 %, and the presence of comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), smoking, obesity (defined as body mass index, BMI>25), and oncologic disease. These data were collected before the CTPA examination.

CT imaging protocol and interpretation

CTPA was performed on 64 or 256 slice scanners (CT Philips Inguinity 64, Amsterdam, Netherlands or Revolution GE Healthcare 256, Chicago, Illinois, USA). CT pulmonary angiography protocol at our institution entailed intravenous administration of 50 ml to 100 ml of 400 mg/ml of iodinated contrast material at 3–4 ml/sec using an injector pump (Optivantage® Guerbet, Villepinte, France or Nemoto® injector, Tokyo, Japan). The acquisition parameters were as follows: 120–140 kVp, dose modulation 50–600 mA, collimation of 64 × 0.625 mm or 256 × 0.625 mm, rotation time 0.35 s, 0.98 pitch, and slice thickness of 0.625 mm.

A low-quality study was considered to be the one with images not optimal for suitable assessment of the anatomy of the pulmonary arterial tree. Imaging analysis was performed at diagnostic workstations with certified diagnostic monitors, based on an effective slice thickness of 1 mm. Image post-processing was performed using multiplanar reconstruction and maximum intensity projection techniques. Images were evaluated in an angiographic window (W: 700, L: 100 Hounsfield units, HU). The CTPA examinations were reviewed to evaluate pulmonary embolism by two general radiologists experienced in chest imaging with 6 (Z.T.) and 16 (M.S.) years of experience. They were blinded to the clinical condition of the patients or the laboratory results. Discrepancies were resolved by consensus between two experienced general radiologists. Patients were divided into 4 groups: a group with positive PE and a group with negative PE for both COVID-19 and non-COVID-19 patients.

Tab. 1. Baseline characteristics, COVID-19 group

Variables	Diagnosis of PE, COVID-19 group (n=468)				*p*-value
	No (n=378)	No. of patients	Yes (n=90)	No. of patients	
Demographics					
Age (years) [median (IQR)]	58 (46, 70)	378	66 (57, 76)	90	**<0.001**
Female gender	194 (51%)	378	42 (47%)	90	0.4
Indication for CTPA					
Dyspnoea	244 (65%)	378	62 (69%)	90	0.4
Hemoptysis	29 (7.7%)	378	4 (4.4%)	90	0.3
D-dimer positivity	366 (97%)	377	86 (96%)	90	0.5
Cough	245 (65%)	378	54 (60%)	90	0.4
Chest pain	115 (30%)	378	21 (23%)	90	0.2
Febrility	137 (36%)	378	28 (31%)	90	0.4
Comorbidities					
Hypertension	199 (53%)	378	61 (68%)	90	**0.009**
Diabetes mellitus	61 (16%)	378	22 (24%)	90	0.064
COPD	24 (6.3%)	378	9 (10%)	90	0.2
CHD	105 (28%)	378	40 (44%)	90	**0.002**
Smoking	49 (13%)	378	12 (13%)	90	>0.9
Obesity	154 (41%)	378	30 (33%)	90	0.2
Oncologic disease	29 (7.7%)	378	12 (13%)	90	0.088
Laboratory findings					
Heart rate (bpm)	86 (75, 100)	374	90 (80, 101)	90	0.13
O_2 saturation (%)	94 (91, 97)	338	94 (88, 96)	79	**0.042**
D-dimer (mg/L)	1.06 (0.78, 1.92)	372	2.25 (1.31, 5.82)	87	**<0.001**
CRP (mg/L)	52 (14, 114)	378	55 (19, 115)	90	0.5
Leukocytes (10^9/L)	6.5 (4.8, 8.8)	376	8.5 (6.2, 11.1)	89	**<0.001**
Lymphocytes (10^9/L)	1.07 (0.75, 1.53)	374	1.09 (0.87, 1.63)	85	0.2

Abbreviations: CHD – coronary heart disease, COPD – chronic obstructive pulmonary disease, COVID-19 – coronavirus disease 2019, CRP – c-reactive protein, CTPA – computed tomography pulmonary angiography, IQR – interquartile range, PE – pulmonary embolism
Data are given as median (IQR) or counts with respective percentages
p-values in bold denote statistically significant differences ($p<0.05$)

Statistical analysis

COVID-19 and non-COVID-19 patients with pulmonary embolism on CTPA and those without the presence of PE on CTPA were compared. Data were explored and analyzed in R (R Project for Statistical Computing), version 4.0.5. Factors were summarized by counts and percentages. Continuous variables were summarized by the median and quartiles. Comparison of a factor in two groups was done by the Fisher exact test. Wilcoxon-Mann-Whitney test was used to compare population medians in two subpopulations. *P*-values from the tests were adjusted for multiple hypothesis testing, using the Benjamini-Hochberg method. Multivariate logistic regression with PE as the response was used for predictive modeling. Prior to it, the missing data were imputed by the Random Forest imputation algorithm, as implemented in the randomForestSRC library. The full model was simplified using Akaike Information Criterion. The predictive performance of the selected multivariate logistic regression model was assessed by the receiver operating characteristic (ROC) curve and quantified by area under ROC (AUC). Results with a *p*-value below 0.05 were considered statistically significant.

Ethics approval

This retrospective study was approved by our institutional ethical review board with the written consent waived.

RESULTS

In the time period during the COVID-19 pandemic from March 1, 2020, to April 30, 2022 (26 months in total) there were 1774 CTPA examinations performed at the Clinic of Radiology in Martin University Hospital. 76 (4%) of those were excluded because of suboptimal vascular opacification, severe motion artifacts, age below 18, or patients outside of our region. Out of the total number of 1698 CTPA in this study, 468 (27.56%) were COVID-19 positive patients, where COVID-19 was confirmed by a positive PCR test or typical clinical and radiological findings. 1230 (72.44%) patients were COVID-19 negative because of negative PCR tests or lack of typical clinical and radiological findings. Out of 468 COVID-19 patients, pulmonary embolism was found in 90 (19.23%) cases. Out of 1230 non-COVID-19 patients, pulmonary embolism was found in 213 (17.32%) cases (Fig. 1).

In patients with COVID-19 there was a statistically significant difference in the age of patients with PE [on average 66 years of age (57, 76)] and without PE [on average 58 years of age (46, 70)], ($p < 0.001$). In non-COVID-19 patients, this difference was not statistically significant [68 years of age (56, 77) with PE, 66 (51, 76) without PE], ($p = 0.094$). In the non-COVID-19 group, we noticed a significantly decreased number of women with pulmonary embolism (n = 96, 45% of women) compared to the patients with no PE (n = 542, 53% of women, $p = 0.029$). In COVID-19 patients there were also less women with PE (n = 42, 47%) compared to the ones without PE (n = 194, 51%), but this difference was not significant ($p = 0.4$) (Tab. 1, 2).

The most common indication for CTPA was D-dimer positivity (≥0,5 mg/L) whether the patients had COVID-19 or not. In the COVID-19 group, we noticed more indications like cough and fever and less chest pain. Indications like dyspnoea and hemoptysis were similarly represented in both groups.

The most common comorbidity in both COVID-19 and non-COVID-19 patients was arterial hypertension. In COVID-19 patients the occurrence of hypertension in the presence of PE was significantly increased (68% of COVID-19 patients with PE had hypertension, compared to 53% without PE, $p = 0.009$). The second most common comorbidity was coronary heart disease with more cases in COVID-19 patients with PE (44% of COVID-19 patients with PE had CHD, compared to 28% without PE, $p = 0002$). In non-COVID-19 patients, there was no significant difference in comorbidities in relation to PE.

In non-COVID-19 patients, pulmonary embolism was associated with increased heart rate ($p < 0.001$), while this difference was not significant in the COVID group ($p = 0.13$). In the case of PE in both groups, there was a significant decrease in O_2 saturation (COVID-19, $p = 0.042$ and non-COVID-19, $p < 0.001$) and an increase in D-dimer levels (in both groups $p < 0.001$), which correlates with generally known predictors of pulmonary embolism.

When studying inflammatory markers, we noticed a significant increase of CRP and leukocytes ($p < 0.001$) in the case of PE in the non-COVID-19 group, while in the COVID-19 group it was only leukocytes that were increased ($p < 0.001$), since inflammation was present regardless of PE. PE positivity was in general a little bit higher in COVID-19 patients (19.23%) compared to non-COVID-19 patients (17.32%).

Multivariate logistic regression with PE as the response was used for predictive modeling. In Tab. 3 we present statistically significant predictors in both COVID-19 and non-COVID-19 groups and a comparison of both groups with the occurrence of PE.

In the COVID-19 group, there were age and obesity as statistically significant factors. With increased age, there is also an increased probability of PE (odds ratio (OR) 1.04, 95% CI: 1.02–1.05, $p < 0.001$). In obese patients, there was a lower probability of PE (OR 0.57, 95% CI: 0.34–0.94, $p = 0.032$).

In the non-COVID-19 group, there were other significant factors – female gender, COPD, heart rate, O_2 saturation, D-dimer, and CRP. In female gender (OR 0.73, 95% CI: 0.53–1.00, $p = 0.054$), in COPD (OR 0.46, 95% CI: 0.26–0.78, $p = 0.006$) and low O_2 saturation (OR 0.96, 95% CI: 0.94–0.99, $p = 0.002$) there was lower probability of PE. Higher probability of PE was in patients with increased heart rate (OR 1.01, 95% CI: 1.00–1.02, $p = 0.001$) and increased D-dimer (OR 1.09, 95% CI: 1.06–1.11, $p < 0.001$).

When comparing different predictors in both groups we found significant factors to be age, female gender, COPD, heart rate, O_2 saturation, and D-dimer (Fig. 2.). Lower probability of PE was found in the female gender (OR 0.77, 95% CI: 0.60–1.00, $p = 0.052$), in COPD patients (OR 0.6, 95% CI: 0.38–0.90, $p = 0.017$) and in decreased O_2 saturation (OR 0.98, 95% CI: 0.96–1.00, $p = 0.019$). Higher probability of PE was in older age (OR 1.02, 95% CI: 1.01–1.02, $p < 0.001$), increased heart rate (OR 1.01, 95% CI: 1.01–1.02, $p < 0.001$) and increased D-dimers (OR 1.03, 95% CI: 1.02–1.04, $p < 0.001$).

DISCUSSION

The current study focused on the evaluation of the relationship between pulmonary embolism during the COVID-19 pandemic and demographic, presenting symptoms, comorbidities, and laboratory results. In the time period during the COVID-19 pandemic from March 1, 2020, to April 30, 2022 (26 months in total) there were a total of 1698 CTPA examinations

Tab. 2. Baseline characteristics, non-COVID-19 group

Variables	Diagnosis of PE, non-COVID-19 group (n=1230)				*p*-value
	No (n=1017)	No. of patients	Yes (n=213)	No. of patients	
Demographics					
Age (years) [median (IQR)]	66 (51, 76)	1017	68 (56, 77)	213	0.094
Female gender	542 (53%)	1017	96 (45%)	213	**0.029**
Indication for CTPA					
Dyspnoea	632 (62%)	1012	142 (67%)	213	0.2
Hemoptysis	42 (4.2%)	1012	13 (6.1%)	213	0.2
D-dimer positivity	915 (90%)	1012	195 (92%)	212	0.5
Cough	210 (21%)	1012	42 (20%)	213	0.7
Chest pain	426 (42%)	1012	84 (39%)	213	0.5
Febrility	81 (8.0%)	1012	21 (9.9%)	213	0.4
Comorbidities					
Hypertension	688 (68%)	1013	153 (72%)	213	0.3
Diabetes mellitus	230 (23%)	1013	43 (20%)	213	0.4
COPD	147 (15%)	1013	22 (10%)	213	0.11
CHD	491 (48%)	1013	102 (48%)	213	0.9
Smoking	278 (27%)	1014	46 (22%)	213	0.08
Obesity	406 (40%)	1013	95 (45%)	213	0.2
Oncologic disease	163 (16%)	1012	38 (18%)	213	0.5
Laboratory findings					
Heart rate (bpm)	85 (72, 100)	996	92 (79, 109)	212	**<0.001**
O_2 saturation (%)	97.0 (94.0, 98.0)	873	95.0 (91.8, 97.0)	180	**<0.001**
D-dimer (mg/L)	1.29 (0.84, 2.48)	934	3.87 (1.62, 7.43)	194	**<0.001**
CRP (mg/L)	11 (3, 46)	997	32 (11, 96)	210	**<0.001**
Leukocytes (10^9/L)	8.4 (6.5, 10.8)	1010	9.8 (7.7, 11.9)	210	**<0.001**
Lymphocytes (10^9/L)	1.46 (1.01, 2.05)	962	1.37 (1.06, 2.01)	203	0.7

Abbreviations: CHD – coronary heart disease, COPD – chronic obstructive pulmonary disease, COVID-19 – coronavirus disease 2019, CRP – c-reactive protein, CTPA – computed tomography pulmonary angiography, IQR – interquartile range, PE – pulmonary embolism
Data are given as median (IQR) or counts with respective percentages
p-values in bold denote statistically significant differences ($p<0.05$)

performed. Filippi *et al.* (2021) and Miró *et al.* (2020) reported PE incidence in COVID-19 patients to be 18.7% and 16.4%. According to their conclusion PE was a frequent complication of COVID-19 and clinicians needed a high degree of suspicion because clinical and laboratory parameters couldn't drive diagnosis. McGettrick *et al.* (2021) reported that COVID-19 also predisposed to pulmonary thromboembolism and the associated incidence of PE may be substantially higher than has been reported in association with other viral or bacterial pneumonic illnesses. Riyahi *et al.* (2021) reported that in a multi-center study of 413 patients hospitalized with COVID-19 and suspected of PE, pulmonary embolism was found in 25% (95% CI: 21%–29%). Chamorro *et al.* (2021) reported that PE was seen on CTPA in 89 of the 342 patients with COVID-19 (26%, 95% CI: 21.7–30.1%), and 24 of the 147 patients without COVID-19 (16.3%, 95% CI: 11.2–23.1%). This difference was statistically significant ($p = 0.0197$). The difference in the prevalence of PE in 2019 (13.2%) and in the COVID-19 negative group in 2020 (16.3%) did not attain statistical significance ($p = 0.43$). Rindi *et al.* (2021) reported that according to the latest meta-analysis by Suh *et al.* (2021) PE occurred in 16.5% of patients

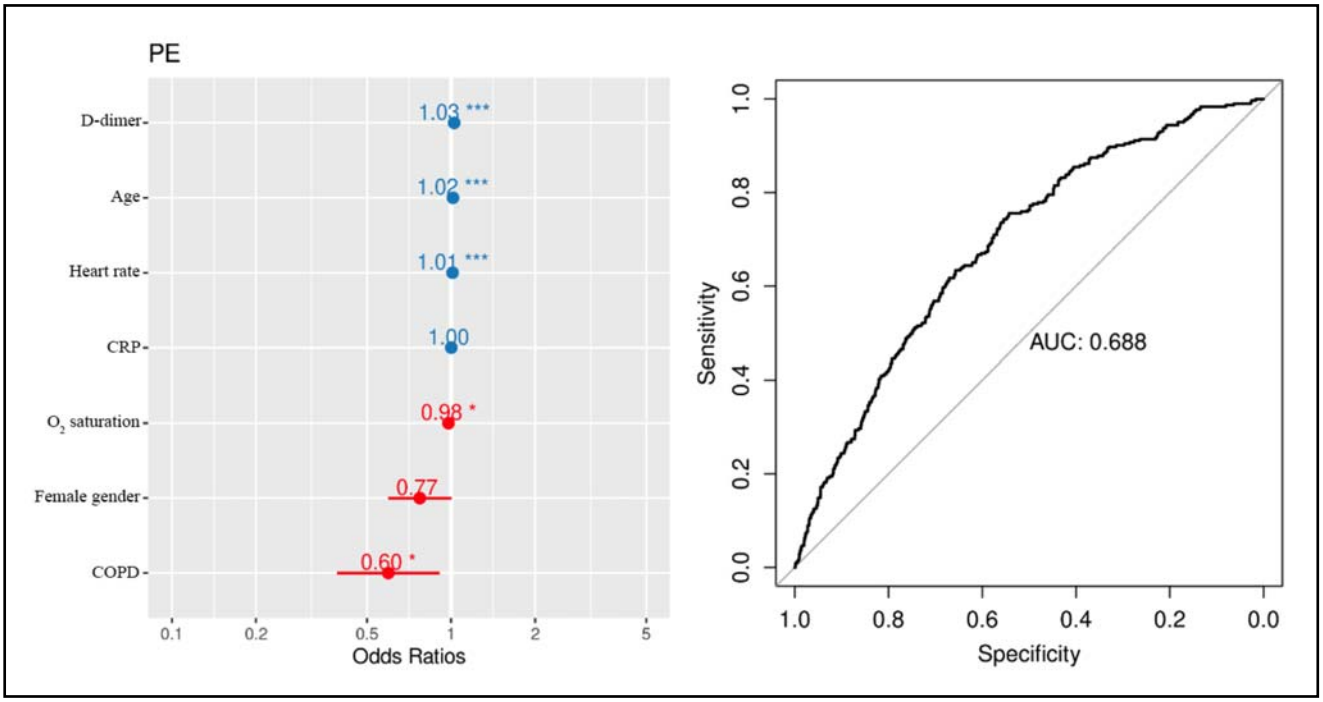

Fig. 2. Multivariate logistic regression with PE as the response was used for predictive modeling. The predictive performance of the selected multivariate logistic regression model was assessed by the ROC curve and quantified by area under ROC (AUC).
Abbreviations: AUC – area under the receiver operating characteristic, COPD – chronic obstructive pulmonary disease, CRP – c-reactive protein, PE – pulmonary embolism, ROC – receiver operating characteristic

hospitalized for COVID-19. Porfidia *et al.* (2021) reported a recent meta-analysis of 3487 COVID-19 patients from 30 studies that produced a 26% pooled incidence of venous thromboembolism, but concluded that the existing evidence was low-quality and heterogenous. A recent meta-analysis by Kwee *et al.* (2021) reported a 17.9% incidence of PE in emergency department, 23.9% in general wards and 48.6% in intensive care unit (ICU). A meta-analysis of 4382 hospitalized patients with COVID-19 by Liu *et al.* (2021) showed a 17.6% incidence of PE, with a substantially higher rate among those with severe (i.e. ICU admitted) versus general (i.e. not ICU admitted) disease (21.7% vs. 12.5%).

Raza *et al.* (2021) reported that global data strongly indicated that a sex-based disparity existed in COVID-19 clinical outcomes, with men being more affected by initial COVID-19 infection, hospitalization, and poor clinical outcomes. This was also confirmed in our study. Chamorro *et al.* (2021) reported that in 2020 PE was more common in males, both in the COVID-19 group (65.2%) and in the non-COVID-19 group (58.3%), ($p = 0.54$). On the other hand Tuck *et al.* (2021); Yassin *et al.* (2021); Kaminetzky *et al.* (2020) and Poyiadji *et al.* (2020) concluded no significant difference in age and gender regarding the incidence of PE.

In COVID-19 patients the occurrence of hypertension in the presence of PE was significantly increased ($p = 0.009$). The second most common comorbidity was coronary heart disease ($p = 0.002$). Alaithan *et al.* (2021) reported that the smoking status (OR 1.94, 95% CI: 1.4–3.8) and obesity (OR 4.1, 95% CI: 1.5–8.9) were independent predictors of PE among patients with COVID-19. The results were different in our study, where there was a lower probability of PE in COVID-19-positive obese patients. Rogier *et al.* (2021) reported that COVID-19 negative patients were more often active smokers, similarly to our study. Cui *et al.* (2021) reported that PE in patients with COVID-19 has been found to be different from classic PE in patients without COVID-19 in demographic, clinical, and laboratory characteristics.

In the case of PE in both groups, there was a significant decrease in O_2 saturation (COVID-19, $p = 0.042$ and non-COVID-19, $p < 0.001$) and an increase in D-dimer levels (in both groups $p < 0.001$), which correlated with generally known predictors of pulmonary embolism. When studying inflammatory markers, we noticed a significant increase of CRP and leukocytes ($p < 0.001$) in the case of PE in the non-COVID-19 group, while in the COVID-19 group it was only leukocytes that were increased ($p < 0.001$), since inflammation was present regardless of PE. Riyahi *et al.* (2021) compared the relationship between the D-dimer, CRP, leukocyte, and lymphocyte count and the incidence of PE which was found insignificant although patients with positive PE showed higher levels of D-dimer and CRP compared to the patients with negative PE. Also, the rising D-dimer was found to be highly significant. Yassin *et al.* (2021) reported that patients with positive PE showed higher D-dimer and CRP levels and lower lymphocytic counts compared to the patients with negative PE. However, no

Tab. 3. Statistically significant predictors in both COVID-19 and non-COVID-19 groups and comparison of both groups with the occurrence of PE

Characteristic	OR	95% CI	p-value
Multivariate Logit COVID-19			
Age	1.04	1.02, 1.05	**<0.001**
Obesity	0.57	0.34, 0.94	**0.032**
Multivariate Logit non-COVID-19			
Female gender	0.73	0.53, 1.00	0.054
COPD	0.46	0.26, 0.78	**0.006**
Heart rate	1.01	1.00, 1.02	**0.001**
O_2 saturation	0.96	0.94, 0.99	**0.002**
D-dimer	1.09	1.06, 1.11	**<0.001**
CRP	1.0	1.00, 1.00	**0.039**
Multivariate Logit together			
Age	1.02	1.01, 1.02	**<0.001**
Female gender	0.77	0.60, 1.00	0.052
COPD	0.6	0.38, 0.90	**0.017**
Heart rate	1.01	1.01, 1.02	**<0.001**
O_2 saturation	0.98	0.96, 1.00	**0.019**
D-dimer	1.03	1.02, 1.04	**<0.001**

Abbreviations: CI – confidence interval, COPD – chronic obstructive pulmonary disease, COVID-19 – coronavirus disease 2019, CRP – c-reactive protein, OR – odds ratio, PE – pulmonary embolism
p-values in bold denote statistically significant differences ($p<0.05$)

significant relation was found between the level of the D-dimer, CRP, white blood cells count, neutrophil, and lymphocyte count and the incidence of PE. Poyiadji *et al.* (2020) concluded that an increase in the D-dimer level of 6 μg/ml had an odds ratio of 2.7 for developing a PE. Alaithan *et al.* (2021) reported that 87.3% of patients with COVID-19 had elevated D-dimer levels compared with 21.5% of patients without COVID-19. However, the elevated D-dimer level was not significantly associated with PE among patients with COVID-19 (OR 0.7, 95% CI: 0.4–1.8). Chamorro *et al.* (2021) concluded that there were no significant differences in D-dimer levels between patients with COVID-19 and those without it. Results of our study had shown a significant increase of D-dimer in the case of PE in both COVID-19 and non-COVID-19 groups. However, the mean value of D-dimer was not increased in the COVID-19 group compared to non-COVID-19 patients. Bukhari *et al.* (2021) reported that measuring D-dimer remained an effective test for ruling out PE in patients with COVID-19 as in patients without COVID-19. Kwee *et al.* (2021) concluded that D-dimer assessment may help to select patients with COVID-19 for CTPA, using D-dimer cutoff levels of at least 1000 μg/L. Elberts *et al.* (2021) reported that the performance of D-dimer testing for PE was similar between COVID-19 and non-COVID-19 patients. Results from this multicenter retrospective study did not find a significant difference in sensitivity of D-dimer for PE due to concomitant COVID-19 infection. Trunz *et al.* (2021) reported that it is currently not recommended to use D-dimer levels to diagnose COVID-19-associated PTE or decide which patients should undergo imaging to diagnose PE. However, similarly to non-COVID-19 patients, normal D-dimer values can effectively rule out PTE in the context of low pretest probability. Poyiadji *et al.* (2020) recorded that the patients with high D-dimer and high CRP were significantly more susceptible to developing PE.

Multivariate logistic regression with PE as the response was used for predictive modeling. In the COVID-19 group, there were age and obesity as statistically significant factors. With increased age, there was also an increased probability of PE ($p < 0.001$). The COVID-19 disease commonly affected older patients who have already suffered from serious comorbidities that predispose to the occurrence of pulmonary embolism. In obese patients, there was a lower probability of PE ($p = 0.032$). Obese patients are more likely to have other diseases that are independent risk factors

for severe COVID-19. In these patients we often noted pulmonary findings of large inflammatory infiltrates, which together with a lower quality of CT examination in obese patients reduced the accuracy of assessment of peripherally occurring embolism. When comparing different predictors in both groups we found significant factors to be age, female gender, COPD, heart rate, O_2 saturation, and D-dimer. Lower probability of PE was found in the female gender ($p = 0.052$), in COPD patients ($p = 0.017$) and in decreased O_2 saturation ($p = 0.019$). Patients with COPD formed a very small group, which could distort the statistical results. O_2 saturation was not reported in critically ill patients who were already on oxygen therapy, which could distort the statistical results. Higher probability of PE was in older age ($p < 0.001$), increased heart rate ($p < 0.001$) and increased D-dimers ($p < 0.001$) which correlates with generally known predictors of pulmonary embolism.

There are several limitations to the current study. Firstly, it's a retrospective study and therefore subject to biases typical for this study design. Retrospective data collection was the main limitation of this study, making it difficult to check for factors influencing the outcomes, including the severity of the disease, treatment protocols, and regular laboratory and clinical data collection. Secondly, the CTPAs were performed only in those patients with clinical and laboratory data suspicious for PE therefore the overall correct incidence and prevalence of PE in COVID-19 patients cannot be determined. Additionally, given the overlap of symptoms in COVID-19 and PE, some PE is likely to have been missed in patients that did not undergo a CTPA.

CONCLUSION

COVID-19 is associated with an increased risk of thromboembolic complications, including pulmonary embolism. This was also confirmed by our study. Considering predictors of PE regardless of COVID-19 positivity, there was a significantly lower risk of PE in the female gender and COPD, and a higher risk with increasing age, heart rate, and D-dimer levels.

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Conflict of interest

No author has any conflict of interest to declare in relation to this study.

Data availability

Anonymous data could be shared on demand.

Code availability

Not applicable.

Ethics approval

This retrospective study was approved by our institutional ethical review board with the written consent waived.

Author contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by MS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate

This was a retrospective study based on routine clinical data, so written informed consent was not acquired.

Consent for publication

Not applicable.

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