DOI: 10.4149/BLL_2023_102

Bratisl Med J 2023; 124 (9)
670 – 675

CLINICAL STUDY

The role of computed tomography pulmonary angiography in COVID-19 patients with suspected pulmonary embolism

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ABSTRACT

OBJECTIVES: This study is aimed to determine the location and distribution of pulmonary embolism (PE) and presence of signs potentially indicative of right heart overload on computed tomography pulmonary angiography (CTPA) in COVID-19 and non-COVID-19 patients. We also evaluated the extent and severity of COVID-19-associated lung changes in relation to PE.

METHODS: The total number of 1,698 patients with CTPA included in the study were divided into 2 groups according to their COVID-19 status and each group was divided into 2 subgroups based on their PE status. These groups and subgroups were compared in terms of location of PE, diameter of pulmonary artery, right heart strain, ground-glass opacities (GGO), consolidations and other imaging features.

RESULTS: In COVID-19 patients, there was a significant predominance of PE in peripheral branches of pulmonary artery ($p < 0.001$). There was an increased right-to-left ratio of ventricular diameters in cases with PE ($p = 0.032$ in patients with COVID-19 and $p < 0.001$ in non-COVID-19 patients). There was no association between the extent and severity of the disease and distribution of PE.

CONCLUSION: COVID-19 is associated with a higher incidence of peripheral location of PE and presence of GGO. There were signs indicative of right heart overload in cases with PE regardless of COVID-19 *(Tab. 3, Fig. 1, Ref. 29)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, computed tomography, CTPA, pneumonia, pulmonary embolism.

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Acknowledgements: This publication was produced with the support of the Integrated Infrastructure Operational Program for the project "New possibilities for the management of serious diseases in medical and preventive care with regard to the safety of health professionals", ITMS: 313011AUA5, and co-financed by the European Regional Development Fund. The work was financially supported by the European Regional Development Fund-Project "Centre for Advanced Applied Sciences", grant number CZ.02.1.01/0.0/0.0/16_019/0000778, and OP Integrated Infrastructure for phase II of project "Center for biomedical research – BIOMEDIRES", ITMS: 313011W42,8 co-financed by the European Regional Development Fund. We thank the Cedars-Sinai Medical Center's International Research and Innovation in Medicine Program and the Association for Regional Cooperation in the Fields of Health, Science and Technology (RECOOP HST Association) for their support of our study and Cedars-Sinai Medical Center – RECOOP Research Center (CRRC).

Introduction

Three years after the beginning of the COVID-19 pandemic, it remains a frequent cause of morbidity and death internationally and it still remains a challenge for the medical community. A number of studies highlighted the wide spectrum of complications seen in COVID-19, including cardiovascular, thromboembolic, neurologic, and inflammatory complications (1). Venous thromboembolism (VTE) and pulmonary embolism (PE) are well-recognized complications of COVID-19, that were seen in up to 30 % of patients in the intensive care unit (ICU) (2). The biochemical coagulation phenotype in COVID-19 likely differs from disseminated intravascular coagulopathy and sepsis-induced coagulopathy (3). The pathogenesis of COVID-19-associated VTE involves hypercoagulability and endothelial damage, as shown by different studies. In COVID-19, two distinct pathophysiological mechanisms are believed to independently and simultaneously cause PE, namely immobility and local immune-induced thrombosis. The first pathological mechanism is characterized by blood stasis, the leading risk factor for thromboembolic disease. The second one is attributed to pulmonary microvascular endothelial damage associated with systemic and local proinflammatory factors, leading to a coagulation cascade. This condition is aggravated by hypoxia, which augments thrombosis by both increasing blood viscosity and activating hy-

poxia-inducible transcription factor-dependent signaling pathway (4). The main targets of severe acute respiratory syndrome of coronavirus-2 (SARS-CoV-2) infection are pulmonary epithelial cells, lymphocytes and vascular endothelium, especially in the elderly (5). Manifestations of COVID-19 range from asymptomatic infection and mild upper respiratory illness with flu-like symptoms to severe bilateral pneumonia, critical respiratory condition requiring intensive care unit admission and mechanical ventilation, acute respiratory distress syndrome, multi-organ failure and death (1). In patients with prominent pneumonia, both damage to the lung vascular bed and necrosis of the lung parenchyma were observed (6). These findings are remarkably similar to that of PE. Autopsy studies report widespread microthrombosis and endothelial injury more prominently within COVID-19-affected lungs compared to other pulmonary infections (6). Lung autopsies of COVID-19 patients revealed microangiopathy of alveolar capillaries with 69–91 % of thrombi in segmental and subsegmental pulmonary arteries (7, 8). PE in COVID-19 patients is seen at various stages of the illness and can occur despite thromboembolic prophylaxis with low-molecular-weight heparin (9).

The current modality of choice for PE imaging is computed tomography pulmonary angiography (CTPA). Considering its widespread availability and high accuracy in making the diagnosis of PE, there is a low-threshold tendency for its overutilization. Thrombotic lesions found in COVID-19-related PE involve distal and peripheral arteries of the lungs more frequently when compared to PE found in non-COVID-19 patients (8, 10). A meta-analysis of 4,382 hospitalized patients with COVID-19 has shown a 17.6 % incidence of PE, with a substantially higher rate among those with severe condition (1). Thus, the incidence of PE in COVID-19 varies widely in the literature and therefore the uncertainty as to which patients should be imaged remains (11).

The primary goal of the present study was to determine the location and distribution of PE, presence of signs potentially indicative of right heart overload on CTPA in COVID-19 and non-COVID-19 patients. We also evaluated the extent and severity of COVID-19-associated lung changes in relation to PE.

Materials 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 in Bratislava, Slovakia. This retrospective study was approved by our institutional ethical review board with the written consent waived. This was a retrospective study based on routine clinical data, so no written informed consent was required. No author has any conflict of interest to declare in relation to this study. This study enrolled all consecutive adult patients with suspected acute pulmonary embolism who had undergone CTPA 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 term "CT pulmonary angiography" to identify CTPA. The hospital electronic medical record (MEDEA, Bratislava, Slovak Republic) for these patients was reviewed to identify clinical and laboratory data. All patients included in the study were 18 years of age or older. We excluded patients with no data on their clinical condition and cases with unavailable laboratory results. Patients with technically inadequate CT studies and those outside of the region were excluded as well. Two cohorts are detailed below.

A: Patients with COVID-19, i.e., those with positive polymerase chain reaction (PCR) tests or high index of clinical and radiological suspicion, consistent symptoms (respiratory symptoms, fever, dry cough, dyspnea, myalgia) and lung parenchyma lesions characteristic for COVID-19 infection on 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. Radiological features of COVID-19 on lung CT include bilateral peripheral subpleural ground-glass opacities, inter-/intralobular septal thickening, airspace opacification, alveolar consolidations, traction bronchiectasis, and organizing pneumonia (12).

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

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). The CTPA examinations were reviewed 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 and their laboratory results. Discrepancies were resolved by consensus between two experienced general radiologists. CTPAs were retrospectively reviewed to extract the following imaging features: presence of pulmonary embolism, ground-glass opacities, consolidations, fibrotic changes, pleural effusion, right heart strain, pneumothorax, mass, and non-COVID-19 pneumonia. The diameter of pulmonary artery was measured and mediastinal lymph node enlargement was assessed. Based on CTPA results, each group of patients (COVID-19 and non-COVID-19 patients) was divided into 2 subgroups: a subgroup with positive PE and subgroup with negative PE. Depending on the location of the most proximal and distal filling defects, the thromboembolic involvement was classified as: a) central, if the most proximal thrombus was located in the trunk of the pulmonary artery, in the main pulmonary arteries, or in the proximal lobar or segmental arteries, b) peripheral, if the distal segmental or subsegmental arteries were involved, or c) both. The distribution of the pulmonary thromboembolic disease (whether these were seen in lung areas demonstrating COVID-19 changes) was also noted. The presence of vascular signs potentially indicative of right heart overload (dilation of the right heart chambers and reflux of contrast agent into the inferior vena cava (IVC)) were also noted. The right ventricular (RV) and left ventricular (LV) diameters were measured to calculate the RV/LV ratio, a surrogate marker of embolic burden on the heart. The right heart chamber

was measured on a 4-chamber plane and right ventricular dilation was considered to be present when the right ventricular chamber was larger than the left one, that is, when the right/left ventricle ratio exceeded the value of 1.0. In accordance with the Fleischner Society´s Glossary of Terms, the COVID-19 changes involving the lung parenchyma were classified by their dominant pattern into four groups: a) normal lungs, b) predominance of ground-glass opacities, c) predominance of consolidations, and d) predominance of fibrotic lines with architectural distortion (13). According to criteria set out by the British Society of Thoracic Imaging (BSTI), the severity of COVID-19 lung changes was visually graded as follows: 1 – normal lungs (0 %), 2 – mild (1–25 %), 3 – moderate (26–50 %), 4 – severe (51–75 %) or 5 – very severe changes (76–100 %) (14).

Statistical analysis

The study 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. The comparison of factors in two groups was done by the Fisher exact test. Wilcoxon-Mann-Whitney test was used to compare population medians in two subpopulations. Results with p-values below 0.05 were considered statistically significant.

Results

In the course of the COVID-19 pandemic, from March 1, 2020, to April 30, 2022 (26 months in total), there were 1,774 CTPA examinations performed at the Clinic of Radiology in Martin University Hospital (Fig. 1), of which 76 (4 %) were excluded because of suboptimal vascular opacification, severe motion artifacts, age below 18, or when patients examined were outside of our region. Out of the total number of 1,698 CTPAs in this study, 468 (27.56 %) were COVID-19-positive patients, in whom COVID-19 was confirmed by a positive PCR test or by typical clinical and radiological findings and 1,230 (72.44 %) patients were considered as being COVID-19 negative because of negative PCR tests or due to lack of typical clinical and radiological findings. Out of 468 COVID-19 patients, pulmonary embolism was found in 90 (19.23 %) cases. Out of 1.230 non-COVID-19 patients, pulmonary embolism was found in 213 (17.32 %) cases.

Considering the distribution of PE in COVID-19 patients, there was a significant predominance of PE in peripheral segmental and subsegmental branches of pulmonary artery (63 % of COVID-19 cases with PE were only peripherally compared to 46 % in non-COVID-19 patients, $p < 0.001$). In both COVID-19 and non-COVID-19 patients there was an increased RV/LV ratio in cases with PE. In COVID-19 patients, the ratio was 0.94 (0.84, 1.10); $p = 0.032$. In non-COVID-19 group, it was higher, namely 0.97 (0.85, 1.18); $p < 0.001$. IVC reflux was significantly more prevalent in non-COVID-19 patients with PE compared to those with no PE (40 % of patients with PE had reflux as compared to 31% in those with no PE; $p = 0.013$). In COVID-19 group, there was no significant difference (33 % in subgroup with PE as compared to 27 % in subgroup without PE; $p = 0.2$) (Tabs 1 and 2).

The most common incidental finding on CTPA, regardless of COVID-19, was lymphadenopathy with no significant difference in relation to PE. The second most common incidental finding was pleural effusion with a significant increase in the case of pulmonary embolism in both COVID-19 and non-COVID-19 groups. Only 15 % of COVID-19 patients without PE had pleural effusion while in those with PE, this number increased to 31 % ($p < 0.001$). In non-COVID-19 patients without PE, pleural effusion was present in 28 % of cases; in cases with PE, it was 40 % ($p < 0.001$).

When evaluating the extent of damage in lung parenchyma caused by COVID-19, no inflammatory changes were noted in 12 % of patients without PE and only in 6.7 % of patients with PE. Mild changes (1–25 % of parenchymal involvement) were present in 42 % of patients without PE and in 49 % of those with PE. Moderate changes (26–50 %) were seen in 27 % of those without PE and in 24 % with PE. A severe involvement (51–75 %) was noted in 9.3 % of patients without PE and in 12 % with PE whilst a very severe involvement (76–100 %) was present in 10 % of patients without PE, and in 7.8 % with PE. None of these lung parenchyma changes were found to be statistically significant in relation to PE (Tab. 3).

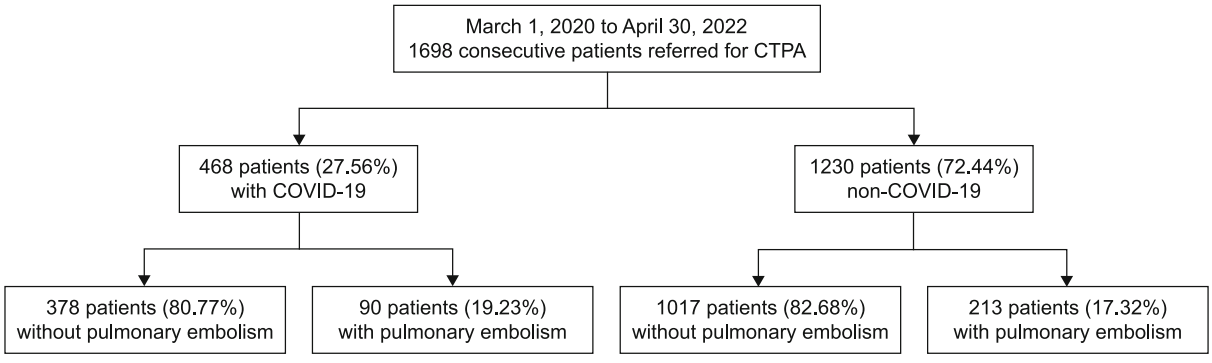

Fig. 1. Flow chart.

Tab. 1. Baseline characteristics of COVID-19 group.

Variables	Diagnosis of PE; COVID-19 group (n=468)				p
	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
Pulmonary embolism					
Central PE		0	6 (6.7%)	90	**<0.001**
Peripheral PE		0	57 (63%)	90	**<0.001**
Central and peripheral PE		0	28 (31%)	90	**<0.001**
PE in covid zones		0	49 (55%)	89	0.06
Evaluability of periphery	293 (78%)	378	69 (77%)	90	0.9
Radiology findings					
RV/LV ratio	0.91(0.81,0.97)	378	0.94 (0.84, 1.10)	90	**0.032**
IVC reflux	101 (27%)	378	30 (33%)	90	0.2
PA diameter (mm)	25.0 (23.0, 29.0)	378	26.0 (25.0, 29.0)	90	**0.039**
Fluidothorax	56 (15%)	378	28 (31%)	90	**<0.001**
Pneumothorax	2 (0.5%)	378	1 (1.1%)	90	0.5
Lymphadenopathy	140 (37%)	378	38 (42%)	90	0.4
Neoplasm	3 (0.8%)	378	1 (1.1%)	90	0.6
Non-covid inflammation	21 (5.6%)	378	8 (8.9%)	90	0.2

Data are given as median (IQR) or counts with respective percentages, p-values in bold denote statistically significant differences ($p < 0.05$)

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

Variables	Diagnosis of PE; non-COVID-19 group (n=1230)				p
	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**
Pulmonary embolism					
Central PE		0	12 (5.7%)	210	**<0.001**
Peripheral PE		0	96 (46%)	210	**<0.001**
Central and peripheral PE		0	101 (48%)	210	**<0.001**
Evaluability of periphery	921 (91%)	1016	191 (91%)	210	0.9
Radiology findings					
RV/LV ratio	0.92 (0.83, 1.04)	965	0.97 (0.85, 1.18)	203	**<0.001**
IVC reflux	312 (31%)	1016	83 (40%)	210	**0.013**
PA diameter (mm)	11.0 (8.0, 15.0)	1017	13.0 (9.0, 16.8)	210	**<0.001**
Fluidothorax	281 (28%)	1017	83 (40%)	210	**<0.001**
Pneumothorax	12 (1.2%)	1017	1 (0.5%)	210	0.7
Lymphadenopathy	260 (26%)	1017	58 (28%)	210	0.5
Neoplasm	87 (8.6%)	1017	13 (6.2%)	210	0.3
Non-covid inflammation	197 (19%)	1017	44 (21%)	210	0.6

Data are given as median (IQR) or counts with respective percentages, p-values in bold denote statistically significant differences ($p < 0.05$)

Tab. 3. COVID-19 changes in lungs.

Variables	Diagnosis of PE; COVID-19 group (n=468)				p
	No (n = 378)	No of patients	Yes (n = 90)	No of patients	
Severity 0% (BSTI)	44 (12%)	378	6 (6.7%)	90	0.2
Severity 1–24% (BSTI)	160 (42%)	378	44 (49%)	90	0.3
Severity 25–49% (BSTI)	101 (27%)	378	22 (24%)	90	0.7
Severity 50–74% (BSTI)	35 (9.3%)	378	11 (12%)	90	0.4
Severity 75–100% (BSTI)	38 (10%)	378	7 (7.8%)	90	0.5
GGOs	309 (82%)	378	75 (83%)	90	0.7
Consolidations	77 (20%)	378	18 (20%)	90	>0.9
Fibrotic changes	8 (2.1%)	378	3 (3.3%)	90	0.4
None	44 (12%)	378	6 (6.7%)	90	0.2

Up to 82 % of COVID-19 patients without PE and 83 % with PE had ground-glass opacities as a dominant radiological finding on CTPA. Lung consolidations were found in 20 % of cases in both groups. The frequency of fibrotic changes was low, with only 2.1 % in COVID-19 patients without PE and 3.3 % with PE. In some cases, a combination of these changes was present.

Discussion

The current study was focused on the evaluation of the distribution of pulmonary thromboembolism, parenchymal COVID-19 changes, and severity of parenchymal involvement. A high prevalence of right heart strain has also been noted, which raises the possibility of PE being more lethal in patients with COVID-19. McGettrick et al report that COVID-19 also predisposes to pulmonary embolism and that associated incidence of PE may be substantially higher than has been reported in association with other viral or bacterial pneumonic illnesses (15). Out of 468 (27.56 %) CTPAs in COVID-19 patients, pulmonary embolism was found in 90 (19.23 %) cases. Out of 1,230 (72.44 %) CTPAs in non-COVID-19 patients, PE was found in 213 (17.32 %) cases. Grillet et al, Leonard-Lorant et al report the incidence of pulmonary emboli in COVID-19 patients to be between 16.5–38 % (16, 17). The large range in PE incidence, reported also by Liu et al, reflects the heterogeneity and small sample size of the studies included, with most studies having less than 100 subjects from single institutions (18). Riyahi et al report that in their multi-center study of 413 patients hospitalized with COVID-19 and suspected for PE, pulmonary embolism was found in 25 % (95% CI: 21–29 %) (19). El-Sayed et al report that PE was diagnosed in 23.6 % of the cases versus 6.9 % in non-COVID-19 patients (20). Chamorro et al report that PE was seen on a CTPA in 89 of 342 patients with COVID-19 (26 %; 95% CI: 21.7–30.1 %), and in 24 of 147 patients without COVID-19 (16.3 %; 95% CI: 11.2–23.1 %) (21). This difference was statistically significant (p=0.0197). The difference in 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). Porfidia et al report a

recent meta-analysis of 3,487 COVID-19 patients from 30 studies produced a 26 % pooled incidence of venous thromboembolism but concluded that the existing evidence was of low-quality and heterogeneous (5).

According to the literature, the most common radiological findings in COVID-19 pneumonia are the ground-glass opacities, which was confirmed also in our study. When evaluating the parenchymal involvement in COVID-19, it was noted that lung changes were not statistically significant in relation to PE. Badr et al report that there was no statistically significant difference between case and control groups in terms of the CT parenchymal findings ($p > 0.05$) (22). Yassin et al and Bompard et al report that the radiological severity of infection was found to be insignificant with the incidence of PE (23, 24). Chamorro et al report that parenchymal involvement in COVID-19 patients with PE was classified as normal in 5.6 % of patients, with a predominance of ground-glass opacities in 32.6 % of patients, with predominance of alveolar consolidations in 40.4 % of patients, and featuring consolidations with architectural distortion in 21.3 % of patients (21). The severity according to the extent of lung involvement was classified as normal in 5.6 % of patients, mild in 15.7 % of patients, moderate in 46.1 % of patients and severe in 32.6 % of patients. No statistically significant differences were found in the distribution of PE between the proximal, medial or distal pulmonary arterial tree and extent of COVID-19 involvement (normal, mild, moderate or severe) ($p = 0.78$), or type of parenchymal involvement (normal, ground-glass opacities, consolidations or consolidations with architectural distortion) ($p = 0.06$). CT showed a moderate or severe pulmonary involvement in 78.7% of patients with COVID-19 and increased prevalence of pulmonary embolism (26 %). Ooi et al report that 7 % of patients had a very severe disease, 23 % had a severe disease, 35 % had a moderate disease, 21 % had a mild disease whilst the remaining 14 % had either normal lungs or non-COVID-19 appearances on CT (25). The severity of disease was higher in the PE-positive group ($p = 0.005$). Half of the patients with moderate, severe, or very severe disease had PE, whilst only 17 % of patients with normal lungs or mild disease had PE and 84 % of PE-positive patients had moderate, severe or very severe disease.

The incidence of peripheral segmental and subsegmental PE was higher in the COVID-19 group in comparison to the non-COVID-19 group (63 % of PE in COVID-19 cases was only peripherally compared to the incidence of 46 % in non-COVID-19 patients, $p < 0.001$). A similar distribution was reported by others. Our results were close to those of Ooi et al, who report that in patients with PE, 75% of thromboemboli were observed within small vessels (subsegmental or smaller) and 25 % within both small and larger vessels (25). There was no association between the severity of the disease and distribution of PE ($p = 0.95$). In 72 % of patients, PE was observed in regions of lungs demonstrating COVID-19 changes. Over 70 % of patients with a disease severity of 3 or more had PE seen in affected lungs, however, the difference was not statistically significant ($p = 0.2$). A recent study on lung autopsy findings noted that alveolar microthrombi were up to 9 times more prevalent in patients who died from COVID-19 when compared to uninfected control lungs (8, 10, 19, 22, 26, 27). We can conclude that thrombotic lesions found in COVID-19-related PE involve distal, peripheral arteries of the lungs more frequently when compared to PE found in non-COVID-19 patients.

In both COVID-19 and non-COVID-19 patients, there was an increased RV/LV ratio in cases with PE. In COVID-19 patients, the ratio was 0.94 (0.84, 1.10); $p = 0.032$. In non-COVID-19 patients, it was higher, namely 0.97 (0.85, 1.18); $p < 0.001$. IVC reflux was significantly more prevalent in non-COVID-19 patients with PE as compared to those with no PE (40 % of patients with PE had reflux as compared to 31 % in patients with no PE; $p = 0.013$). Riyahi et al concluded that prior studies report that about half of the patients with PE have some degree of right ventricular compromise which is associated with PE and syncope as well as higher mortality (19). An estimated 25 % of the pulmonary vasculature needs to be occluded to result in pulmonary hypertension while acute right heart failure requires an occlusion of more than 50 %. Higher rates of RV strain in these patients can be seen because their pulmonary vasculature is already compromised by infection. Right ventricle systolic dysfunction was previously reported in patients with COVID-19 without PE due to the release of vasoactive mediators such as serotonin, thromboxane, and histamine, in response to the acute hypoxic injury and platelet-rich clots, which may also contribute to right heart strain in these patients. Besides, a recent study has demonstrated that patients showed signs of right heart overload on CT, although these differences did not attain statistical significance (19, 21, 23, 27, 28). Badr et al report that right ventricular dysfunction was more common among the case group as compared to the control group, whereas the distribution of left ventricular dysfunction and systolic pulmonary hypertension between the two groups were the same (22). Martiny et al report that half of the COVID-19 patients with patterns resembling infarction pneumonia on CT showed signs of right heart failure and pulmonary hypertension on CT (increased diameter of the pulmonary artery and RV/LV ratio) (29). Median RV/LV ratio tended to be higher in patients whose CTs had shown signs of infarction pneumonia as compared to the patients without this pattern (RV/LV of 0.88 and 0.94, respectively).

There are several limitations to the current study. Firstly, it is 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 solely in patients with clinical and laboratory data suspicious for PE wherefore 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, the presence of PE in some patients is likely to have been missed, namely in those that did not undergo CTPA.

Conclusion

COVID-19 was associated with a higher incidence of peripheral location of PE in comparison to non-COVID-19 group. In

addition to the important exclusion of life-threatening pulmonary embolism, CTPAs showed various associated findings. The most common radiological findings in COVID-19 pneumonia were the ground-glass opacities, but the differences in parenchymal involvement in COVID-19 changes were not statistically significant in relation to PE. There was a presence of signs indicative of right heart overload in cases with PE regardless of COVID-19.

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Received April 3, 2023.
Accepted April 24, 2023.