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Pulmonary Embolism Associated with COVID-19 Occurs in Predominantly Elderly Patients with Comorbidities: A Single Center Retrospective Study

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Abstract

Introduction: Complications of COVID-19 infection have been greatly investigated. The most recent studies found strong association of COVID-19 pneumonia with thromboembolism. The aim of research was to describe clinical and computed tomography pulmonary angiograms (CTPA) characteristics of COVID-19 related pulmonary artery thromboembolism (PE). **Methods:** All consecutive CTPA with positive PE in COVID-19 patients from University Hospital Split, from March 23, 2020 to January 31, 2021 were analyzed. Baseline data were collected from patient's electronic records. CTPA scan analysis identified PE anatomical location (i.e., main, lobar, segmental, or subsegmental). **Results:** A total number of 78 positive CTPA in COVID-19 patients was mainly in elderly with several co-morbidities, high D-dimer levels, at median of 14 days. CTPAs showed involvement of the entire pulmonary artery tree, mainly of the small-to medium diameter pulmonary artery branches, unilaterally ($n = 31$, 39,74%), and bilaterally ($n = 33$, 42.31%). The large-diameter branches were the most rarely affected as a single location ($n = 14$, 17.95%). **Conclusion:** PE occurred in predominantly elderly people, having several comorbidities, and high D-dimer levels. Embolic involvement of pulmonary branches of all sizes were found, the most frequent of small to medium diameter branches. Further investigation is needed to better understand mechanisms and course of the COVID-19 related PE.

Keywords

CT angiography, pulmonary embolism, SARS-CoV-2, COVID-19, thrombosis, cardiovascular complications

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Introduction

The COVID-19 complications have been greatly investigated since the onset of the disease in December 2019 in China. Cardiovascular complications are pretty common causing great morbidity and mortality worldwide. The most recent research found strong association of COVID-19 pneumonia with venous and arterial thromboembolisms (Middeldorp et al., 2020), especially in the elderly population, although the exact mechanisms of the proposed thrombo-inflammation require additional explanation. Radiologists noticed high incidence rate of the pulmonary embolism (PE), even despite thromboprophylaxis given. So far, there are several published case reports (Brüggemann et al., 2020; Cellina & Oliva, 2020; Jafari et al., 2020) and researches (Espallargas et al., 2021; Grillet, 2020; Karolyi et al., 2021; Leonard-Lorant et al., 2020; Lodigiani et al., 2020; Planquette et al., 2021) addressing the PE in a setting of COVID-19 infection. Literature showed the thrombotic complications occurred most often in seriously ill individuals (Middeldorp et al., 2020) even without risk factors and in some cases even despite the given thromboprophylaxis. They were associated with poor outcome in many patients (Zhou et al., 2020), especially in those having high D-dimer levels (Tang et al., 2020).

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The main objective of our research was to describe clinical and computed tomography (CT) characteristics on a large sample of confirmed pulmonary emboli in patients with COVID-19.

Methods

The consecutive CT pulmonary artery angiograms (CTPA) performed for suspected PE in COVID-19 positive patients from March 23, 2020 to January 31, 2021 were retrieved. Patients with confirmed PE on CTPA were included in the study. Given the retrospective non-interventional research setting, the informed consent form was waived. All personal information was anonymized prior to publication. Each procedure was in accordance with the ethical standards of our institution.

Demographic, clinical, and laboratory data were collected from patient's electronic records. COVID-19 was confirmed by a positive qRT-PCR test (LightMix® Modular SARS and Wuhan CoV E-gen and RdRP-gen kit, Cobas 480 Roche).

Imaging data were extracted from imaging data base. CTPAs were analyzed by radiological presentation (location and appearance of PE) and were described based on PE location of the most proximal luminal defect (i.e., main, lobar, segmental, or subsegmental level). CT angiograms were acquired on 128 slice multislice CT (Philips, Inguenity Elite) after i.v. injection of 50 to 70 mL high concentration iodinate contrast media, using a bolus-tracking technique, and threshold on the main pulmonary artery.

Non-parametric tests were selected to analyze the data, given the sample size, and normality of distribution (Smirnov-Kolmogorov test). A median (interquartile range, Q1–Q3) was used for data description.

Results

Of a total number of 280 CTPA performed in COVID-19 patients, PE was diagnosed in 78 angiograms. Patients with PE were predominantly elderly people with median 71 (Q1–Q3 62.5–80.5) years, with slight male predominance ($n=49$, 62.82%). Majority of them ($n=64$, 82.06%) had at least one comorbidity and 14 (17.94%) was without any comorbidity. Hypertension was the most common one, found in 34 (43.58%) PE patients, alone or in combination with other diseases, such as diabetes or cardiac diseases. The next most common comorbidity was diabetes mellitus type II, found in 11 (14.10%) patients, alone or in combination with hypertension. The third most common comorbidity was carcinoma (colon, breast, bladder, kidney, and bladder) in 10 (12.82%) patients. Other rarely found comorbidities were autoimmune diseases (i.e., psoriasis), cardiac diseases, gallbladder stones, and psychiatric disorders. Any association of particular comorbidity and CT presentation of PE was not noticed. PE patients had high D-dimer levels (median 12.51, Q1–Q3 8.00–28.04). PE occurred at median of 14 (Q1–Q3 11–19.5) days from setting the COVID-19 diagnosis. In three patients, the PE symptoms occurred several days to several weeks following hospital discharged after confirmed COVID-19 negativization and complete clinical recovery (all three patients had been previously hospitalized at non-ICU). The rest of the patients were COVID-19 positive at time of CTPA preformed. A total of 50 patients (61.10%) were PE diagnosed on the days of admission, others ($n=28$, 38.90%) were hospitalized. All hospitalized patients were given thromboprophylaxis before PE onset; however, data about thromboprophylaxis in patients diagnosed at admission were partially incomplete (therefore not shown). Basic demographic and clinical data are summarized in Table 1.

CTPA in almost half of the PE patients showed the unilateral pulmonary embolism, most commonly involving one of the segmental or subsegmental branches ($n=23$, 29.49% of a total number of PE patients) or two or more of them unilaterally ($n=8$, 10.25%), generally including regions of COVID-19 inflammation-related CT changes. The similar percent of the pulmonary tree affection was bilateral, involving multilobar/multisegmental levels in 33 patients (42.31%). It included affection of branches of all-sizes and numerous combinations of pulmonary embolism locations, not necessarily related to CT inflammatory changes, shown in Table 1. The pulmonary trunk, main, and lobar arteries were the most rarely affected as a single vessel ($n=14$, 17.95%), Table 1. The right side of the lung was in general more often affected comparing to the left. CT appearance of thromboembolic events on pulmonary artery is presented on Figure 1.

Discussion

In our population-based sample, PE occurred in predominantly elderly people, that had several comorbidities (hypertension in a high percentage, followed by diabetes, and carcinomas), and high D-dimer levels, with a median of 14 days from onset of COVID-19. These predisposing factors are generally in accordance with the previous published literature (Bompard, 2020; Grillet, 2020; Leonard-Lorant et al., 2020; Lodigiani et al., 2020). Possible mechanisms of thrombosis in found comorbidities were probably related to an endothelial injury or higher levels of inflammatory markers, common in physiopathology of these entities. Approximately two-weeks for the PE occurrence after COVID-19 onset is almost identical in all previous researches (Espallargas et al., 2021; Planquette et al., 2021). However, in our study in three patients, PE occurred after being discharged from hospital, felt well for a short time and some of them even did not have any

Table 1. Baseline and CT Pulmonary Angiography Characteristics of 78 COVID-19 Patients with Pulmonary Embolism.

Characteristics	COVID-19 patients with pulmonary emboli, *n* = 78
Age (years)—median (Q1-Q3)	71 (62.5–80.5)
Male—no (%)	49 (62.8)
D-dimes—median (Q1-Q3)	12.51 (8.00–28.04)
Onset of PE (days)—median (Q1-Q3)	14 (11–19.5)
Sites of PE:	
Main pulmonary artery	Truncus pulmonalis, *n* = 2
	Right main, *n* = 2
Lobar artery	RML *n* = 3, RLL *n* = 4, LLL *n* = 2, LUL *n* = 1
Segmental	RLL *n* = 5, RUL *n* = 1, LUL *n* = 3, LLL *n* = 2
Subsegmental	RLL *n* = 2, RUL *n* = 2, RML *n* = 2
	LLL *n* = 4, LUL *n* = 2
Multilobar/segmental, unilateral:	RUL + RML + RLL *n* = 4
	RML + RLL *n* = 3
	left main + LUL + LLL *n* = 1
Multilobar/multisegmental, bilateral:	SS in LUL + RLL *n* = 2
	S LUL + RML *n* = 1
	RLL and LLL S *n* = 2
	S and SS RML + RLL *n* = 1
	S in RUL + LLL *n* = 1
	RML + RLL + LLL *n* = 1
	RUL + RML + LLL *n* = 2
	SS in all lobes *n* = 7
	S both LL *n* = 3
	S both UL *n* = 3
	S LUL + RUL *n* = 1
	S LUL + RML + RLL *n* = 1
	Both main + both UL + RML *n* = 1
	Both main + all lobes *n* = 1
	L main + both LL *n* = 2
	R main + both LL *n* = 1
	R main + both UL *n* = 1
	R main + both UL + LLL *n* = 1
	R main + LLL *n* = 1

Note. PE = pulmonary emolism; RML = right middle lobe; RLL = right lower lobe; LLL = left lower lobe; LUL = left upper lobe; RUL = right upper lobe; L = left; R = right; UL = upper lobe; LL = lower lobe; S = segmental; SS = subsegmental.

inflammatory consolidations visible at the time of CTPA scanning. The similar observation was published, to our knowledge, just in one case-study (Karolyi et al., 2021). The finding of COVID-19 negativization and an occurrence of thrombotic events is confronting current research results showing high PE incidence in seriously ill patients with COVID-19 pneumonia in critical care units (Grillet, 2020; Leonard-Lorant et al., 2020; Middeldorp et al., 2020) and it warrants further investigation. In general, the occurrence of thromboembolism in COVID-19 might suggest consideration of better therapeutic options (Kowalewski et al., 2020; Ranucci, 2020). It is important that effective thromboprophylaxis practice is re-evaluated for all some patients with COVID-19 infection.

Secondly, pulmonary embolism involved each branch of the pulmonary tree. PE occurred more frequently on the right side of the lung, was located typically into or near the CT detectable COVID-19 inflammatory changes and more often involved small-to medium diameter branches unilaterally or bilaterally. These results are generally in accordance with majority of recently published studies (Espallargas et al., 2021; Grillet, 2020; Leonard-Lorant et al., 2020; Lodigiani et al., 2020; Planquette et al., 2021), who described PE distribution within pulmonary tree. The potential pathogenic mechanism proposed was an in situ microvascular thrombosis within diseased lung region mainly related to COVID-19 inflammation (Wichmann et al., 2020) or concomitant endothelial injury effect (Smadja et al., 2020), leading a possible explanation of a higher PE incidence in the small-diameter vessels in diseased lung region. The relatively high incidence of bilateral and multisegmental/multilobar involvement should raise suspicion of mechanisms other than local inflammation involved. Some authors found high levels of cytokines, among which increased expression of interleukin-6 might play role in deep venous thrombosis incidence

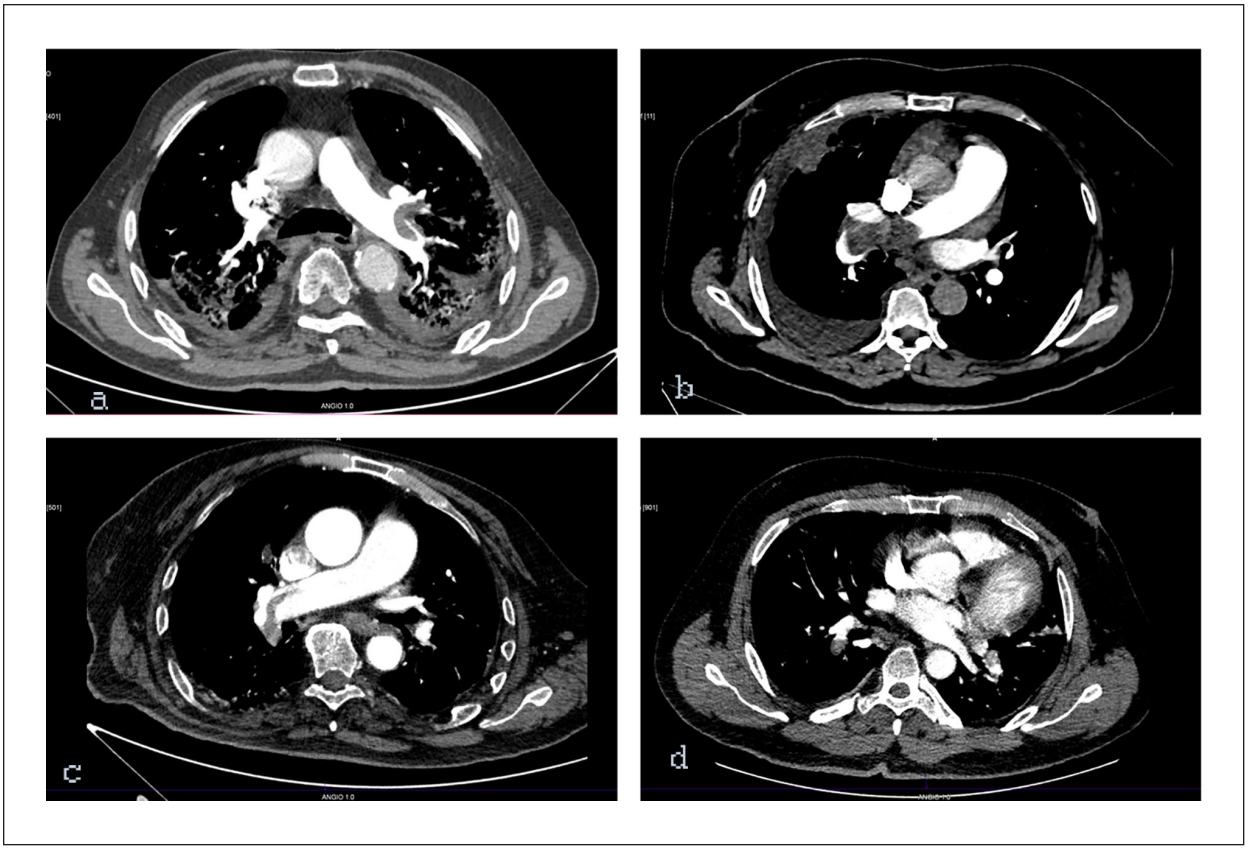

Figure 1. Representative CT pulmonary angiograms showing pulmonary emboli in COVID-19 patients in acute phase (a and b) of the disease and after overcoming virus infection (c and d).

(Zhang et al., 2020). As was further proposed in the study of Espallargas et al. (2021), higher frequency of right lung involvement is higher blood flow distribution to the right lung. However, the exact mechanisms of PE in COVID-19 are yet to be investigated and would certainly help in understanding of PE occurrence within pulmonary tree.

Conclusions

This study conducted on a large sample of positive CTPA in COVID-19 patients showed PE occurred in predominantly elderly people, having several comorbidities, and high D-dimer levels. Pulmonary branches of all sizes were affected, more commonly small-to medium sized branches, unilaterally, and bilaterally in almost equal percent. Further investigation is needed to better understand the mechanisms and course of the COVID-19 related PE.

Declaration of Conflicting Interests

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