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CT features of pulmonary embolism in patients with COVID-19 pneumonia

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Abstract. – OBJECTIVE: The aim of this study was to describe the Computed Tomography (CT) features of pulmonary embolism in patients hospitalized for acute COVID-19 pneumonia and to evaluate the prognostic significance of these features.

PATIENTS AND METHODS: This retrospective study included 110 consecutive patients who were hospitalized for acute COVID-19 pneumonia and underwent pulmonary computed tomography angiography (BTPA) on the basis of clinical suspicion. The diagnosis of COVID-19 infection was determined by CT findings typical of COVID-19 pneumonia and/or a positive result of a reverse transcriptase-polymerase chain reaction test.

RESULTS: Of the 110 patients, 30 (27.3%) had acute pulmonary embolism and 71 (64.5%) had CT features of chronic pulmonary embolism. Of the 14 (12.7%) patients who died despite receiving therapeutic doses of heparin, 13 (92.9%) had CT features of chronic pulmonary embolism and 1 (7.1%) of acute pulmonary embolism. CT features of chronic pulmonary embolism were more common in deceased patients than in surviving patients (92.9% *vs.* 60.4%, *p*=0.01, respectively). Low oxygen saturation and high urine microalbumin creatinine ratio at admission in COVID-19 patients are important determinants of mortality after adjusting for sex and age in logistic procedures.

CONCLUSIONS: CT features of chronic pulmonary embolism are common in COVID-19 patients undergoing Computed Tomography Pulmonary Angiography (CTPA) in the hospital. The coexistence of albuminuria, low oxygen saturation and CT features of chronic pulmonary embolism at admission in COVID-19 patients may herald fatal outcomes.

Key Words:
COVID-19 pneumonia, CT features, Chronic pulmonary embolism, In-hospital mortality.

Abbreviations
PE, Pulmonary Embolism; COVID-19, coronavirus disease 2019; CRP, C- reactive protein.

Introduction

COVID-19, the virus responsible for the current pandemic, mostly affects the respiratory system[1,2]. Although symptoms are not specific, common symptoms are non-productive cough, fever, myalgia or fatigue, high leukocyte count, and radiographic evidence of pneumonia[3]. Although the majority of infected individuals develop only mild symptoms or are asymptomatic, in others the spectrum of the disease may progress to severe pneumonia and multiple organ failure[4]. COVID-19 pneumonia causes systemic hyperinflammation and abnormal coagulation profile[5]. In addition, cytokine storm syndrome is thought to cause a hypercoagulable state in individuals with COVID-19[6,7]. Venous thromboembolism, which is a common cardiovascular and/or respiratory complication in hospitalized patients due to COVID-19, is one of the known sequelae of the disease[8]. COVID-19 can cause systemic coagulation activation and life-threatening pulmonary embolisms[9,10]. Pulmonary embolism (PE) appears to be an important problem in COVID-19[11]. In suspected clinical PE in COVID-19 patients, the physician should use additional diagnostic methods to confirm or exclude PE, even if D-dimer levels are within the normal range[12]. Early detection of pulmonary embolism in patients with COVID-19 infection is important in the management of these patients[13]. New data showing the long-term risks of pulmonary vascular sequelae after COVID-19 indicate that the current approach (visual evaluation by a single radiologist) used to identify vascular abnormalities during the acute phase is not sufficient to detect pulmonary vascular disease, which may have an important chronic component[14].

Pulmonary embolism is a relatively common complication in COVID-19 patients that can increase the risk of death. The aim of this study was to describe the Computed Tomography (CT) features of pulmonary embolism in patients hospitalized

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for acute COVID-19 pneumonia and to evaluate the prognostic significance of these features.

Patients and Methods

This retrospective study included 110 consecutive patients who were hospitalized for acute COVID-19 pneumonia and underwent Computed Tomography Pulmonary Angiography (CTPA) on the basis of clinical suspicion. Demographics and clinical and laboratory data were obtained from electronic hospital medical records.

Contrast-enhanced CT was performed to exclude PE when additional oxygen was needed in COVID-19 pneumonia patients with limited disease extension, when non-contrast CT findings could not explain the severity of respiratory failure[15]. Additional indications for CTPA were based on acute dyspnea, oxygen desaturation (>5% decrease from baseline), hemoptysis, syncope, chest pain, increase in D-dimer levels, or sudden worsening of the patient's clinical condition[16].

Symptoms for COVID-19 pneumonia included dry cough, expectoration, fever >37.3, throat pain, dyspnea, fatigue, gastrointestinal symptoms (diarrhea, nausea, and vomiting), myalgia, headache, loss of taste, odor[17].

Patients were included according to the following criteria: patients over 18 years of age who were hospitalized for acute COVID-19 pneumonia and had chest CT angiography performed on the basis of clinical suspicion. The diagnosis of SARS-CoV-2 infection was made by CT findings typical of COVID-19 pneumonia and/or by a positive reverse transcriptase-polymerase chain reaction test[18]. All initial samples were received *via* nasopharyngeal swab; some patients were done a second or third sampling.

Exclusion criteria were: (I) patients with non-contrast chest CT scans; (II) patients with artifacts on pulmonary CT angiography hindering image quality; (III) patients who were hospitalized for conditions judged unrelated to COVID-19 infection[19].

In addition to general supportive therapy, patients received therapeutic anticoagulation with low molecular weight heparin (enoxaparin) or unfractionated heparin in case of glomerular filtration rate <30 mL/min for 3 months.

Multidetector Computed Tomography (MDCT)

CT angiograms were taken after injection of 50-75 mL of high-iodine-containing contrast medium (MSCT, Philips Medical System, Brillance 64; Best, The Netherlands) in a 64-row scanner. Images were made using the 160-250 HU threshold and bolus tracking technique in the main pulmonary artery. Sections of 1 mm section thickness were obtained in the mediastinal and parenchymal windows[20].

Image Analysis

The consensus of two pulmonologists, who did not know the clinical data of the patients, was evaluated as the reference standard for the diagnosis of PE. Embolism (or pulmonary thrombosis) in the main or lobar pulmonary arteries as central, and those in only segmental or subsegmental arteries were categorized as peripheral. The most proximal location of the PE determines its category (central or peripheral)[21]. The following features were used to define COVID-19 pneumonia: presence of ground glass opacities (GGO), consolidation, GGO/consolidation, air bronchogram, vascular or bronchial wall thickening, or crazy-paving pattern as peripheral distribution, lower lobe dominance, and bilateral multiple foci[22]. Signs of acute pulmonary embolism are partial filling defect with acute angle, enlarged complete artery occlusion, polo mint mark, railway track mark, triangular subpleural consolidation. Signs of chronic pulmonary embolism are partial filling defect that makes an obtuse angle with the vessel wall, shrunken complete artery occlusion, band/web, intimal irregularities, thickened small arteries, post-stenotic dilatation, tortuous vessel, bronchial collaterals, non-bronchial collaterals, variation in the size of segmental vessels, mosaic perfusion pattern, bronchial dilatation, chronic infarct appearance such as linear band, pleural nodule[23]. The presence of two or more of the direct acute or chronic radiologic signs was accepted as acute or chronic pulmonary embolism for this study[23]. However, cases with almost all CT features of acute pulmonary embolism were accepted as acute pulmonary embolism on the background of chronic disease if they also had CT features of chronic pulmonary embolism.

Measurements

Blood samples were obtained within 48 hours after admission or at admission. Urine biochemical parameters were measured in spot urine within 48 hours of admission.

Statistical Analysis

Data were defined as mean (SD) for continuous variables and as percentage for categorical

variables. Fisher's exact test or Chi-square test in comparative analyzes for categorical data were used. For continuous variables, differences between groups were compared using the *t*-test or the Mann-Whitney U test according to distribution characteristics. Odds ratios, 95% CI and *p*-values were calculated with logistic regression models using stepwise model selection technique. Predictors of mortality were determined by logistic regression between age, gender, oxygen saturation, lymphocyte count and albuminuria level. Univariate analyzes in all cases were first performed to identify possible predictors.

All variables that made significant contributions to the univariate analysis were included. Finally, the main predictors were determined by reducing the multivariate model using a stepwise model selection technique. *p*-value <0.05 was considered statistically significant. All statistical analyzes with SPSS Statistics software were performed (version 17.0) (SPSS Inc., Chicago, IL, USA).

Results

Between July 1, and December 30, 2020, outpatients referred by the Emergency Department underwent 7,136 chest CT scan for the suspicion or evaluation of COVID-19 pneumonia (Figure 1). 544 patient whose diagnosis was confirmed by clinical and chest CT findings specific to COVID-19 pneumonia and/or positive reverse transcriptase-polymerase chain reaction test was hospitalized. 116 patients with clinically suspected pulmonary embolism were referred for CT pulmonary Angiogram. Five patients with inconclusive CT pulmonary angiography and one patient who was considered unrelated to COVID-19 infection were excluded from the study. Successful CT pulmonary angiogram was obtained in 110 patients.

Of the 110 patients, 97 (88.2%) had positive Polymerase Chain Reaction (PCR), 1 (0.9%) had positive antibody (IgM) and 12 (10.9%) had negative PCR. Of the 110 patients, 61 (55.5%) were male, 49 (44.5%) were female, and the mean age was 63.3 (13.9) years.

Of the 110 patients, 30 (27.3%) had acute pulmonary embolism and 71 (64.5%) had CT features of chronic pulmonary embolism.

36.7% (11/30) of patients with acute pulmonary embolism have CT features of chronic pulmonary embolism. Patients with CT features of chronic pulmonary embolism had larger main pulmonary artery diameter [28.1 (3.7) *vs.* 25.1 (3.2), *p*=0.001, respectively], higher urine microalbumin creatinine ratio at admission [138.2 (246.8) *vs.* 45.6 (41.5), *p*=0.03, respectively] than those with any signs of acute PE.

The clinical features and radiological findings of the deceased and surviving patients are given in Table I. Of the 14 (12.7%) patients who died despite receiving therapeutic doses of heparin, 13 (92.9%) had CT features of chronic pulmonary embolism and 1 (7.1%) of acute PE.

CT features of chronic pulmonary embolism were more common in deceased patients than in surviving patients (92.9% *vs.* 60.4%, *p*=0.01, respectively).

Laboratory findings of deceased and surviving patients are given in Table II. Patients who died had a higher urine microalbumin creatinine ratio (*p*=0.01), lower lymphocyte count (*p*=0.001), higher CRP level (*p*=0.002), higher urine creatinine level (*p*=0.002), and lower oxygen saturation

Table I. Clinical features and radiological findings of COVID-19 patients.

	Surviving patients n:96	Deceased patients n:14	*p*-value
Mean age, years Poststetonic dilatation	61.8±14.0	74.0±6.0	0.002
Male sex %	51.0	85.7	0.01
Cerebral %	6.3	14.3	0.2
Oncologic %	1.0	0	0.7
Heart disease %	8.3	7.1	0.8
Lung disease %	3.1	14.3	0.06
Chronic kidney disease %	3.1	7.1	0.4
Cough %	59.4	64.3	0.7
Sputum, %	5.2	7.1	0.7
Dyspnea %	54.2	64.3	0.4
Chest pain %	3.1	0	0.5
Temperature >37.7°C %	33.3	42.9	0.4
Chills %	31.3	42.9	0.3

Table continued

Table I *(continued)*

	Surviving patients n:96	Deceased patients n:14	*p*-value
Syncope/presyncope %	1.0	0	0.7
Hemoptysis %	0	0	
Fatigue %	88.5	85.7	0.7
Body Pain %	68.8	78.6	0.4
Sore throat %	34.4	14.3	0.1
Headache %	16.7	0	0.09
Gastrointestinal symptoms %	12.5	14.3	0.8
Loss of taste, odor %	20.8	21.4	0.9
Oxygen saturation at admission	91.3±5.8	86.0±8.2	0.003
Pulmonary artery diameter	26.7±3.5	28.8±5.0	0.05
Enlarged complete artery occlusion %	31.3	21.4	0.4
Polo mint %	15.6	0	0.1
Railway track %	6.3	0	0.3
Partial filling defect with acute angle %	32.3	7.1	0.05
Triangular subpleural consolidation %	25.0	7.1	0.1
1. Internal air lucency %	25.0	7.1	0.1
2. Broad pleurally based %	25.0	7.1	0.1
3. Truncated apex %	10.4	7.1	0.7
4. Convex border of apex %	7.3	0	0.2
5. Linear stranding from apex to hilum %	16.7	7.1	0.3
6. Thickened vessels leading to the apexof the opacity %	13.5	0	0.1
Eccentric filling defect %	16.7	42.9	0.02
Shrunken complete artery occlusion %	58.3	92.9	0.01
Thickened small arteries%	62.5	92.9	0.02
Poststenotic dilatation %	44.8	78.6	0.01
Band/web %	20.8	28.6	0.5
Tortuous vessel %	11.5	28.6	0.08
Bronchial collaterals %	8.3	14.3	0.4
Nonbronchial collaterals %	2.1	7.1	0.2
Unilateral pleural effusions %	0	0	
Bilateral pleural effusions %	2.1	14.3	0.02
Chronic infarct appearance such as linear band, pleural nodule %	25.0	35.7	0.3
Peripheral parenchymal densities %	8.3	14.3	0.4
Variation in the size of segmental vessels %	3.1	0	0.5
Bronchial dilatation %	1.0	7.1	0.1
Mosaic perfusion pattern %	19.8	57.1	0.002
Central pulmonary arteries %	11.5	7.1	0.6
Lobar %	6.3	14.3	0.2
Segmental %	57.3	64.3	0.6
Subsegmental %	15.6	14.3	0.8
Unilateral pleural thickening %	3.1	0	0.5
Bilateral pleural thickening %	3.1	14.3	0.06
Pericard %	2.1	0	0.5
Atelectasis %	1.0	0	0.7
Chronic pulmonary embolism %	60.4	92.9	0.01
GGO %	76.0	71.4	0.7
Consolidation %	2.1	0	0.5
GGO mixed consolidation %	18.8	21.4	0.8
Air bronchogram %	7.3	14.3	0.3
Vascular or bronchial wall thickening %	20.8	7.1	0.2
Crazy paving pattern %	6.3	28.6	0.007
Plasma %	9.4	0	0.2
Antiretroviral %	97.9	92.9	0.2
Hydroxychloroquine %	84.4	85.7	0.8
Anti–IL-6 drugs (tocilizumab) %	5.2	7.1	0.7
Intensive care unit admission %	5.2	71.4	0.0001
Oxygen therapy %	83.3	100	0.09
Noninvasive ventilation	7.3	85.7	0.0001
Mechanical ventilation %	1.0	78.6	0.0001

Table II. Laboratory findings of COVID-19 patients.

	Surviving patients n:96	Deceased patients n:14	*p*-value
Ferritin n:94/13	479.7±388.2	805.1±670.1	0.1
Microalbumin / creatinine n:76/9	72.9±100.9	407.3±494.6	0.07
Microalbumin n:76/10	51.2±79.2	244.6±213.4	0.01
Microprotein / creatinine n:60/7	404.5±487.9	1,309.4±1,486.6	0.1
Urine creatinine n:55/8	77.2±54.0	129.1±118.0	0.2
Urine quantitative protein n: 60/7	250.3±316.0	615.2±515.5	0.1
Glucose n:90/13	153.7±77.6	176.2.0±75.7	0.3
HbA1c n:73/10	6.6±1.3	6.9±1.1	0.5
Hb n:96/14	13.0±1.7	12.9±1.7	0.8
White blood cell count mm2 n:96/14	8,529.4±3,730.7	13.448.5±7,562.6	0.03
Lymphocyte n: n:96/14	1,210.4±677.2	598.5±241.0	0.0001
Thrombocyte n:96/14	297.2±132.0	307.2±178.5	0.8
Ttriglyceride n:86/11	140.7±79.8	125.6±60.2	0.5
cholesterol n:86/11	170.4±48.2	131.0±42.5	0.01
HDL n:86/11	41.5±11.8	36.9±9.8	0.2
LDL n:86/11	99.7±35.6	68.5±30.4	0.007
D-Dimer n:96/14	1,634.4±4,045.0	1,106.8±1,024.0	0.6
Procalcitonin n:88/13	0.38±1.4	0.42±0.45	0.9
CRP n:96/14	69.4±54.2	142.5±88.7	0.009
Creatinine n:96/14	0.92±0.32	1.40±0.81	0.04
RDW n:96/14	13.9±2.0	14.0±1.4	0.8

Data are mean (standard deviation).

Table III. The predictors of mortality for COVID-19 after adjusting for gender and age in logistic procedures.

COVID-19	OR (95% CI)	*p*-value
Microalbumin at admission	1.0 (1.0 to 1.0)	0.001
Oxygen saturation at admission	0.8 (0.7 to 0.9)	0.0001

Multivariate logistic model showing adjusted odds ratios of statistically significant variables with confidence intervals (CI). Non-significant variables considered for inclusion included age, gender, and lymphocyte count.

(p=0.001) than survivors. Low oxygen saturation and high urine microalbumin creatinine ratio at admission in COVID-19 patients are important determinants of mortality after adjusting for sex and age in logistic procedures (Table III). The characteristic CT angiography findings of those who have died is seen in Figures 2-24.

Discussion

The present study indicated that CT features of chronic pulmonary embolism are common in hospitalized COVID-19 patients undergoing CTPA. In addition, these patients have a larger main pulmonary artery diameter and higher urine microalbumin level than patients with acute pulmonary embolism. CT features of chronic pulmonary embolism in present patients are not very likely to occur with COVID-19 pneumonia. It can be thought that COVID-19 is more serious in patients with chronic pulmonary embolism and these patients need more hospital treatment. Severe COVID-19 pneumonia occurring in these patients may switch chronic vascular disease from the compensated stage to the decompensated stage. Most of the studies[24-29] in the literature are related to acute pulmonary embolism co-occurring with COVID-19 infection. Later studies[14,30-33] focused on chronic vascular diseases developing after COVID-19 infection. What is investigated here is related to how many cases of acute pulmonary embolism with COVID-19 may develop chronic thromboembolic pulmonary hypertension (CTEPH). However, our study suggests that these patients with pre-existing chronic vascular changes may develop CTEPH much higher than expected. The important shortcoming of our study is that echocardiography (ECHO) evaluation was not performed in the 3rd month of the patients' treatment. We could have had preliminary information about the development of CTEPH with a

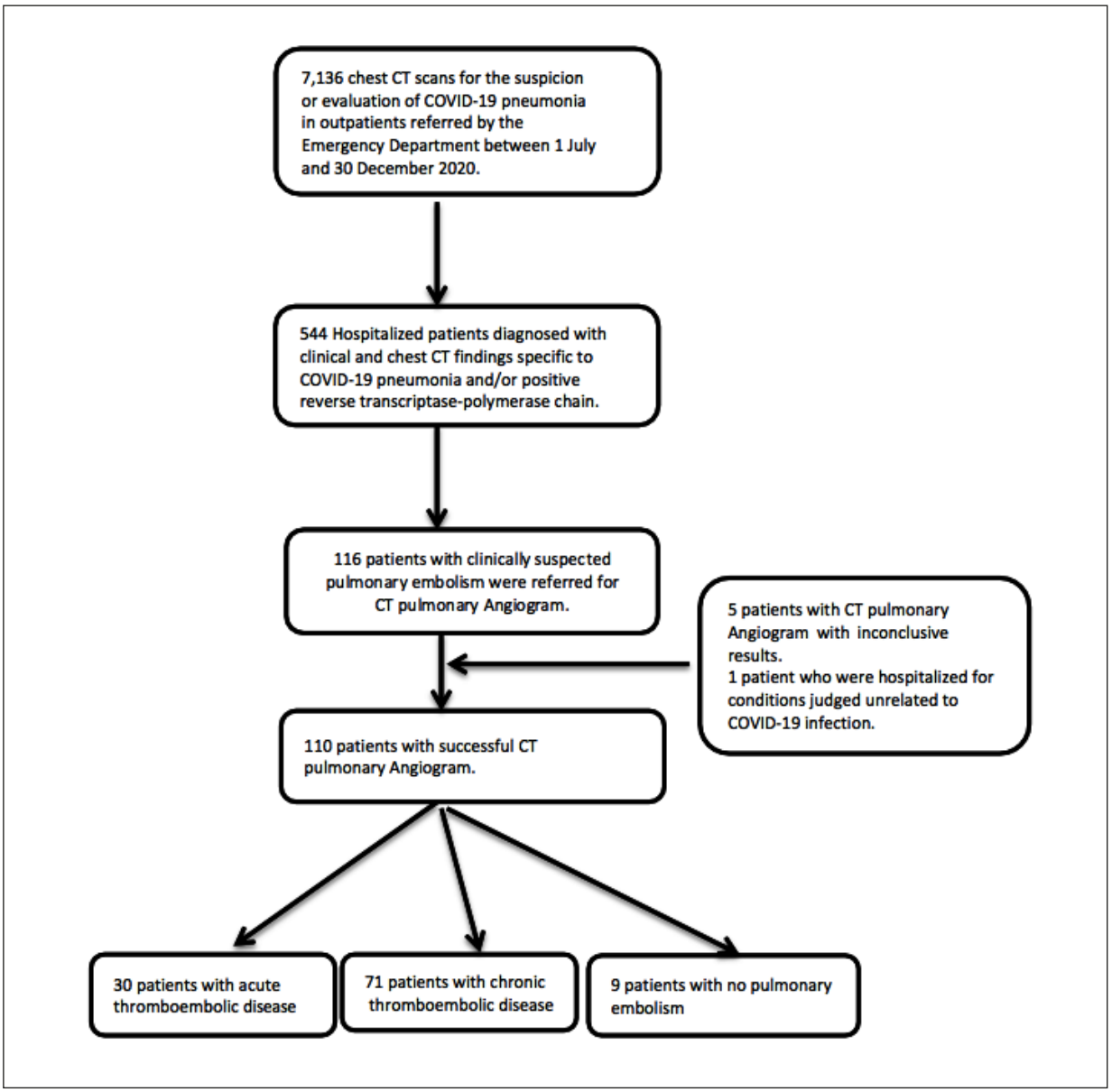

Figure 1. Study flow chart.

previous ECHO assessment. It may be difficult to evaluate pulmonary arteries for chronic vascular changes in CT angiography with widespread parenchymal densities due to COVID-19, but ignoring their presence is an important obstacle to the full definition of the picture. New data showing the long-term risks of pulmonary vascular sequelae after COVID-19 indicate that the current approach (visual evaluation by a single radiologist) used to identify vascular abnormalities during the acute phase is not sufficient to detect pulmonary vascular disease, which may have an important chronic component[14]. Diagnosis and treatment of CTEPH or chronic thromboembolic disease is difficult in developing countries, so patients continue their lives with alternative diagnosis such as asthma, chronic obstructive pulmonary disease (COPD) and wrong treatment[34]. In our country, the diagnosis of chronic pulmonary embolism is rarely made, and it is rarely treated appropriately. Dual-Energy CT Angiography (DECT) revealed pulmonary artery thrombus, mainly in the segmental arteries (83%), in 34% of patients, and parenchymal ischemia unrelated to the presence of visible pulmonary artery thrombus in 68% of patients, which may reflect microthrombosis associated with COVID-19 pneumonia[19]. These data support the present study. With the wide-

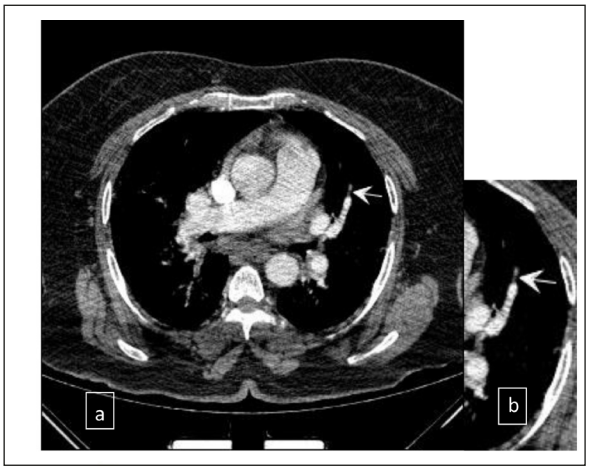

Figure 2. Gİ, 69 years old female patient, PCR (+). **a-b**, (zoomed in): total occlusion in the lingular segment artery (arrow).

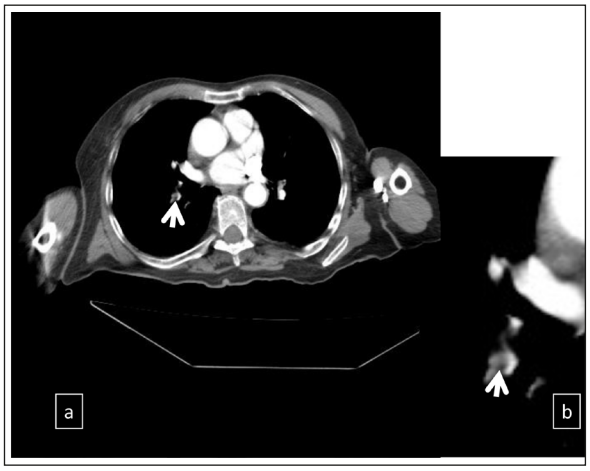

Figure 3. KE. 89 years old male patient, Antibody Positive. **a-b**, (zoomed in): web view in the right lower lobe basal posterior segment artery (arrow).

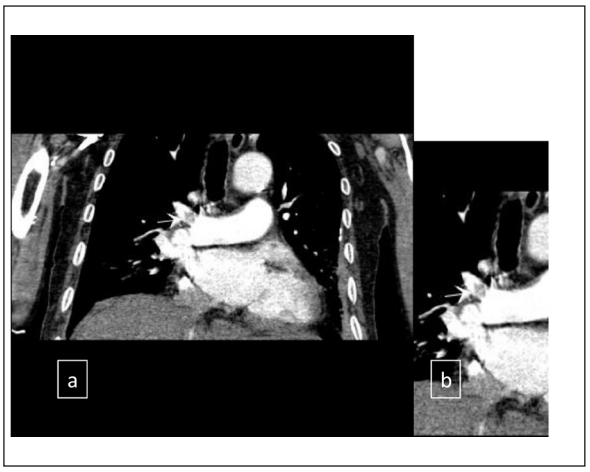

Figure 4. KE. 76 years old male patient, PCR (+). **a-b**, (zoomed in): acute thrombus in the anterior trunk of the right upper lobe (arrow).

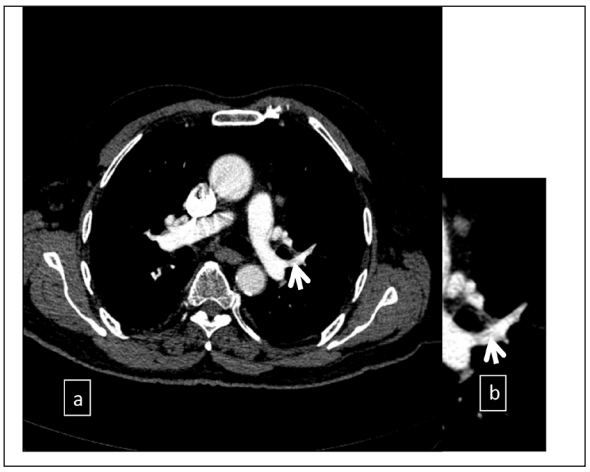

Figure 5. MT. 76 years old male patient, PCR (+). **a-b**, (zoomed in): web view of left upper lobe apical segment artery (arrow).

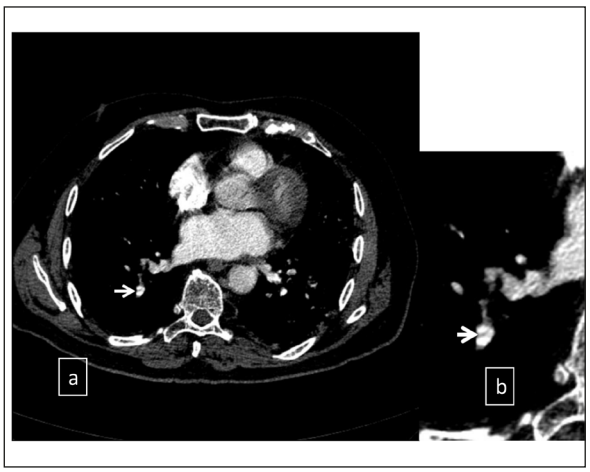

Figure 6. **a-b**, (zoomed in): web view of the right lower lobe basal posterior segment artery (arrow).

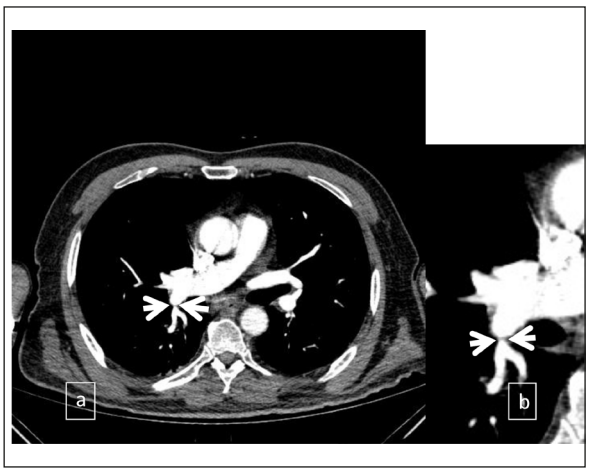

Figure 7. NK. 68 years old male patient, PCR (+). **a-b**, (zoomed in): focal stenosis of right lower lobe superior segment artery (arrow).

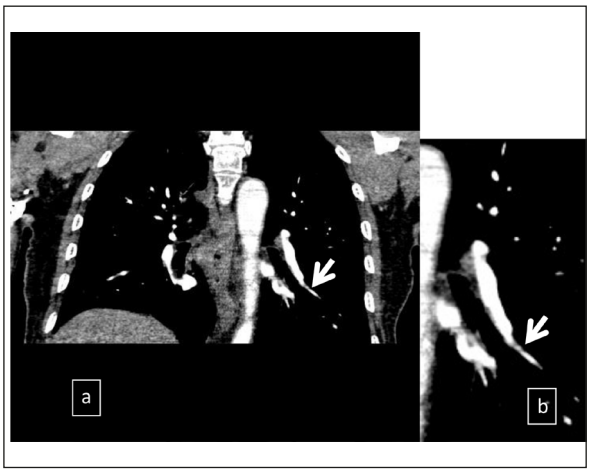

Figure 8. a-b, (zoomed in): abrupt narrowing in left lower lobe segment artery (arrow).

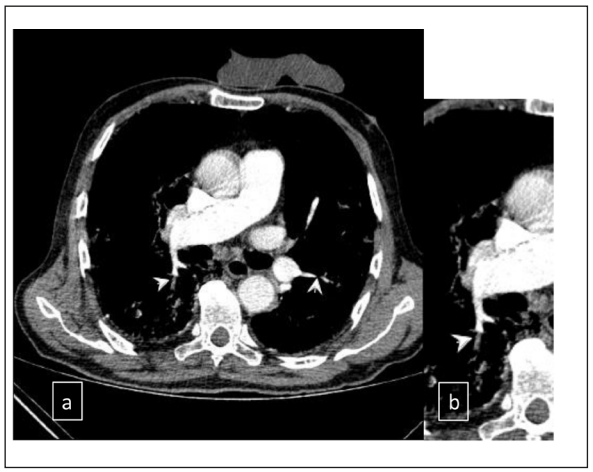

Figure 9. NK. 68 years old male patient, PCR (+). **a-b**, (zoomed in): total occlusion in the right and left lower lobe segment artery (arrows).

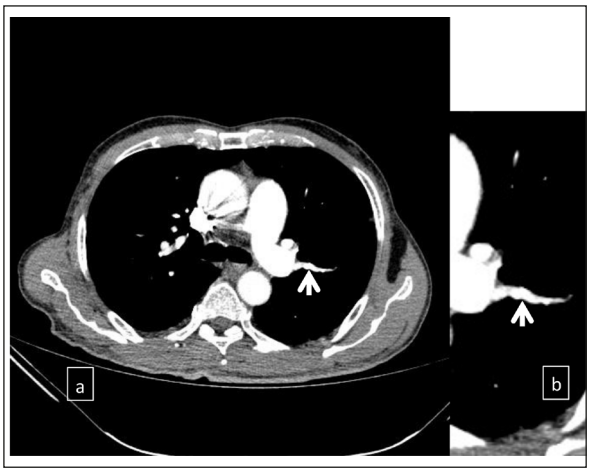

Figure 10. a-b, (zoomed in): intimal irregularity of the left upper lobe posterior segment artery (arrow).

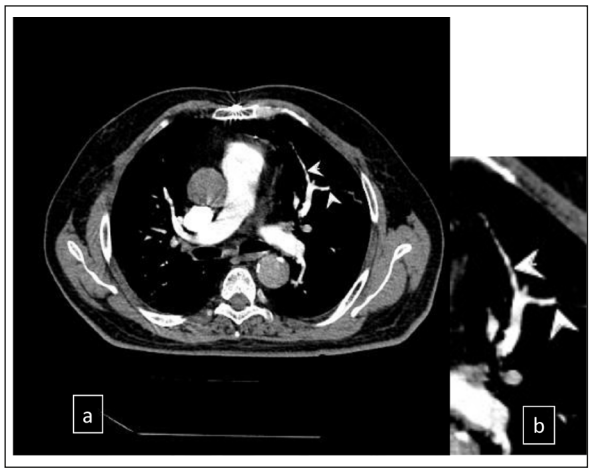

Figure 11. MB. 70 years old male patient, PCR (+). **a-b**, (zoomed in): Poststetonic dilatation and total occlusion in the segmental arteries of the left upper lobe (arrows).

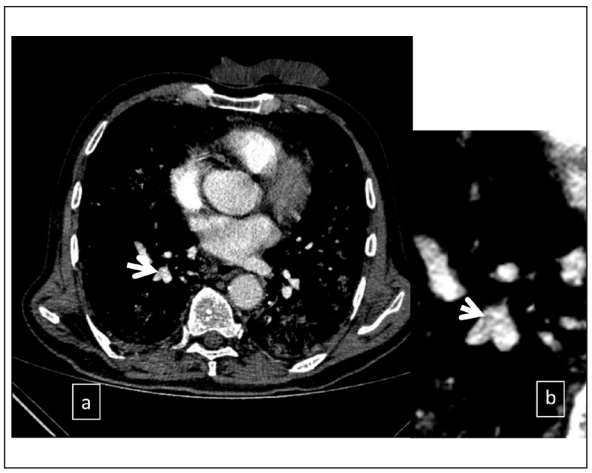

Figure 12. AU .71 years old male patient, PCR (+). **a-b**, (zoomed in): web appearance in the right lower lobe segment artery (arrow).

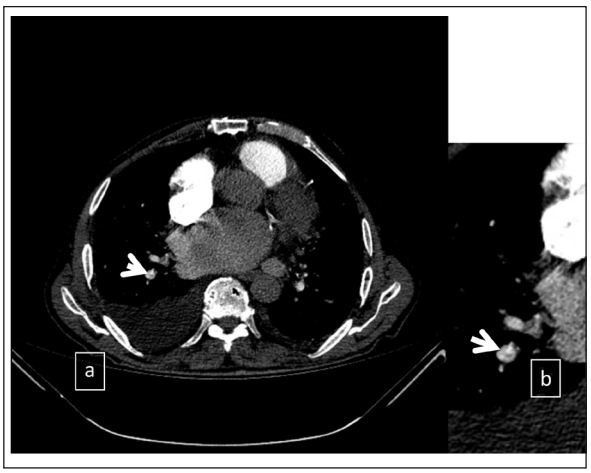

Figure 13. HS.73 years old male patient, PCR (+). **a-b**, (zoomed in): bilateral pleural effusion, more on the right and web view of the right lower lobe segment artery (arrow).

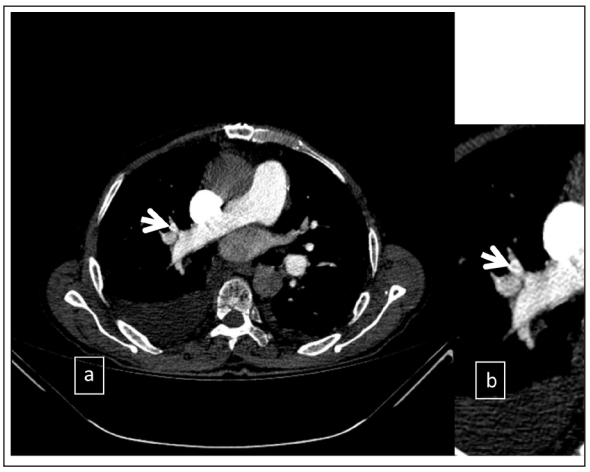

Figure 14. a-b, (zoomed in): band appearance in the right upper lobe segment artery (arrow).

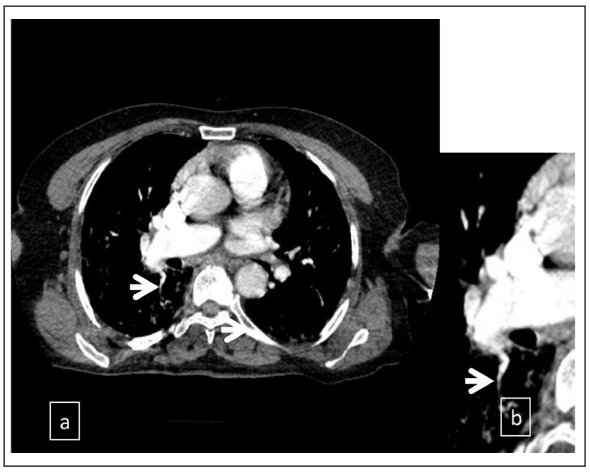

Figure 15. GE. 82 years old female patient, PCR (+). **a-b**, (zoomed in): total occlusion in the right lower lobe superior segment artery (arrow).

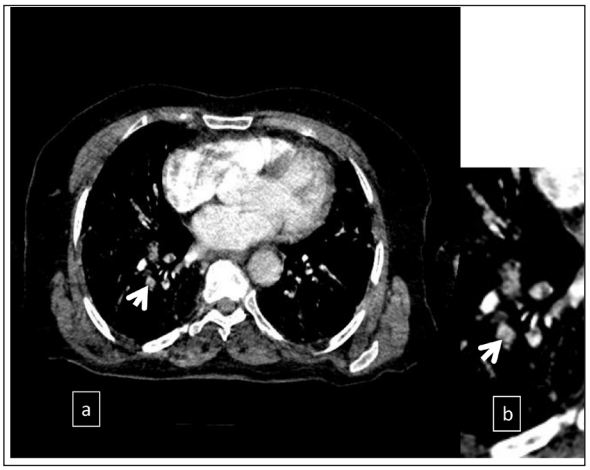

Figure 16. a-b, (zoomed in): web appearance in the right lower lobe basal posterior segment artery (arrow).

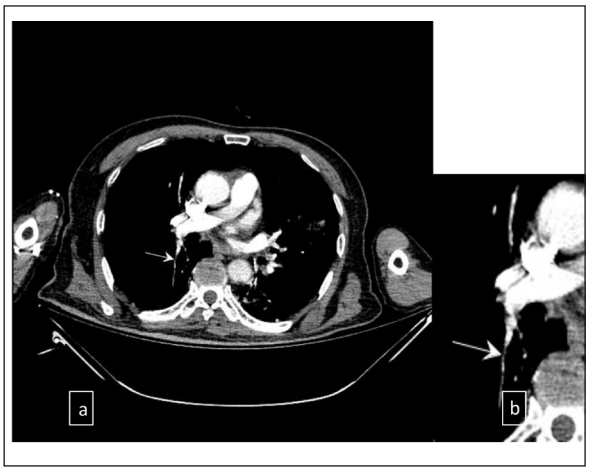

Figure 17. GK. 72 years old male patient, PCR (+). **a-b**, (zoomed in): total occlusion in the right lower lobe superior segment artery (arrow).

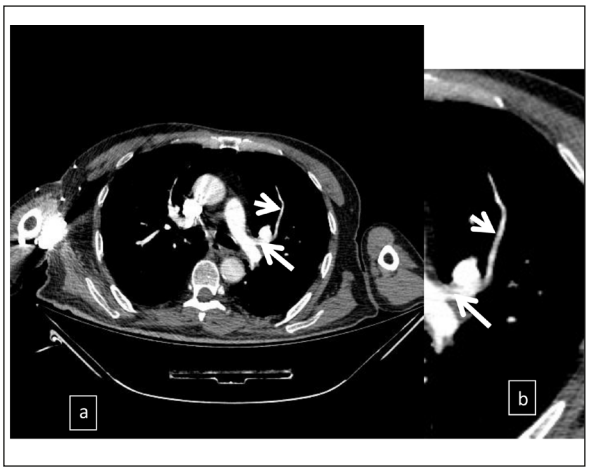

Figure 18. a-b, (zoomed in): stenosis (arrow) and web view (long arrow) in the left upper lobe anterior segment artery.

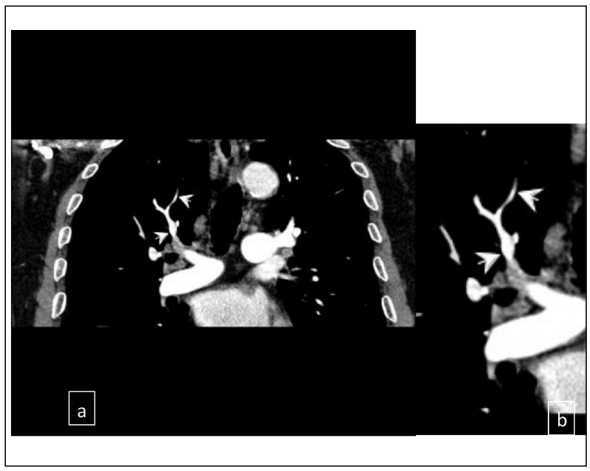

Figure 19. ZA. 77 years old male patient, PCR (+). **a-b**, (zoomed in): poststetonic dilatation in the right upper lobe apical segment artery (arrow).

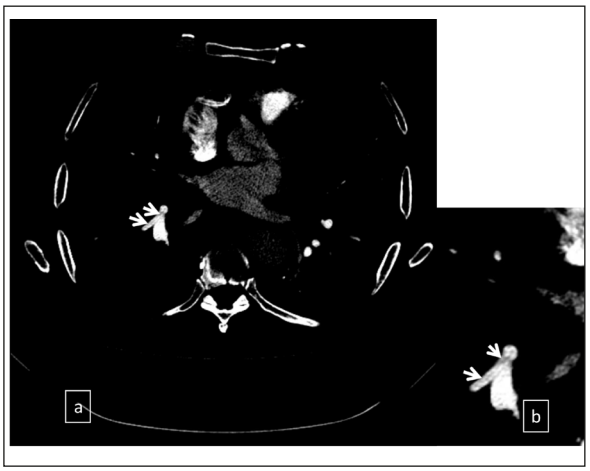

Figure 20. a-b, (zoomed in): web appearance in the right lower lobe segment artery (arrow).

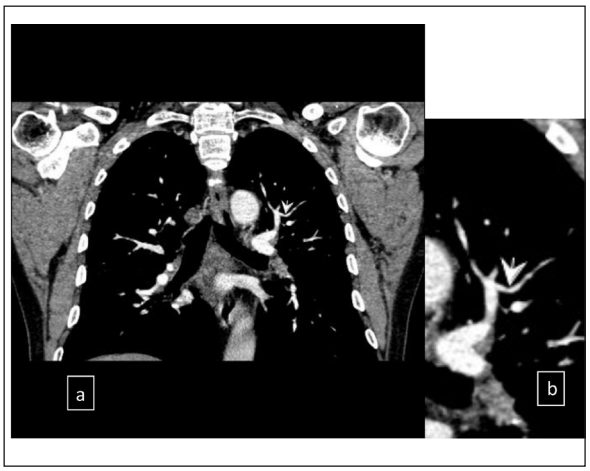

Figure 21. MAT. 76 years old male patient, PCR (+). **a-b**, (zoomed in): tortuous view and thinning in the left upper lobe segment artery (arrow).

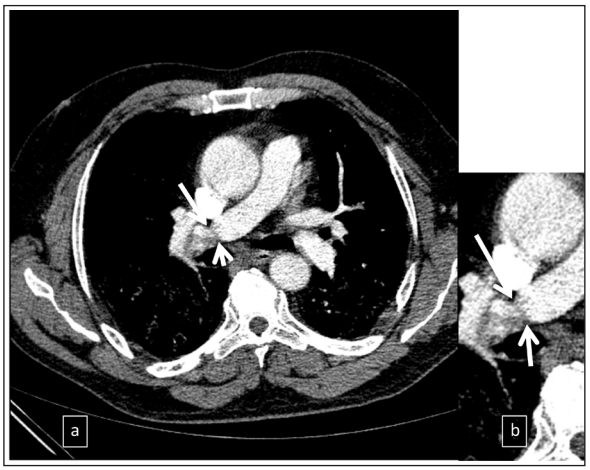

Figure 22. HİG. 68 years old male patient, PCR (+). **a-b**, (zoomed in): focal stenosis in the right pulmonary artery (arrows).

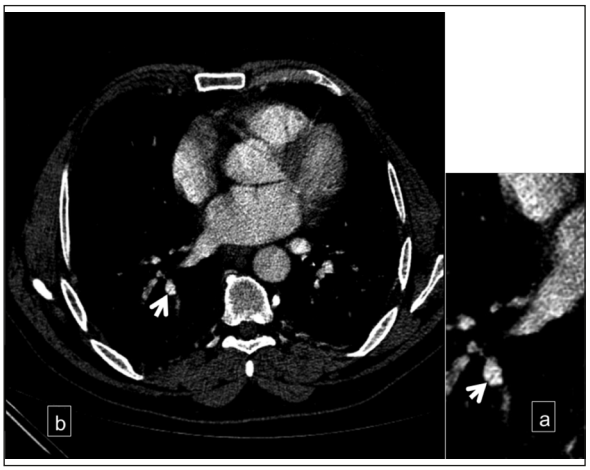

Figure 23. a-b, (zoomed in): band appearance in the right lower lobe basal posterior segment artery (arrow).

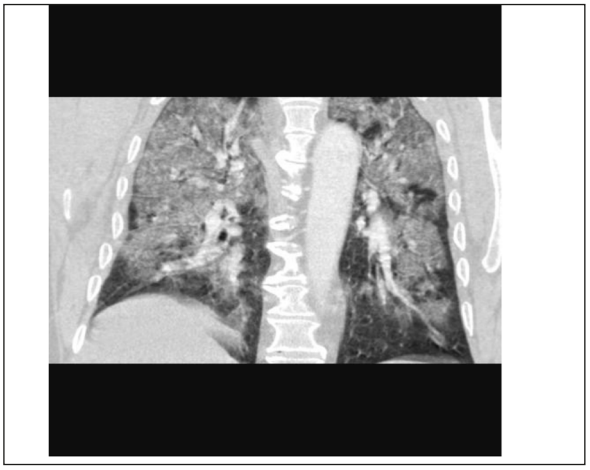

Figure 24. Coronal contrast-enhanced CT scan shows bilateral ground glass opacities.

spread use of pulmonary DECT angiography, it is possible that a much higher rate of peripheral thrombus can be detected in COVID-19 pneumonia. We could not notice any information in the literature about chronic vascular changes in CT of COVID-19 patients. However, two studies[35,36] in patients with COVID-19 have shown that the enlargement of the pulmonary artery diameter, which is an indirect sign of chronic pulmonary embolism, is associated with mortality.

In studies[24-29,37], the incidence of acute pulmonary embolism in COVID-19 patients varies between 1.9% and 35.3%. In another retrospective study[38], the cumulative incidence of pulmonary embolism increased to 50% in the intensive care unit (ICU). In a meta-analysis[39], the incidence of in-hospital PE (or

pulmonary thrombosis) among general wards and intensive care unit patients was 14.7% and 23.4% of cases, respectively. Segmental/subsegmental pulmonary arteries in the pulmonary embolism cases in this study were involved more frequently than the main/lobar arteries[39]. The rates in these studies are similar to the incidence of acute pulmonary embolism in our study. In an autopsy study[40] performed on 11 patients who died, thrombus was detected in small and medium-sized pulmonary arteries in all 11 patients. Wichmann et al[1] reported pulmonary microthrombi in 100% of COVID-19 autopsy cases. In a study[41] of lung samples from patients who died from COVID-19, histological features of vascular wall thickening in the pulmonary arteries were detected. The authors suggested that some people infected with this virus may become susceptible to developing clinically significant pulmonary arterial hypertension in the future[42]. As can be seen, autopsy studies[1,40,41] partially support our current study. However, studies investigating organized thrombi in the pulmonary arteries of patients who died from COVID-19 are needed.

The clinical picture in patients with CT features of chronic pulmonary embolism may be an acute presentation of the underlying chronic disease. In COVID-19, direct activation of the coagulation cascade by a cytokine storm may develop pulmonary artery thrombus[1,43]. In COVID-19, pulmonary artery thrombus may develop with inflammatory mechanisms triggered by alveolar and endothelial damage as a result of diffuse alveolar damage[44]. Endothelial damage can occur by host response or by direct viral infection of endothelial cells[44]. In susceptible patients with pre-existing endothelial dysfunction associated with male gender, smoking, hypertension, diabetes, obesity, CTEPH and other cardiovascular disease, COVID-19 may be associated with more serious and adverse outcomes[44]. In the presence of chronic vascular changes, entry of the virus into the endothelium may be facilitated, resulting in the development of a severe inflammatory response, diffuse pulmonary thrombosis, and a life-threatening clinical picture.

In present study, CT features of chronic pulmonary embolism were more common in deceased patients than in surviving patients. In addition, patients who died have higher urine microalbumin creatinine ratio, lower oxygen saturation and lower lymphocyte count at admission from surviving patients. Furthermore, oxygen saturation and urine microalbumin creatinine ratio at admission to COVID-19 are important determinants of mortality after adjusting for sex and age in logistic procedures. Albuminuria is thought to be a biomarker of microvascular and macrovascular endothelial dysfunction[45]. The combination of albuminuria, low oxygen saturation and CT features of chronic pulmonary embolism in COVID-19 pneumonia at admission may be the cause of fatal outcomes with more severe endothelial dysfunction.

Limitations

The limitation of our study included its retrospective nature, which makes it more difficult to draw absolute conclusions. Furthermore, the study was conducted in single-center outpatients with a relatively small sample size. Another limitation of this study is that right heart catheterization or echocardiography was not performed to measure pulmonary artery pressure.

Conclusions

CT features of chronic pulmonary embolism are common in COVID-19 patients, undergoing hospital CTPA and require long-term follow-up. The coexistence of albuminuria, low oxygen saturation and CT features of chronic pulmonary embolism at admission in COVID-19 patients may herald fatal outcomes.

Authors' Contributions

M.E and A.E. planned to work. M.E. made the analysis. S.K. and F.A.İ. prepared the draft.
All authors participated in the interpretation of the results and the writing of the article.

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Conflict of Interests

The authors declare that there is no potential conflict of interest.

Ethics Approval

This study was conducted according to the Declaration of Helsinki. The study was accepted by the Kirikkale University Clinical Research Ethics Committee (Decision No.: 2021.04.07, Meeting number: 2021/07).

Informed Consent

The consent form was waived because of the retrospective nature of the study.

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References

1) Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med 2020; 173: 268-277.
2) Chamorro EM, Ostolaza TYR, Núñez MP, Nacenta SB, Rodríguez-Guerra CCC, Sanz LI. Pulmonary embolisms in patients with COVID-19: a prevalence study in a tertiary hospital. Radiologia 2021; 63: 13-21.
3) Naserghandi A, Allameh SF, Saffarpour R. All about COVID-19 in brief. New Microbes New Infect 2020; 35: 100678.
4) Akel T, Qaqa F, Abuarqoub A, Shamoon F. Pulmonary embolism: A complication of COVID 19 infection. Thromb Res 2020; 193: 79-82.
5) Alonso-Fernández A, Toledo-Pons N, Cosío BG, Millán A, Calvo N, Ramón L, de Mendoza SH, Morell-García D, Bauça-Rossello JM, Núñez B, Pons J, Palmer JA, Martín L, Peñaranda M, Pou JA, Sauleda J, Sala-Llinas E. Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: A prospective study. PLoS One 2020; 15: e0238216.
6) Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolysis 2021; 51: 1107-1110.
7) Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-847.
8) Tal S, Spectre G, Kornowski R, Perl L. Venous Thromboembolism Complicated with COVID-19: What Do We Know So Far? Acta Haematol 2020; 143: 417-424.
9) Sakr Y, Giovini M, Leone M, Pizzilli G, Kortgen A, Bauer M, Tonetti T, Duclos G, Zieleskiewicz L, Buschbeck S,Ranieri VM, Antonucci E. Pulmonary embolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: a narrative review. Ann Intensive Care 2020; 10: 124.
10) Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18: 1995-2002.
11) Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, Douair A, Barbin E, Fraix A, Bouchot O, Benmansour O, Godeau G, Mecheri Y, Lebourdon R, Yvorel C, Massin M, Leblon T, Chabbi C, Cugney E, Benabou L, Aubry M, Chan C, Boufoula I, Barnaud C, Bothorel L, Duceau B, Sutter W, Waldmann V, Bonnet G, Cohen A, Pezel T, Critical Covid-19 France Investigators. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. Eur Heart J 2020; 41: 3058-3068.
12) Javorac J, Živanović D, Stojkov S, Miličić JĐ, Fradelos E, Savić N. COVID-19 associated pulmonary embolism with D-dimer values within the referent range: a case report and review of the literature. Eur Rev Med Pharmacol Sci 2021; 25: 7971-7975.
13) Watchmaker JM, Goldman DT, Lee JY, Choi S, Mills AC, Toussie D, Finkelstein M, Sher AR, Jacobi AH, Bernheim AM, Chung MS, Eber CD, Lookstein RA. Increased Incidence of Acute Pulmonary Embolism in Emergency Department Patients During the COVID-19 Pandemic. Acad Emerg Med 2020; 27: 1340-1343.
14) Overton PM, Toshner M, Mulligan C, Vora P, Nikkho S, de Backer J, Lavon BR, Klok FA; PVRI Innovative Drug Development Initiative. Pulmonary thromboembolic events in COVID-19 – A systematic literature review. Pulm Circ 2022; 12: e12113.
15) Revel MP, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A. COVID-19 patients and the radiology department-advice from the European Society of Radiology and the European Society of Thoracic Imaging. Eur Radiol 2020; 30: 4903-4909.
16) Gervaise A, Bouzad C, Peroux E, Helissey C. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. Eur Radiol 2020; 30: 6170-6177.
17) Ding X, Xu J, Zhou J, Long Q. Chest CT findings of COVID-19 pneumonia by duration of symptoms. Eur J Radiol 2020; 127: 109009.
18) Planquette B, Le Berre A, Khider L, Yannoutsos A, Gendron N, de Torcy M, Mohamedi N, Jouveshomme S, Smadja DM, Lazareth I, Goudot G, Fournier L, Bruel C, Diehl JL, Mourad JJ, Meyer G, Priollet P, Messas E, Sanchez O, Beaussier H, Mirault T, Zins M, Chatelier G, Emmerich J. Prevalence and characteristics of pulmonary embolism in 1042 COVID-19 patients with respiratory symptoms: A nested case-control study. Thromb Res 2021; 197: 94-99.
19) Grillet F, Busse-Coté A, Calame P, Behr J, Delabrousse E, Aubry S. COVID-19 pneumonia: microvascular disease revealed on pulmonary dual-energy computed tomography angiography. Quant Imaging Med Surg 2020; 10: 1852-1862.
20) Bhalla AS, Das A, Naranje P, Irodi A, Raj V, Goyal A. Imaging protocols for CT chest: A recommendation. Indian J Radiol Imaging 2019; 29: 236-246.
21) Gouin B, Blondon M, Jiménez D, Fernández-Capitán C, Bounameaux H, Soler S, Duce R, Sahuquillo JC, Ruiz-Giménez N, Monreal M, RIETE investigators. Clinical Prognosis of Nonmassive Central and Noncentral Pulmonary Embolism: A Registry-Based Cohort Study. Chest 2017; 151: 829-837.
22) Ooi GC, Khong PL, Muller NL, Yiu WC, Zhou LJ, Ho JCM, Lam B, Nicolaou S, Tsang KWT. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. Radiology 2004; 230: 836-844.
23) Wittram C, Kalra MK, Maher MM, Greenfield A, Mc Loud TC, Shepard JAO. Acute and chronic pulmonary emboli: angiography-CT correlation. Am J Roentgenol 2006; 186: S421-S429.
24) Gul MH, Htun ZM, Perez VJ, Suleman M, Arshad S, Imran M, Vyasabattu M, Wood JP, Anstead M, Morris PE. Predictors and outcomes of acute pulmo-

nary embolism in COVID-19; insights from US National COVID cohort collaborative. Respir Res 2023 21; 24: 59.
25) Hughes K, Hussaini Z, Shah MK, Hilton R, Oxman D. COVID-19 and Acute Pulmonary Embolism: A Case Series and Brief Review. Am J Med Sci 2021; 361: 646-649.
26) Kalemci S, Sarıhan A, Zeybek A, Kargı AB. Acute pulmonary embolism in COVID-19 disease. Int J Cardiol 2020; 319:151.
27) Zuin M, Engelen MM, Bilato C, Vanassche T, Rigatelli G, Verhamme P, Vandenbriele C, Zuliani G, Roncon L. Prevalence of Acute Pulmonary Embolism at Autopsy in Patients With COVID-19. Am J Cardiol 2022; 171: 159-164.
28) Zuin M, Rigatelli G, Bilato C, Quadretti L, Roncon L, Zuliani G. COVID-19 patients with acute pulmonary embolism have a higher mortality risk: systematic review and meta-analysis based on Italian cohorts. J Cardiovasc Med (Hagerstown) 2022; 23: 773-778.
29) Lorenzo C, Francesca B, Francesco P, Elena C, Luca S, Paolo S. Acute pulmonary embolism in COVID-19 related hypercoagulability. J Thromb Thrombolysis 2020; 50: 223-226.
30) Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, Lei C, Chen R, Zhong N, Li S. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J 2020; 55: 2001217.
31) Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, Baldon G, Bartolomei G, Battaglia M, Battistini S, Binda V, Borg M, Cantaluppi V, Castello LM, Clivati E, Cisari C, Costanzo M, Croce A, Cuneo D, De Benedittis C, De Vecchi S, Feggi A, Gai M, Gambaro E, Gattoni E, Gramaglia C, Grisafi L, Guerriero C, Hayden E, Jona A, Invernizzi M, Lorenzini L, Loreti L, Martelli M, Marzullo P, Matino E, Panero A, Parachini E, Patrucco F, Patti G, Pirovano A, Prosperini P, Quaglino R, Rigamonti C, Sainaghi PP, Vecchi C, Zecca E, Pirisi M. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA Netw Open 2021; 4: e2036142.
32) Frija-Masson J, Debray MP, Gilbert M, Lescure FX, Travert F, Borie R, Khalil A, Crestani B, d'Ortho MP, Bancal C. Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post infection. Eur Respir J 2020; 56: 2001754.
33) Dhawan RT, Gopalan D, Howard L, Vicente A, Park M, Manalan K, Wallner I, Marsden P, Dave S, Branley H, Russell G, Dharmarajah N, Kon OM. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med 2021; 9: 107-116.
34) Palla A, Formichi B, Santolicandro A, Di Ricco G, Giuntini C. From not detected pulmonary embolism to diagnosis of chronic thromboembolic pulmonary hypertension: a retrospective study. Respiration 1993; 60: 9-14.
35) Spagnolo P, Cozzi A, Foà RA, Spinazzola A, Monfardini L, Bnà C, Alì M, Schiaffino S, Sardanelli F. CT- derived pulmonary vascular metrics and clinical outcome in COVID-19 patients. Quant Imaging Med Surg 2020; 10: 1325-1333.
36) Esposito A, Palmisano A, Toselli M, Vignale D, Cereda A, Rancoita PMV, Leone R, Nicoletti V, Gnasso C, Monello A, Biagi A, Turchio P, Landoni G, Gallone G, Monti G, Casella G, Iannopollo G, Nannini T, Patelli G, Di Mare L, Loffi M, Sergio P, Ippolito D, Sironi S, Pontone G, Andreini D, Mancini EM, Di Serio C, De Cobelli F, Ciceri F, Zangrillo A, Colombo A, Tacchetti C, Giannini F. Chest CT–derived pulmonary artery enlargement at the admission predicts overall survival in COVID-19 patients: insight from 1,461consecutive patients in Italy. Eur Radiol 2021; 31: 4031-4041.
37) Sakr Y, Giovini M, Leone M, Pizzilli G, Kortgen A, Bauer M, Tonetti T, Duclos G, Zieleskiewicz L, Buschbeck S, Ranieri VM, Antonucci E. Pulmonary embolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: a narrative review. Ann Intensive Care 2020; 10: 124.
38) Bompard F, Monnier H, Saab I, Tordjman M, Abdoul H, Fournier L, Sanchez O, Lorut C, Chassagnon G, Revel MP. Pulmonary embolism in patients with COVID-19 pneumonia. Eur Respir J 2020; 56: 2001365.
39) Roncon L, Zuin M, Barco S, Valerio L, Zuliani G, Zonzin P, Konstantinides SV. Incidence of acute pulmonary embolism in COVID-19 patients: Systematic review and meta-analysis. Eur J Intern Med 2020; 82: 29-37.
40) Lax SF, Skok K, Zechner P, Kessler H, Kaufmann N, Koelblinger C, Vander K, Bargfrieder U, Trauner M. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med 2020; 173: 350-361.
41) Suzuki YJ, Nikolaienko SI, Dibrova VA, Dibrova VY, Vasylyk MV, Novikov MY, Shults NV, Gychka SG. SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells. Vascul Pharmacol 2021; 137: 106823.
42) Suzuki YJ, Nikolaienko SI, Shults NV, Gychka SG. COVID-19 patients may become predisposed to pulmonary arterial hypertension. Med Hypotheses 2021; 147: 110483.
43) Voicu S, Delrue M, Chousterman BG, Stépanian A, Bonnin P, Malissin I, Deye N, Neuwirth M, Ketfi C, Mebazaa A, Siguret V, Mégarbane B. Imbalance between procoagulant factors and natural coagulation inhibitors contributes to hypercoagulability in the critically ill COVID-19 patient: clinical implications. Eur Rev Med Pharmacol Sci 2020; 24: 9161-9168.
44) Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19 [Letter]. Lancet 2020; 395: 1417-1418.
45) Martens RJH, Houben AJHM, Kooman JP, Berendschot TTJM, Dagnelie PC, van der Kallen CJH, Kroon AA, Leunissen KML, van der Sande FM, Schaper NC, Schouten JSAG, Schram MT, Sep SJS, Sörensen BM, Henry RMA, Stehouwer CDA. Microvascular endothelial dysfunction is associated with albuminuria: the Maastricht Study. J Hypertens 2018; 36: 1178-1187.