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Pulmonary embolism in patients with dyspnea after COVID-19 infection

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Abstract. – OBJECTIVE: Pulmonary embolism as a potential complication that may occur late in the course of COVID-19 cases. The aim of our study is to evaluate the frequency of pulmonary embolism in patients with new or ongoing dyspnea after a COVID-19 infection.

PATIENTS AND METHODS: This is a single-center, prospective observational study to evaluate the clinical and radiological outcomes of consecutive patients presenting outpatient clinic diseases to the chest and a new or ongoing dyspnea after a COVID-19 infection. Demographic, clinical and laboratory data were collected. Dyspnea was evaluated according to the New York Heart Association (NYHA) classification.

RESULTS: Pulmonary embolism was detected in 23.8% (25/105) of patients with new or ongoing dyspnea after a COVID-19 infection. Proportion of pulmonary embolism in patients with NYHA classes I, II, III and IV were respectively 8.7%, 20.0%, 30.0% and 35.3% (*p* for trend=0.02). Compared to NYHA class I and II patients with dyspnea, those in NYHA classes III and IV showed a higher rate of pulmonary embolism [31.6% *vs.* 14.6%, OR: 2.7 (1.0 to 7.1), *p*=0.04, respectively]. In Logistic Procedures, NYHA classes of dyspnea (OR: 4.3, 95% CI: 1.2 to 16.6, *p*=0.03) (NYHA class III and IV vs. NYHA class I and II) determine the likelihood of pulmonary embolism after COVID-19 infection.

CONCLUSIONS: Pulmonary embolism is common in patients with new or ongoing shortness of breath after a COVID-19 infection. Pulmonary embolism is more likely to develop in patients with higher NYHA classes.

Key Words:
COVID-19 infection, Pulmonary embolism, New York Heart Association Classes.

Introduction

The Coronavirus Disease 2019 (COVID-19) is one of the biggest clinical problems of recent years[1] COVID-19 can have poor long-term outcomes and residual disability[2,3]. While the long-term pulmonary sequelae of COVID-19 are unknown, the clinically significant pulmonary vascular sequelae may become a public health concern[4,5]. There are few studies[6] investigating the late sequelae of COVID-19. Thromboembolic events may occur later in the course of the disease in COVID-19[7]. In addition, there is growing concern and significant controversy regarding a significant chronic fibrotic disease and pulmonary vascular sequelae among individuals recovering from COVID-19[8].

It is evident that pulmonary embolism develops with COVID-19 infection. However, it is not well known whether pulmonary embolism develops after COVID-19 infection. The aim of our study is to evaluate the frequency of pulmonary embolism in patients with new or ongoing dyspnea after a COVID-19 infection.

Patients and Methods

This is a single-center, prospective observational study, conducted between 10 september and 30 December 2021, to evaluate the clinical and radiological outcomes of consecutive patients presenting outpatient clinic diseases to the chest with a new (within 3 months) or ongoing dyspnea after a COVID-19 infection. Demographic, clinical and laboratory data were collected.

The computed tomography pulmonary angiography (CTPA) indications were obtained within 72 hours of study entry, based on the presence of the new or ongoing dyspnea.

Patients (age: 18 years old and above) were admitted to the study after declaring having a disease with the typical clinical findings of COVID-19 infection and/or a real-time positive reverse transcriptase-polymerase chain reaction (RTPCR) test.

We excluded the following patients: (1) Those who developed dyspnea more than 3 months after being infected with COVID-19, (2) those

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with alternative diagnoses, (3) patients who had had major surgery or trauma within 3 months, (4) patients who did not accept pulmonary CT angiography, (5) those with high creatinine levels, (6) those with pre-existing dyspnea, (7) those who had had a previous pulmonary embolism, (8) pregnant women, (9) those who had been taking anticoagulants for 3 months or more, (10) patients diagnosed with malignant disease, (11) patients with psychiatric and terminal illnesses, (12) patients who did not respond or were not willing to participate in the study, (13) patients with a life expectancy shorter than 6 months, (14) those unable to give informed consent, (15) patients with a recent non-contrast CT.

Patients who were appropriate for our study and who gave informed consent were subjected to pulmonary CT angiography.

Dyspnea was graded according to the New York Heart Association (NYHA) classification and persistent dyspnea was rated as NYHA ≥ 1[9]. The current study assumes that shortness of breath developed immediately after or within three months from the COVID-19 infection is related to previous infections.

Ventilation function with a turbine spirometer was measured Nobreath™ Quark (COSMED™, Rome, Italy). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and peak expiratory flow (PEF) were repeated until three appropriate recordings (less than 5% difference) were gained. The highest of these 3 values was selected for analysis.

Multidetector Computed Tomography (MDCT)

CT angiograms were taken after injecting 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 taken using the bolus tracking technique and 160-250 HU threshold in the main pulmonary artery. Sections of 1 mm thickness were obtained in the mediastinal and parenchymal windows[10].

Image Analysis

The consensus of two pulmonologists, who did not know the clinical data of the patients, was employed as the standard reference for the diagnosis of pulmonary embolisms (PEs). In the pulmonary artery tree, the presence of at least one filling defect was defined as PE[11,12].

In addition, the following features were used to identify parenchymal changes associated with COVID-19 infection: presence of ground glass opacities [GGO], consolidation, GGO/consolidation, air bronchogram, vascular or bronchial wall thickening, crazy-paving pattern, bilateral multiple foci, fibrotic pattern, nodular pattern[13].

Measurements

Blood samples were obtained within 48 hours from the CTPA.

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 evaluated with logistic regression models, using a stepwise model selection technique. Predictors of mortality were determined by logistic regression between age, gender, oxygen saturation, lymphocyte count and albuminuria level. In all cases, univariate analysis was conducted to evaluate possible predictors first.

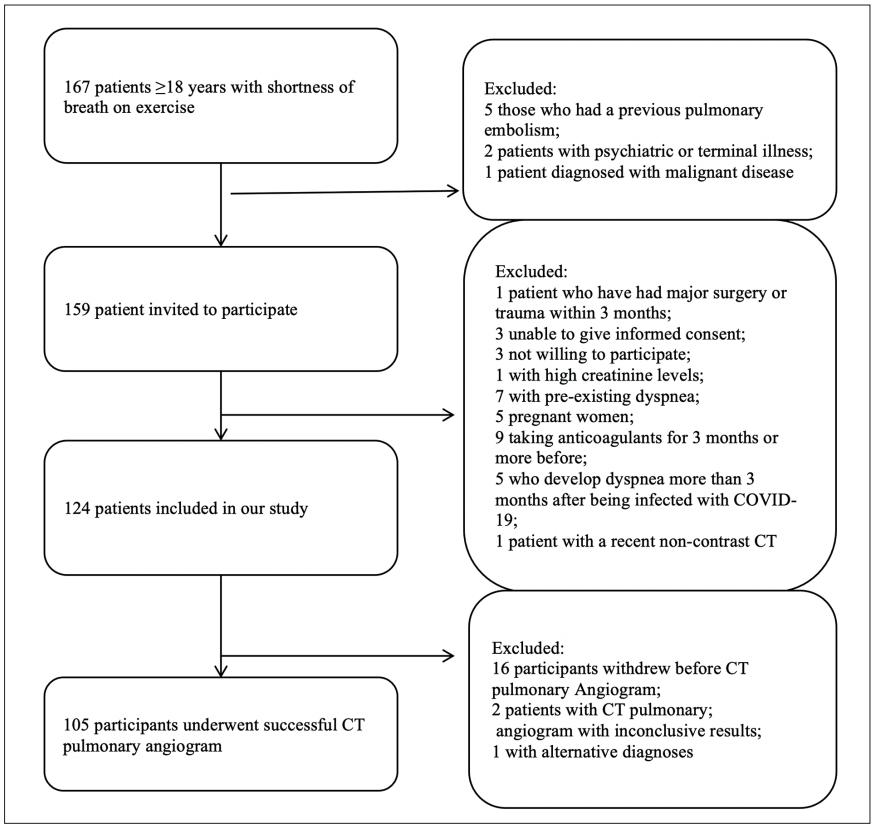
All important variables in the univariate analysis were evaluated in the multivariate analysis. Finally, the main determinants were predicted by decreasing the multivariate model by a stepwise model selection technique. All statistical analyzes were performed using SPSS Statistics software (version 17.0; Chicago, IL, USA.), and p-value < 0.05 was accepted as statistically significant.

Results

Between 30 August and 15 October 2021, 167 patients applied to the chest diseases outpatient clinic with new or ongoing dyspnea after a COVID-19 infection (Figure 1). 62 patients were excluded from the study having exclusion criteria. CT pulmonary Angiogram was successfully performed in 105 patients [PCR (+), n:72 *vs.* PCR (-), n:33].

Pulmonary embolism was detected in 23.8% (25/105) of patients with new or ongoing dyspnea after a COVID-19 infection. Baseline characteristics of patients with pulmonary embolisms are shown in Table I.

Figure 1. Flowchart of the study.



Proportion of pulmonary embolisms in patients with NYHA classes I, II, III and IV were respectively 8.7%, 20.0%, 30.0% and 35.3% (p for trend=0.02).

Compared with NYHA class I and II patients with dyspnea, those in NYHA classes III and IV showed a higher rate of pulmonary embolisms [31.6% *vs.* 14.6%, OR: 2.7 (1.0 to 7.1), p=0.04, respectively].

Compared with those without a pulmonary embolism, patients with it showed a larger pulmonary artery diameter (27.9±2.9 *vs.* 24.8±3.3, p=0.001), higher uric acid level (5.1±1.1 *vs.* 4.6±1.0; p=0.03), higher Pro-BNP level (243.8±270.2 *vs.* 78.8±124.0, p=0.001) and a higher glucose level (150.9±103.0 *vs.* 106.2±40.1, p=0.003).

CT findings about patients with pulmonary embolism are shown in Table II. Patients with a pulmonary embolism showed a larger right atrium (1878.3±434.2 *vs.* 1402.4±402.9, p=0.001), right ventricle (1644.9±567.8 *vs.* 1381.3±389.2, p=0.01), left atrium (2031.62±459.2 *vs.* 1580.2±430.2, p=0.001) and left ventricle area (2022.9±635.8 *vs.* 1602.8±518.2, p=0.001), compared to those without pulmonary embolisms.

The predictors of pulmonary embolism for patients with dyspnea after a COVID-19 infection in Logistic Procedures are shown in Table III. In Logistic Procedures, the NYHA classes of dyspnea (OR: 4.3, 95% CI: 1.2 to 16.6, p=0.03) (NYHA class III and IV *vs.* NYHA class I and II) determine the likelihood of pulmonary embolism after a COVID-19 infection.

Pulmonary embolisms were found to be more likely to develop in patients previously admitted in the critical care unit [80.0% *vs.* 21.0%, OR: 15.0 (95% CI: 1.5-141.8), p=0.003].

CT features of patients with pulmonary embolism are given in Figures 2-4.

Discussion

The present study suggests that pulmonary embolism is common in patients with new or persistent dyspnea after COVID-19 infection. Dyspnea may be ongoing after the initial infection or may occur weeks or months after an asymptomatic period. In addition, pulmonary embolisms showed to be more likely to develop in patients with higher NYHA classes. We have not noticed any studies in the literature related to pulmonary embolisms developed after a COVID-19 infection, but there are cases and case series[14-16].

Table I. Baseline characteristics of patients with pulmonary embolism.

	Pulmonary embolism present (n = 25, 23.8%)	Pulmonary embolism absent (n = 80, 76.2%)	n: 105 *p*-value
Mean age, years	55.4 ± 16.4	42.7 ± 13.1	0.001
Male sex %	32.0	23.8	0.4
Body mass index, mean (SD)	30.7 ± 6.2	28.3 ± 4.5	0.03
Smoking status, No. (%)			
Active, Former	20.0	25.0	0.6
Days since covid symptoms onset, mean	89.9 ± 83.5	83.8 ± 74.4	0.7
Days of onset of shortness of breath after COVID infection, mean	7.2 ± 14.4	7.9 ± 14.3	0.8
Cerebral %	8.0	2.5	0.2
Oncologic %	0	0	
Heart disease %	4.0	1.3	0.3
Lung disease %	4.0	0	0.07
Chronic kidney disease %	0	0	
Hospitalization	28.0	26.3	0.8
Length of hospital stay	4.7 ± 10.0	2.5 ± 5.1	0.1
ICU admission	16.0	1.3	0.003
Cough %	52.0	53.8	0.8
Sputum %	36.0	32.5	0.7
Syncope/presyncope %	8.0	6.3	0.7
Hemoptysis %	0	5.0	0.2
Fatigue or muscle weakness %	80.0	65.0	0.1
Sleep difficulties	48.0	36.3	0.2
Hair loss %	16.4	27.5	0.2
Smell disorder %	8.0	7.5	0.9
Palpitations %	56.0	50.0	0.6
Joint pain %	32.0	40.0	0.4
Decreased appetite %	4.0	2.5	0.6
Taste disorder %	4.0	7.5	0.5
Dizziness %	44.0	18.8	0.01
Diarrhea or vomiting	4.0	5.0	0.8
Chest pain %	44.0	51.3	0.5
Sore throat or difficult to swallow %	4.0	1.3	0.3
Skin rash%	0	6.3	0.2
Myalgia%	36.0	30.0	0.5
Headache%	36.0	40.0	0.7
Low grade fever%	4.0	7.5	0.5
Ronchus	8.0	7.5	0.9
Ral	24.0	13.8	0.2
Oxygen saturation	95.3 ± 2.9	96.7 ± 1.7	0.004
Pulmonary artery diameter	27.9 ± 2.9	24.8 ± 3.3	0.001
Abnormal ECG	24.0	15.0	0.2
Clot load	4.0 ± 0.7	3.8 ± 0.7	0.5
FVC%	87.0 ± 16.4	89.2 ± 14.8	0.5
FEV_1%	84.5 ± 21.5	83.9 ± 15.0	0.8
FEV_1/FVC	81.0 ± 9.5	80.6 ± 8.9	0.8
Uric acid	5.1 ± 1.1	4.6 ± 1.0	0.03
Pro BNP	243.8 ± 270.2	78.8 ± 124.0	0.001
Troponin	0.006 ± 0.003	0.005 ±0.004	0.5
Glucose	150.9 ± 103.0	106.2 ± 40.1	0.003
D-Dimer	0.90± 0.8	0.61 ± 0.7	0.09
Hb	13.1 ± 1.9	13.3 ± 1.7	0.7
RDW	14.85 ±2.1	14.3 ± 1.7	0.2
Triglyceride n:	205.7 ± 101.6	180.1 ± 175.2	0.5
Cholesterol n:	211.0 ± 56.2	187.3 ± 35.8	0.02
HDL	44.4 ± 10.7	49.1 ± 11.1	0.09
LDL	127.4 ± 49.8	105.2 ± 28.9	0.01
CRP	9.4 ± 8.9	6.4 ± 7.4	0.1
Creatinine	0.75 ± 0.17	0.71 ± 0.14	0.2

Table II. CT findings of patients with pulmonary embolism.

	Pulmonary embolism present (n = 25, 23.8%)	Pulmonary embolism absent (n = 80, 76.2%)	n: 105 *p*-value
The RV/LV diameter ratio	0.83 ± 0.18	0.79 ± 0.14	0.3
Right atria mm^2	1878.3 ± 434.2	1402.4 ± 402.9	0.001
Right ventricle mm^2	1644.9 ± 567.8	1381.3 ± 389.2	0.01
Left atria mm^2	2031.62 ± 459.2	1580.2 ± 430.2	0.001
Left ventricle mm^2	2022.9 ± 635.8	1602.8 ± 518.2	0.001
GGO	20.0	12.7	0.3
Consolidation	4.0	0	0.07
GGO mixed consolidation	0	1.3	0.5
Air bronchogram	0	0	
Vascular or bronchial wall thickening	16.0	5.1	0.07
Crazy paving pattern	0	0	
Fibrotic pattern	0	2.5	0.4
Nodular pattern	8.0	3.8	0.3
Central pulmonary arteries %	0		
Lobar %	4.2		
Segmental %	91.7		
Subsegmental %	4.2		

However, in the follow-up studies lasting from 6 months to 2 years in patients rehabilitated from severe acute respiratory syndromes (SARS), the most common abnormality detected was an impaired diffusing capacity of the lungs (DLCO), which ranged from 15.5% to 43.6%17-19. Park et al[20] showed that 37% of Middle East respiratory syndrome (MERS) survivors at the 1-year follow-up still had a deterioration in DLCO. Mo et al[21] evaluated non-critical cases of COVID-19 among survivors discharged 25-40 days after initial symptoms and found impairment in diffusing capacity in 51 (47.2%) out of 110 cases. In a prospective study[22] conducted in Italy, four months after hospital discharge, carbon monoxide diffusion capacity, used as a marker of pulmonary-vascular integrity, was low in 52% of COVID-19 patients. Frija-Masson et al[23] analyzed 50 patients retrospectively and found an isolated decreasing in diffusing capacity in 13 (26%) out of 50 patients after 30 days from the infection. According to the authors, widespread damage to alveolar epithelial cells and endothelial cells due to COVID-19 infection may produce alveolar and chronic vascular remodeling leading to lung fibrosis and/or pulmonary hypertension[4,23]. Furthermore, the incidence of pulmonary embolism in COVID-19 patients varied between 1.9% and 35.3% in studies[24,25], and the cumulative incidence of pulmonary embolism in the intensive care unit rose to 50%. In COVID-19, pulmonary artery thrombus may develop by direct activation of the coagulation cascade by a cytokine storm[25], or by inflammatory mechanisms triggered by alveolar and endothelial damage, as a result of diffuse alveolar damage[26]. Endothelial damage can occur by host response or by direct viral infection of endothelial cells[26]. Endothelial damage and inflammation, which may occur with viral infection, are likely to lead to late pulmonary thrombus.

Table III. The predictors of pulmonary embolism for patients with dyspnea after a COVID-19 infection in Logistic Procedures.

	OR (95% CI)	Pulmonary embolism *p*-value
Age	1.1 (1.0 to 1.1)	0.04
NYHA class	4.3 (1.2 to 16.6)	0.03
Pulmonary artery diameter	1.2 (1.0 to 1.5)	0.03

Note: Multivariate logistic model showing adjusted odds ratios of statistically significant variables with confidence intervals (CI). Non-significant variables considered for inclusion included age, gender, BMI, smoking, FEV_1/FVC, pulmonary artery diameter, oxygen saturation, D-dimer, pro-BNP, troponin, uric acid and right/left ventricle ratio, glucose, cholesterol.

In the current study, pulmonary embolism is more likely to develop in patients previously admitted in the critical care unit. In severely ill patients, more severe inflammation and subsequent pulmonary thrombus may develop more frequently.

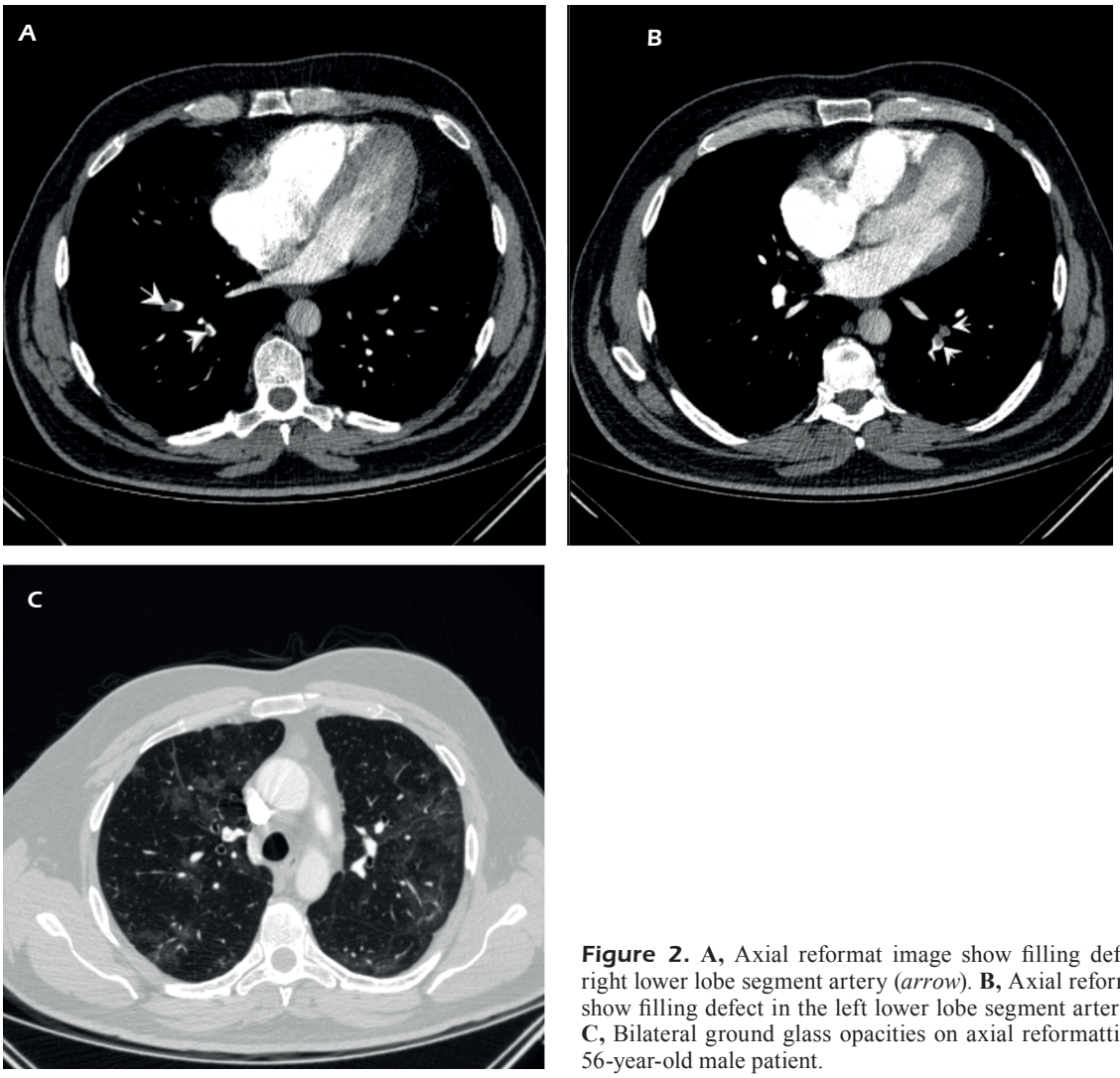


Figure 2. A, Axial reformat image show filling defect in the right lower lobe segment artery (*arrow*). **B,** Axial reformat image show filling defect in the left lower lobe segment artery (*arrow*). **C,** Bilateral ground glass opacities on axial reformatting image. 56-year-old male patient.

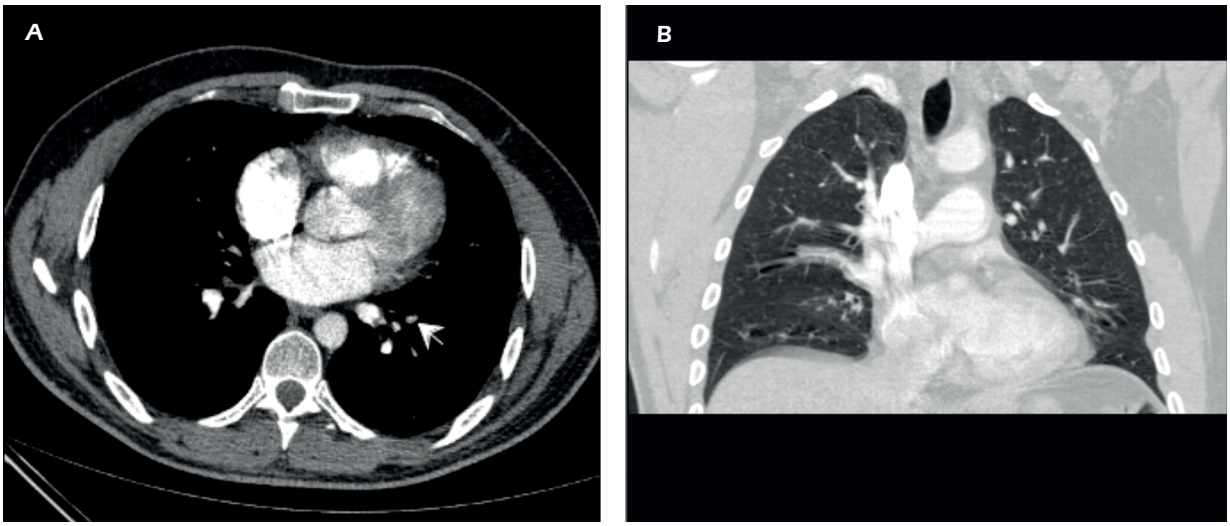


Figure 3. A, Axial reformat image show filling defect in the left lower lobe segment artery (*arrow*). **B,** Normal parachymal window on coronal reformatting image. 43-year-old male patient.

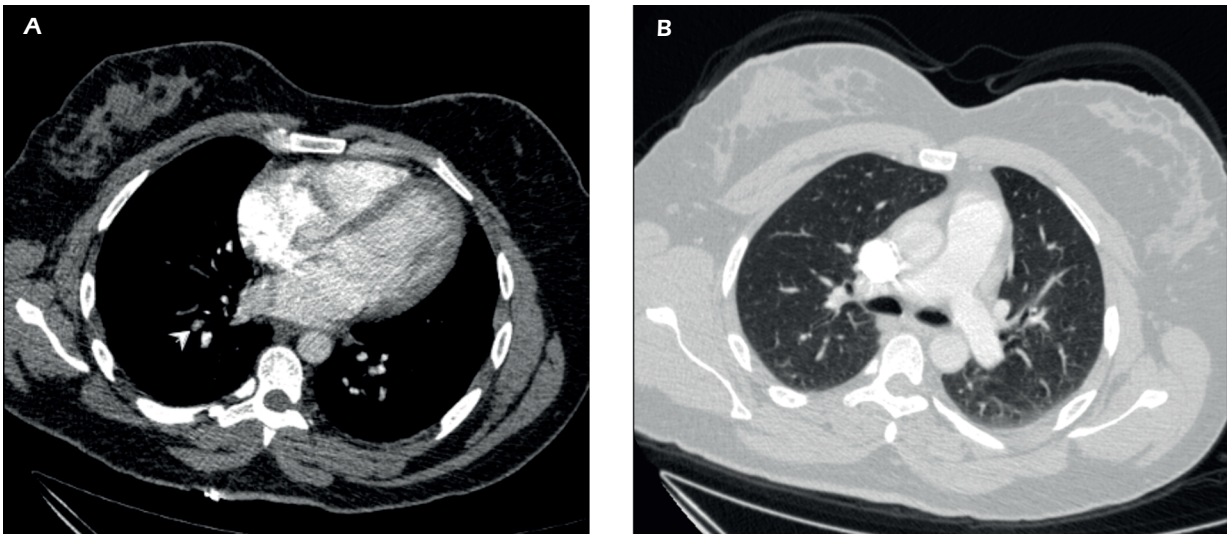


Figure 4. A, Axial reformat image show filling defect in the right lower lobe segment artery (*arrow*). **B,** Axial reformatting image showing normal parenchyma window. 41-year-old female patient.

Limitations

It should be noted that this study had some limitations. The number of studied patients was relatively small; moreover, the study was single-centered, which may make it difficult to generalize the results. However, the prospective nature of the study may still be important.

Conclusions

Pulmonary embolism is common in patients with new or ongoing dyspnea after COVID-19 infection, which requires developing treatment strategies. There are significant and graded associations between NYHA functional classes and the incidence of a pulmonary embolism in these patients, which may guide the physician during the clinical practice. The potential for pulmonary vascular sequelae to be a public health concern should not be underestimated.

Conflict of Interest

The authors of this article do not declare any relationship with any company whose products or services may be related to the subject of the article.

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The authors state that this work has not received any funding.

Authors' Contribution

M.E, A.E. and A.B. planned the work. M.E. made the analysis. F.A.İ. and H.A. prepared the draft. All authors participated in the interpretation of the results and in the writing of the article.

Ethical 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: 13/01, Meeting date: 9.09.2021).

Informed Consent

Consent form for the study was obtained from all patients.

References

1) Stachura T, Celejewska-Wójcik N, Polok K, Górka K, Lichołai S, Wójcik K, Krawczyk J, Kozłowska A, Przybyszowski M, Włoch T, Górka J, Sładek K. A clinical profile and factors associated with severity of the disease among Polish patients hospitalized due to COVID-19 – an observational study. Adv Respir Med 2021; 89: 124-134.
2) Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies. Semin Thromb Hemost 2020; 46: 763-771.
3) Hall J, Myall K, Lam JL, Mason T, Mukherjee B, West A, Dewar A. Identifying patients at risk of post-discharge complications related to COVID-19 infection. Thorax 2021; 76: 408-411.

4) 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.

5) Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, Kurz K, Koppelstätter S, Haschka D, Petzer V, Boehm A, Aichner M, Tymoszuk P, Lener D, Theurl M, Lorsbach-Köhler A, Tancevski A, Schapfl A, Schaber M, Hilbe R, Nairz M, Puchner B, Hüttenberger D, Tschurtschenthaler C, Aßhoff M, Peer A, Hartig F, Bellmann R, Joannidis M, Gollmann-Tepeköylü C, Holfeld J, Feuchtner G, Egger A, Hoermann G, Schroll A, Fritsche G, Wildner S, Bellmann-Weiler R, Kirchmair R, Helbok R, Prosch H, Rieder D, Trajanoski Z, Kronenberg F, Wöll E, Weiss G, Widmann G, Löffler-Ragg J, Tancevski I. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. Eur Respir J 2021; 57: 2003481.

6) Chevinsky JR, Tao G, Lavery AM, Kukielka EA, Click ES, Malec D, Kompaniyets L, Bruce BB, Yusuf H, Goodman AB, Dixon MG, Nakao JH, Datta SD, MacKenzie WR, Kadri SS, Saydah S, Giovanni JE, Gundlapalli AV. Late Conditions Diagnosed 1-4 Months Following an Initial Coronavirus Disease 2019 (COVID-19) Encounter: A Matched-Cohort Study Using Inpatient and Outpatient Administrative Data-United States, 1 March-30 June 2020. Clin Infect Dis 2021; 15: S5-S16.

7) Vechi HT, Maia LR, Alves MM. Late acute pulmonary embolism after mild Coronavirus Disease 2019 (COVID-19): a case series. Rev Inst Med Trop São Paulo 2020; 62: e63.

8) McDonald LT. Healing after COVID-19: are survivors at risk for pulmonary fibrosis? Am J Physiol Lung Cell Mol Physiol 2021; 1: L257-L265.

9) Rich S. Primary pulmonary hypertension: executive summary from the World Symposium on primary pulmonary hypertension. Evian, France: WHO; 1998.

10) 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.

11) Gouin B, Blondon M, Jiménez D, Fernández-Capitán C, Bounameaux H, Soler S, Duce R, Carles Sahuquillo JC, Ruiz-Giménez N, Monreal M. Clinical Prognosis of Nonmassive Central and Noncentral Pulmonary Embolism: A Registry-Based Cohort Study. Chest 2017; 151: 829-837.

12) De Monyé W, Sanson BJ, Mac Gillavry MR, Pattynama PM, Büller HR, van den Berg-Huysmans AA, Huisman MV; ANTELOPE-Study Group. Embolus location affects the sensitivity of a rapid quantitative D-dimer assay in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med 2002; 1: 345-348.

13) Ooi GC, Khong PL, Muller NL, Yiu WC, Zhou LJ, Ho JC, Lam B, Nicolaou S, Tsang KW. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. Radiology 2004; 230: 836-844.

14) Taha M, Nguyen P, Sharma A, Taha M, Samavati L. Forty-One-Year-Old Man with Pulmonary Embolism 5 Months After COVID-19. Clin Med Insights Circ Respir Pulm Med 2021; 8:1179548420986659.

15) Vechi HT, Maia LR, Alves MDM. Late acute pulmonary embolism after mild Coronavirus Disease 2019 (COVID-19): a case series. Rev Inst Med trop S Paulo 2020; 4: e63.

16) Kanso M, Cardi T, Marzak H, Schatz A, Faucher L, Grunebaum L, Morel O, Jesel L. Delayed pulmonary embolism after COVID-19 pneumonia: a case report. Eur Heart J Case Rep 2020; 4: 1-4.

17) Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, Ko FW, Chan MC, Chan DP, Tong MW, Rainer TH, Ahuja AT, Cockram CS, Sung JJ. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax 2005; 60: 401-409.

18) Hui DS, Wong KT, Ko FW, Tam LS, Chan DP, Woo J, Sung JJ. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest 2005; 128: 2247-2261.

19) Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology 2010; 15: 543-550.

20) Park WB, Jun KI, Kim G, Choi JP, Rhee JY, Cheon S, Lee CH, Park JS, Kim Y, Joh JS, Chin BS, Choe PG, Bang JH, Park SW, Kim NJ, Lim DG, Kim YS, Oh MD, Shin HS. Correlation between Pneumonia Severity and Pulmonary Complications in Middle East Respiratory Syndrome. J Korean Med Sci 2018; 33: e169.

21) 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.

22) 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.

23) 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.

24) 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; 16: 124.

25) 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; 30: 2001365.

26) 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. Lancet 2020; 395: 1417-1418.