

Lung Perfusion Scintigraphy in Early Post-COVID-19: A Single Centre Retrospective Study

Running Title: Lung scintigraphy in early post-COVID-19

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Conflict of Interest

No potential conflicts of interest relevant to this article exist.

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Authors' contributions

SD: conceived the study, interpretation of data, and writing the manuscript. MR, TL, RTG, DS: Data collection and interpretation of results. All authors read and approved the final manuscript.

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Abstract

Purpose: The incidence of thromboembolic complications in COVID-19 infection is well-recognized. The present study retrospectively evaluated the type and prevalence of lung perfusion defects in early post-COVID-19 patients with hypoxia and was aimed to identify the risk factors for mismatched perfusion defects.

Methods: We analyzed the single-photon emission computed tomography/computed tomography (SPECT/CT) of 54 early post-COVID-19 patients (male: 44). Logistic regression analysis was used to examine the risk.

Results: The mean age of the study population was 55.4 years (range: 34-76). All received prophylactic anticoagulation from the day of hospitalization to the date of perfusion scan. The median interval between COVID-19 positive reports and lung perfusion scan was 22 days. Lung perfusion defects (of any type) were observed in the majority (87%). Twenty-three subjects (42.6%) had mismatched perfusion defects. Mismatched perfusion defects were segmental in 14 subjects (25.9%) and subsegmental in 11 subjects (20.4%). Higher age is a risk for mismatched perfusion defects (Odds ratio: 1.06, 95% CI: 0.99-1.13, p=0.06). The subjects with serum D-dimer \geq 2500 ng/ml on the day before the scan were not at higher risk for having mismatched perfusion defects (OR: 1.14; 95% CI: 0.34-3.9, p=0.83).

Conclusion: Despite prophylactic anticoagulation, the mismatched perfusion defects suggestive of pulmonary thromboembolism were observed. Serum D-dimer in early post-COVID-19 is a poor predictor of mismatched perfusion defects. Confirmed evidence of pulmonary embolism by imaging studies should support the decision to extend anticoagulant prophylaxis in post-COVID-19.

Keywords: early post-COVID-19, D-dimer, lung perfusion scan, novel Coronavirus disease -2019,

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel member of the enveloped RNA beta coronavirus family causes the coronavirus disease 2019 (COVID-19). Most COVID-19 patients are either asymptomatic or mildly symptomatic.

The thrombogenic potential of SARS-CoV-2 infection is well-recognized (1). The coagulation abnormalities along with prolonged bed rest due to hospitalization lead to high incidences of venous thromboembolism (VTE) and thromboembolic complications, mostly pulmonary embolism (PE). Thromboprophylaxis with low-molecular-weight heparin is currently recommended for the treatment of hospitalized COVID-19 patients. Despite adequate anticoagulant therapy, the incidence of both VTE and PE especially in severe and critically ill COVID-19 patients had been reported (1). An observational study of over five hundred COVID-19 patients admitted to eight intensive care units (ICU) in France reported 22.7% thrombotic complications, mostly PE (2). A meta-analysis of over seven thousand COVID-19 patients showed the pooled in-hospital incidence of PE in the general ward and ICU was 14.7% and 23.4%, respectively (3). Currently, there is no recommendation on prophylactic anticoagulation for COVID-19 patients with raised serum D-dimer at the time of discharge.

Multi-detector CT pulmonary angiography (CTPA) is the gold standard for diagnosing PE. A ventilation/perfusion (V/Q) scan is an alternative to CTPA for diagnosing PE. However, there is a potential risk of infection transmission during V/Q scan (4). The lung perfusion scintigraphy by single-photon emission computed tomography/computed tomography (SPECT/CT) is a safe alternative for diagnosing PE, especially for COVID-19 patients. The role

of SPECT/CT in diagnosing PE in COVID-19 patients has been established (4). A perfusion scan of the COVID-19 patient is useful to evaluate residual clot burden and small vessel injuries (5). At least one wedge-shaped peripheral perfusion defect estimated as \geq 50% involvement of a pulmonary segment without corresponding CT image abnormality is indicative of PE in COVID-19 (4).

After recovery from active infection, a few COVID-19 patients, especially those who were severe and critically ill, continue to have hypoxia. The causes of persistent hypoxia in early post-COVID-19 are not fully understood. Impaired lung perfusion is considered as one of the underlying pathophysiological mechanisms. The presence of perfusion defects in early post-COVID-19 patients with persistent hypoxia was previously not investigated. The present study retrospectively evaluated the type and prevalence of lung perfusion defects in early post-COVID-19 patients with hypoxia and was aimed to identify the risk factors for mismatched perfusion defects.

Methods

Study Design and Participants: We conducted a retrospective analysis of a cohort of 54 early post-COVID-19 patients admitted to the pulmonary medicine department of our institute between August 2020 and March 2021. The Institutional Ethics Committee approved this retrospective study and the requirement to obtain informed consent was waived off. All subjects were microbiologically confirmed SARS-CoV-2 infection (either by RT-PCR or Rapid Antigen Testing). After two consecutive negative RT-PCR reports for SARS-CoV-2, these patients were shifted from the COVID wards to the pulmonary ward for ongoing hypoxia. The study subjects were stratified into two categories: moderate COVID-19 i.e. those who received low (e.g. nasal cannula) or high flow (e.g. face mask, non-rebreathing mask, and high flow nasal cannula)

oxygen therapy and severe COVID-19 i.e. those who received invasive and/or non-invasive ventilator support during active COVID-19 infection.

Data Collection: The demographic characteristics, comorbidities, clinical profile, laboratory reports, and treatment received were extracted from the medical records.

Imaging protocol: After intravenous injection of 4-6 mCi of ^{99m}Tc - macro-aggregated albumin containing $4-6 \times 10^5$ particles, SPECT imaging with low dose CT was carried out in supine position. Planar imaging was done in multiple projections (anterior and posterior; right lateral and left lateral; right anterior oblique and posterior oblique; left anterior oblique and left posterior oblique). The images were reconstructed in the transaxial, coronal, and sagittal views and were reviewed for perfusion defects. The mismatched perfusion defects in this study were based on a mismatch between CT and scintigraphy images. The perfusion defects were further categorized into the following:

- i. Mismatched segmental perfusion defect: Wedge-shaped peripheral defect involving $\geq 50\%$ of a pulmonary segment in all three orthogonal planes and without corresponding parenchymal abnormalities in the CT images.
- ii. Mismatched sub-segmental perfusion defect: At least one wedge-shaped peripheral defect involving $< 50\%$ of a pulmonary segment in all three orthogonal planes and without corresponding parenchymal abnormalities in the CT images.
- iii. Matched segmental perfusion defect: Any perfusion defect involving $\geq 50\%$ of a pulmonary segment in all three orthogonal planes with corresponding parenchymal abnormalities (e.g. consolidation, ground-glass opacities, fibrosis, etc.) in the CT images.

iv. Matched sub-segmental perfusion defect: Any perfusion defect involving <50% of a pulmonary segment in all three orthogonal planes with corresponding parenchymal abnormalities (e.g. consolidation, ground-glass opacities, fibrosis, etc.) in the CT images.

Statistical Analysis

The study variables were expressed as mean \pm SD, median with interquartile range, and proportion. The odds ratio with 95% confidence intervals was calculated by using logistic regression analysis to examine the association of risk factors with mismatched perfusion defects (segmental/subsegmental, and both). The risk factors assessed in this study were age, gender, serum D-dimer on the day before the perfusion study, and interval (in days) between lung scintigraphy and positive COVID-19 reports, and the severity of disease (categorical variables). The statistical analysis was performed with SPSS, version 20.0 (IBM). A p-value of <0.05 was taken as statistically significant.

Results

Demographic profile

The total study population was 54, and the majority were men ($n = 44$, 81.5%). The mean age was 55.4 years (median: 56; range: 34 -76). The history of diabetes mellitus, hypertension, and coronary artery disease was present in 19 (35.2%), 24 (44.4%), and 3 (5.6%) subjects respectively. Fourteen subjects had moderate COVID-19 infections (25.9%) and 40 had severe COVID-19 infections (74.1%). All patients received low-molecular-weight heparin prophylaxis from the day of hospitalization to the date of the perfusion scan. The serum D-dimer on the day before perfusion scan was available for 44 subjects. The median serum D-dimer was 3540 ng/ml (IQR: 1457-6549, range: 500-15000). The median interval between COVID-19

positive reports and lung perfusion scan was 22 days (IQR: 15-33; range: 8-107). The single person with the highest interval was on an oral apixaban tablet.

The perfusion Scintigraphy

The lung perfusion defects (of any type) were observed in 47 subjects (87%). The matched perfusion defects were the commonest and were observed in 39 subjects (72.2%). The type and prevalence of perfusion defects are presented in Table 1. The perfusion defects between moderate and severe COVID-19 were not different. Mismatched perfusion defects were observed in 23 subjects (42.6%). The majority (61%) of mismatched perfusion were segmental. Six subjects had both matched and mismatched segmental perfusion defects. The mismatched segmental perfusion defects were more on the right lung as compared to the left (8 vs. 4, p<0.01).

There was no significant difference in serum D-dimer between the subjects with only mismatched segmental perfusion defects and subjects with only matched segmental perfusion defects (median 3700 ng/ml vs. median 3804 ng/ml; p >0.05). The logistic regression analysis showed increasing age is at higher risk for mismatched perfusion defects (OR: 1.06, 95% CI: 0.99-1.13, p=0.06). The longer interval between positive COVID-19 results and scintigraphy study was not at lower risk of mismatched perfusion defects (OR: 0.66; 95% CI: 0.22-1.96, p=0.5). The risk for mismatched perfusion defects in men was not higher compared to women (OR: 1.14; 95% CI: 0.28-4.62, p=0.9). Severe COVID-19 were also not at higher risk of having mismatched perfusion defects compared to moderate COVID-19 (OR: 0.67; 95% CI: 0.19-2.27, p=0.5). The patients with serum D-dimer \geq 2500 ng/ml before the day of the scan were

not at higher risk for having mismatched perfusion defects (OR: 1.14; 95% CI: 0.34-3.9, p=0.83).

Discussion

The present study showed mismatched perfusion defects suggestive of pulmonary embolism in early post-COVID-19 patients, despite receiving anticoagulation prophylaxis from the day of hospitalization. Lung perfusion defects in COVID-19 were matched, mismatched, and the distribution was segmental, sub-segmental. Higher age is at risk for having mismatched perfusion defects.

The SARS-CoV-2 binds with the angiotensin-converting enzyme-2 (ACE-2) receptor present on the cell surface. The binding of the virus on ACE-2 receptors leads to up-regulation of angiotensin II and activation of the renin-angiotensin-aldosterone system (RAAS). Both RAAS and angiotensin II enhance platelet activity and activate the coagulation cascade. RAAS and angiotensin II also increase the expression of IL-6 and other inflammatory markers, which further amplifies the coagulation cascade (6). Increased levels of clotting factors with disruption of the normal homeostasis of vascular endothelial cells in COVID-19 lead to microangiopathy and thrombus formation. Lung autopsies of COVID-19 patients demonstrated endothelial injury with intracellular virus in the pulmonary vasculature, microangiopathy, and widespread thrombosis with occlusion of alveolar capillaries (7). The deposition of fibrin and thrombin in the pulmonary microvasculature leads to impaired lung perfusion. The sub-segmental mismatched perfusion defects in our study confirm the small vessel injuries.

CTPA helps to visualize the clots within the pulmonary vasculature, and most investigators used it for diagnosing PE in COVID-19. A Dutch study observed majority of PE diagnosed by CTPA in COVID-19 patients were in segmental or more proximal arteries (8). Another study found the majority of PE diagnosed by CTPA was sub-segmental (93%) in distribution (9). Therefore, PE in COVID-19 involves both segmental and sub-segmental pulmonary arteries. CTPA can miss the thrombus in distal sub-segmental small vessels and unable to assess the tissue perfusion. Thus, there is a risk of underestimation of PE in COVID-19 by CTPA (5). Idilman et al. Identified 25.8% perfusion defects on dual-energy computed tomography of 31 mild-to-moderate COVID-19 patients (10). The majority of PE (75%) in their study was without macroscopic thromboembolism in CTPA. Except for few case reports and small case series, the lung perfusion defects, especially in early post-COVID-19 were not much investigated (11, 12, 13). The prevalence of segmental mismatched perfusion defects i.e. PE in our study was similar to the previous study (3). The longer interval between COVID-19 positive reports and scan didn't reduce the risk for mismatched perfusion defects. Therefore, despite anticoagulant prophylaxis, PE of COVID-19 takes a longer period to resolve. Mismatched perfusion defects in our study were more on the right side, similar to the observation by Peltzer et al (14).

Serum D-dimer is considered a sensitive test to diagnose thrombotic states including PE. A systematic review and meta-analysis showed serum D-dimer in severe COVID-19 was significantly higher and correlate with the disease severity (15). The serum D-dimer in COVID-19 patients rise due to the activation of the blood coagulation cascade secondary to systemic inflammatory response or as a direct consequence of the virus itself. Serum D-dimer in COVID-

19 patients' correlates poorly with the VTE score (16). Several investigators tried to find the cut-off values of D-dimer to identify the risk of PE in active COVID-19 infection. Cui et al. found serum D-dimer of 1500 ng/ml has 85.0% sensitivity and 88.5% specificity for predicting VTE (17). Lorant et al. observed serum D-dimer threshold of 2660 µg/L detected all PE by CTPA in COVID-19 patients (18). We observed subjects with serum D-dimer \geq 2500 ng/ml were not at higher risk of having mismatched perfusion defects. Therefore, raised serum D-dimer in early post-COVID-19 is not necessarily attributed to underlying PE.

This study had several limitations. The study was a single-center retrospective study and not all early post-COVID-19 patients with hypoxia were investigated. The serial serum D-dimer of all patients was also not available. The number of study subjects was small and no mild COVID-19 patients were enrolled.

The present study showed the SPECT/CT images suggestive of pulmonary embolism were independent of serum D-dimer before the day of scanning. An elevated serum D-dimer in early post-COVID-19 should not be a criterion for post-hospitalization anticoagulant therapy unless imaging studies confirm the PE. Carefully designed prospective studies are necessary to identify the post-COVID-19 patients who will require extended thromboprophylaxis.

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Types of perfusion abnormalities	Moderate COVID-19 (N=14) n (%)	Severe COVID-19 (N=40) n (%)	Total (N=54) n (%)
Perfusion defects (Any)	14 (100%)	33 (82.6%)	47 (87%)
Mismatched perfusion defects	7 (50%)	16 (40%)	23 (42.6%)
Segmental	3 (21.4%)	11 (27.5%)	14 (25.9%)
Sub-segmental	4 (28.6%)	7 (17.5%)	11 (20.4%)
Both segmental &sub-segmental	0	2 (5%)	2 (3.7%)
Matched-perfusion defects	11 (78.6%)	28 (70%)	39 (72.2%)
Segmental	6 (42.9%)	13 (32.5%)	19 (35.2%)
Sub-segmental	7 (50%)	23 (57.5%)	30 (55.6%)
Both segmental &sub-segmental	2 (14.3)	8 (20%)	10 (18.5%)
Both matched and mismatched perfusion defects	4 (28.6%)	11 (27.5%)	15 (27.8%)

Table 1 Distribution of various types of lung perfusion abnormalities

Graphical Abstract

