Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s13139-022-00776-0

ORIGINAL ARTICLE

Identification and Follow-up of COVID-19 Related Matching Ventilation and Perfusion Defects on Functional Imaging Using VQ SPECT/CT

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Received: 9 June 2022 / Revised: 13 September 2022 / Accepted: 14 September 2022

Abstract

Purpose Available clinical data have revealed that coronavirus disease 2019 (COVID-19) is associated with a risk of pulmonary microthrombosis and small airway disease. These patients present with varying degrees of perfusion abnormalities. The purpose of this study was to evaluate the use of a ventilation/perfusion single-photon emission computed tomography/computed tomography (VQ SPECT/CT) in the detection and follow-up of persistent lung perfusion abnormalities that were suspected to be due to pulmonary microthrombosis, small airway disease, or both.

Methods A retrospective study was conducted at the department of nuclear medicine of Universitas Academic Hospital in Bloemfontein, South Africa. We reviewed the studies of 78 non-hospitalized patients with COVID-19 infection referred to our department from July 2020 to June 2021 for a perfusion only SPECT/CT study or a VQ SPECT/CT study. Pulmonary embolism was suspected in all 78 cases.

Results Seventy-eight patients were studied. The median (interquartile range) age was 45 (41–58) years, and the majority ($n=69$; 88.5%) were females. Twenty-two (28.2%) of these patients had matching VQ defects with mosaic attenuation on CT. All nine of the patients who had follow-up studies had these abnormalities persistently, even after 1 year.

Conclusion We confirm that the VQ scan is a safe and effective tool to identify and follow-up recovered COVID-19 patients with persistent ventilation and perfusion abnormalities suspicious of small airway disease and pulmonary microthrombosis.

Keywords VQ SPECT/CT · Pulmonary microthrombosis · COVID-19 · Small airway disease · Mosaic hypoattenuation

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus that has been responsible for the coronavirus disease 2019 (COVID-19) pandemic. Since its discovery, millions of cases have been recorded worldwide with thousands of deaths. Thrombotic complications, including microvascular thrombosis, venous thromboembolic disease, and stroke were associated with this disease [1]. Evidence today suggests that the thrombotic manifestations of COVID-19 are due to the ability of the virus to invade endothelial cells via angiotensin-converting enzyme 2 (ACE-2) expressed on the endothelial cell surface [1–3]. This causes subsequent inflammation of the endothelium, complement activation, generation of thrombin, platelet, and leukocyte recruitment. All these factors eventually lead to immunothrombosis, ultimately causing thrombotic complications, including microthrombosis [1]. A prothrombotic state at the pulmonary level is a risk factor for perfusion abnormalities [4]. Existing clinical data have also highlighted that COVID-19 is associated with a long-term risk of persistent small airway disease as a result of small airway trapping, which can manifest as mosaic

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Published online: 24 September 2022

hypoattenuation on computed tomography (CT) images, especially in patients with severe disease [3–6].

More than 87% of patients have reported the persistence of at least one symptom after recovery from COVID-19 [3]. In our facility, we observed that a subset of patients had persistent cardiopulmonary symptoms after recovery form COVID -19. These patients were investigated for pulmonary embolism (PE) with a ventilation/perfusion (VQ) single-photon emission computed tomography/computed tomography (SPECT/CT) scan, and our findings were published [7]. However, some of these patients showed a consistent pattern of persistent matched ventilation and perfusion defects, with mosaic hypoattenuation on CT, likely suggestive of small airway disease, pulmonary microthrombosis, or a combination of both. Data in the literature have pointed to the fact that CT could detect suspected air trapping manifesting, as areas of mosaic hypoattenuation in the lungs of patients who have recovered from COVID-19 [5, 8, 9]. Some of these findings have been persistent for up to a few months after the diagnosis of COVID-19 [4, 5]. Of significant note is that these studies have failed to demonstrate extensively the significant reduction or absence of perfusion in those areas with mosaic hypoattenuation on CT. We intended to demonstrate the utility and significance of the VQ SPECT/CT scan in the identification and follow-up of recovered COVID-19 patients who presented with persistent cardiopulmonary symptoms and matched ventilation and perfusion defects, with mosaic hypoattenuation on CT.

Materials and Methods

The study was a retrospective cohort study conducted in a tertiary institution. Ethics approval was obtained from the appropriate ethics committee. We reviewed all the perfusion-only SPECT/CT and VQ SPECT/CT studies of 412 patients who had been investigated for PE as a complication of COVID-19 between July 2020 and June 2021. Seventy-eight of these patients were included in the study and had their VQ scans evaluated. The inclusion criteria of this study included de-isolated non-hospitalized patients diagnosed with COVID-19 being investigated for PE, age ≥ 18 years, increased D-dimer levels, and patients who had a VQ SPECT/CT study. The exclusion criteria of this

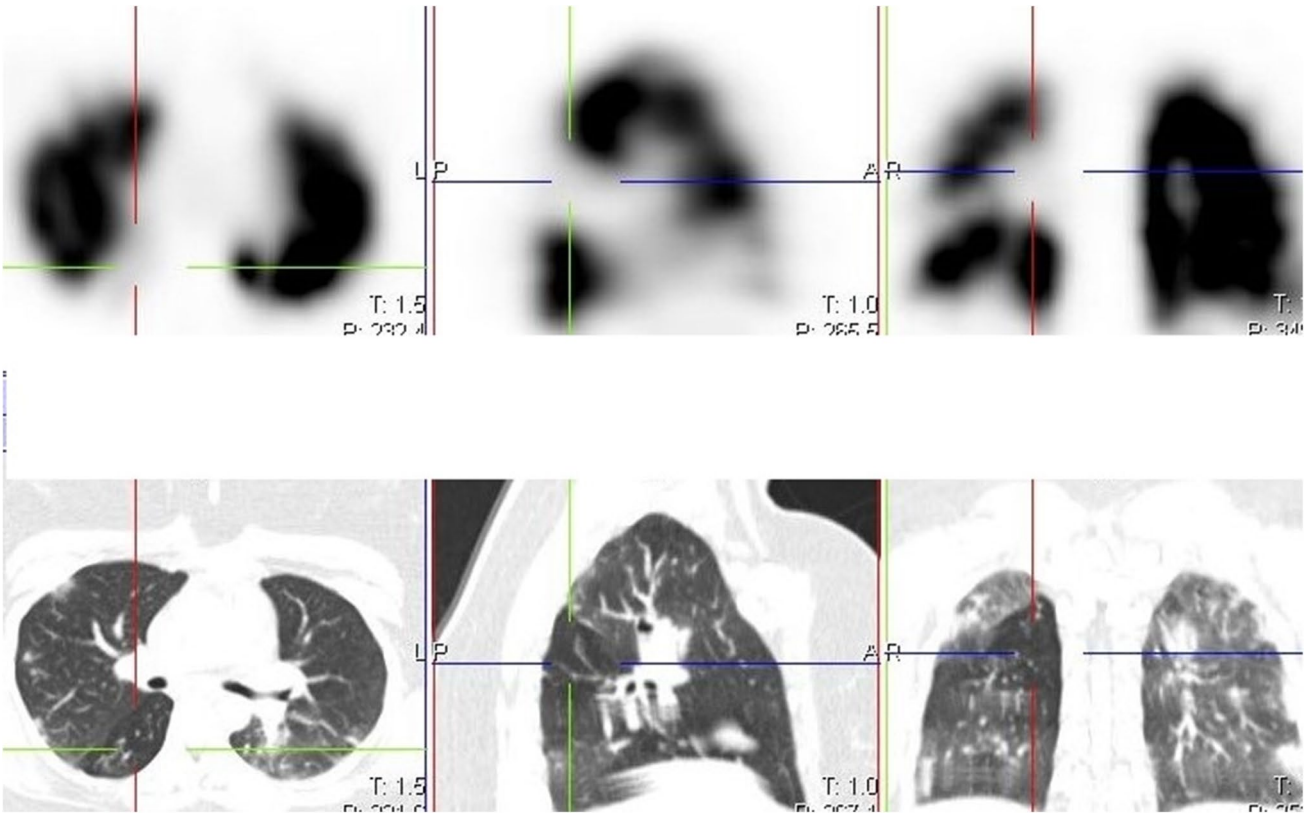

Fig. 1 Perfusion SPECT (above) and CT (below) of a 35-year-old female, who presented with persistent shortness of breath, 2 days after de-isolation following COVID-19. The SPECT images show a large perfusion defect in the medial segment of the right middle lobe, with corresponding mosaic hypoattenuation on the CT

study included all patients without a diagnosis of COVID-19, those who had a VQ SPECT study only, without a CT component, and hospitalized patients or patients with severe disease.

VQ SPECT/CT Imaging

The ventilation studies were carried out with 20–25 milliCurie (mCi) of technetium-99 metastable (^{99m}Tc) diethylenetriamine pentacetate (DTPA), using the SmartVent radioaerosol delivery system (Diagnostic Imaging Ltd., UK). Perfusion studies were performed with 3–5 mCi of ^{99m}Tc macro-aggregated albumin (MAA). The images from the ventilation and perfusion procedure were acquired with either a 16-slice SPECT/CT camera (Siemens Symbia T16 TruePoint, Siemens Medical Solutions USA, Inc.), or a 2-slice SPECT/CT camera (Siemens Symbia T2 TruePoint; Siemens Medical Solutions USA, Inc.). Both cameras are dual-headed gamma cameras, with a similar workstation and image processing unit.

The two gamma cameras had a low-energy high-resolution collimator attached. Single-photon emission computed tomography/computed tomography imaging was acquired immediately after the ventilation procedure at 15 s/stop, with 3° steps, in a 128×128 matrix. Perfusion SPECT imaging was then acquired after injection of the perfusion tracer at 12 s/stop, with 3° steps, in a 128×128 matrix. This was followed by a low-dose non-contrast chest CT scan, while the patient remained in the same position.

Image Processing and Data Analysis

All images were processed using the Syngo workstations of both gamma cameras. Single-photon emission computed tomography/computed tomography images were reconstructed using an iterative algorithm, and SPECT/CT fusion images were obtained using the multimodality Syngo imaging software on both workstations.

The data of each patient were collected using an Excel 2019 spreadsheet (Microsoft, USA) and analyzed by means of the statistical package Stata version 16 (StataCorp, USA). Two experienced nuclear medicine physicians with a total of 28 years of experience interpreted the scans, using the European VQ SPECT criteria.

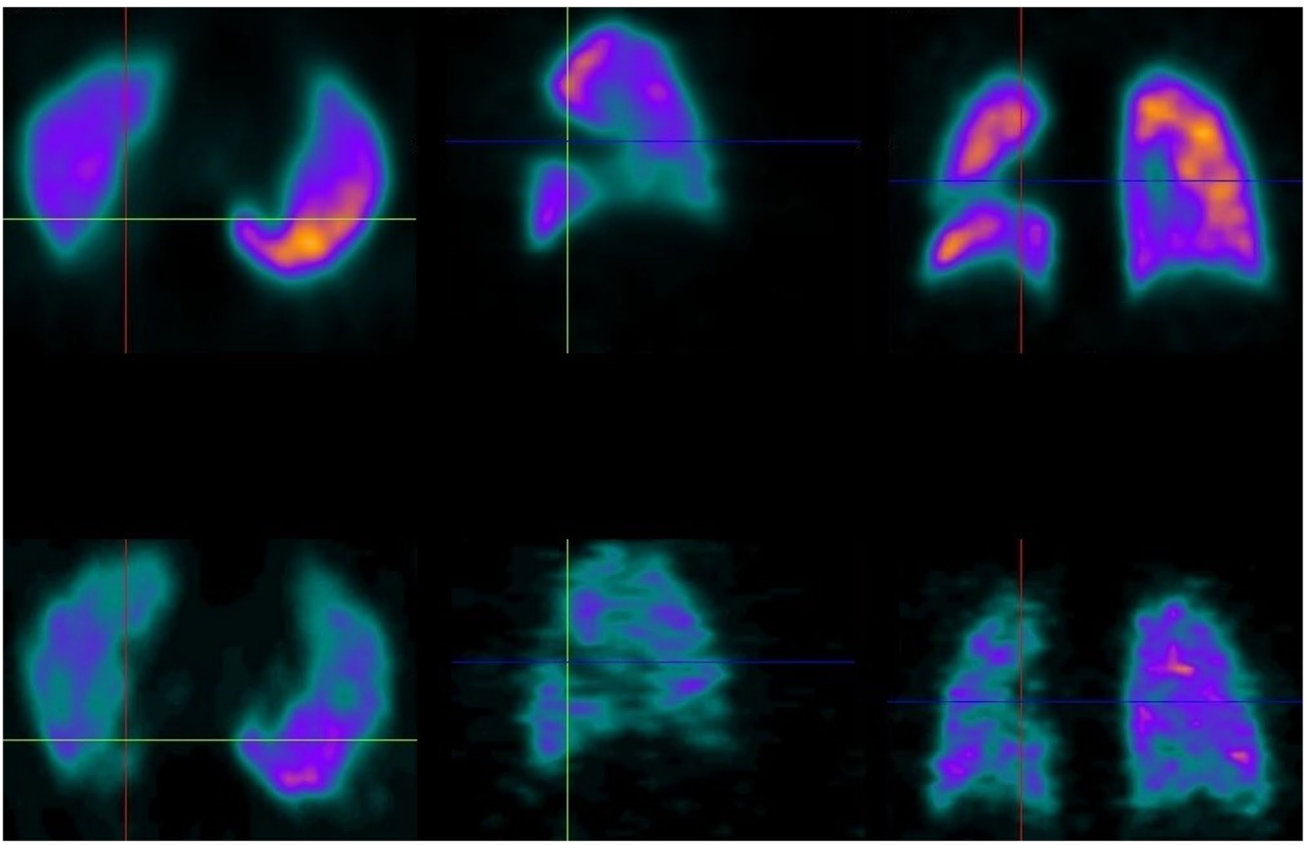

Fig. 2 Perfusion SPECT (above) and ventilation SPECT (below) of the same patient in Fig. 1 a, performed a year after the baseline study shows persistence of the perfusion defect, which is matched on the ventilation images

Table 1 Demographic and clinical characteristics

Characteristics	$N=78$
Age in years, *median (IQR* [a]	45 (41–58)
Sex, *n* (%)	
Female	69 (88.5)
Male	9 (11.5)
Scan findings with COVID-19 mosaic hypoperfusion, *n* (%)	
Yes	56 (71.8)
No	22 (28.2)
Follow-up study, *n* (%)	
Yes	9 (40.9)
No	13 (59.1)
Anticoagulation therapy, *n* (%)	
Yes	6 (27.3)
No	16 (72.7)
Microcalcification in regions with matched defect, *n* (%)	
Yes	13 (59.0)
No	9 (40.9)

[a]IQR (interquartile range)

Results

The median age was 45 (interquartile range [IQR] 41–58) years, and the majority ($n=69$; 88.5%) were females. Twenty-two (28.2%) of these patients had matching VQ defects with mosaic hypoattenuation on CT, which was highly suspicious for COVID-19-induced pulmonary microthrombosis, small airway trapping, or both. All 22 patients had a baseline perfusion only or VQ SPECT/CT study performed. Nine (40.9%) of the 22 patients had at least one follow-up VQ SPECT/CT. Of the nine patients who had a follow-up study, all (100%) had persistent matching perfusion defects. Six of these patients (66.7%) were on long-term therapeutic anticoagulation, as they were also diagnosed with PE during the same period of the study. Ten (45.5%) of the patients had a single matched perfusion defect; nine (40.9%) had two matched perfusion defects; two (9.1%) had four matched perfusion defects; while only one (4.5%) had 3 matched perfusion defects.

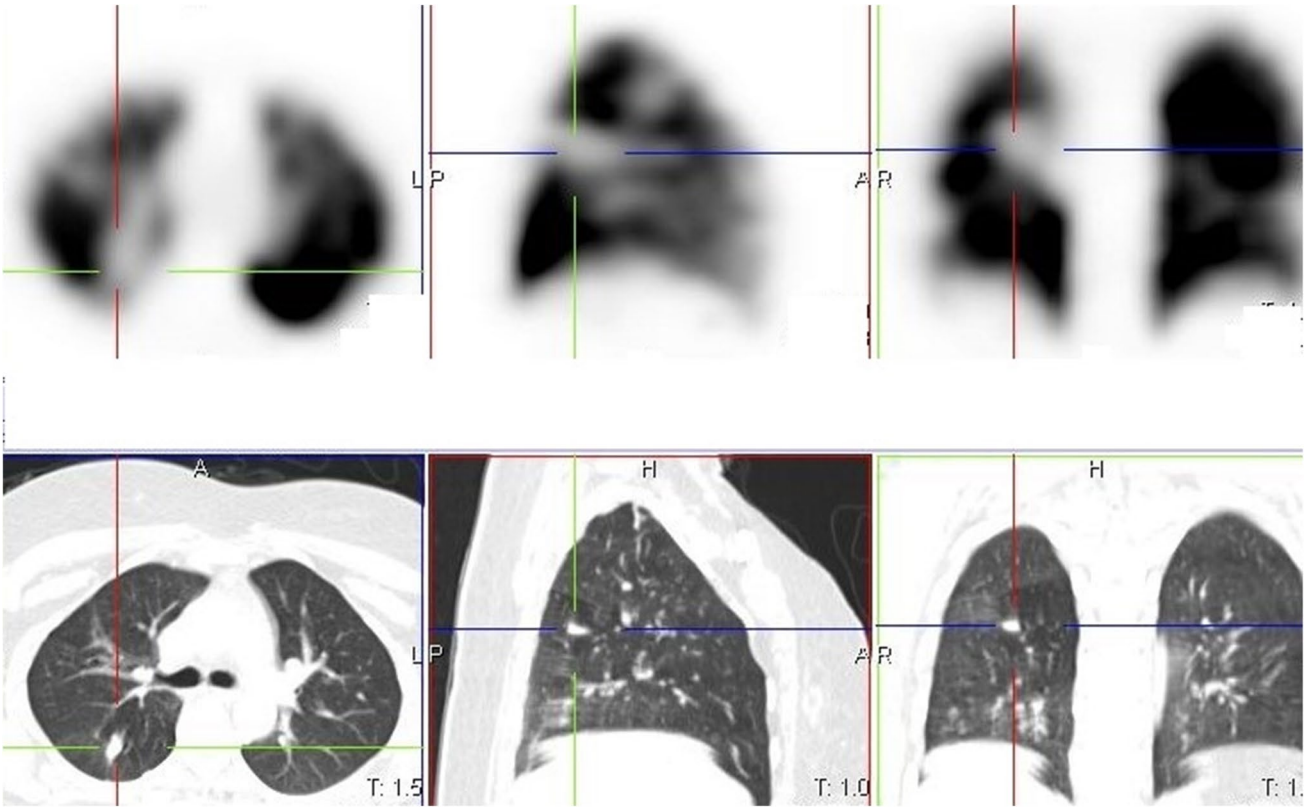

Fig. 3 Perfusion SPECT (above) and CT (below) of a 35-year-old female, who presented with persistent chest pain and shortness of breath, 5 days after de-isolation following COVID-19. The SPECT images show a large perfusion defect in the medial segment of the right middle lobe, with corresponding mosaic hypoattenuation on the CT. However, there is evidence of calcification noted on CT in the affected segment

Discussion

Our findings revealed that 28.2% of non-hospitalized COVID-19 patients, presenting to our facility with persistent cardiopulmonary symptoms for a VQ scan, showed matched perfusion defects on their scans, with mosaic hypoattenuation on the CT, a pattern we propose to refer to as COVID-19 mosaic hypoperfusion. Follow-up scans in nine of these patients showed that these findings were persistent. This is the first study conducted that identified and followed-up these patients up to a year, with a VQ SPECT/CT study. Other studies reported that some recovered COVID-19 patients with persistent respiratory symptoms had lung CT findings of mosaic hypoattenuation and small airway trapping as a result of small airway disease [4, 5, 8]. However, they have not been able to show clearly that perfusion abnormalities were observed that matched these mosaic hypoattenuated areas. They were also not able to follow-up these patients up to a year to show that these abnormalities remained persistent over such a long period of time. In our research, the scans of all the patients who had follow-up studies, showed that the perfusion and ventilation defects remained unchanged, without improvement or deterioration, even after a year, as illustrated in Figs. 1 and 2. Alpana et al. demonstrated on CT that persistent parenchymal and airway abnormalities in the form of air trapping and mosaic attenuation occurred more than 6 months after recovery from initial SARS-CoV-2 infection [8]. The Swiss COVID-19 multicenter study determined that in their study population, 66% and 13% of severe and mild COVID-19 patients, respectively, had persistent mosaic hypoattenuated areas in their lung CT, with evidence of air trapping after 4 months [4]. They concluded that this was more common in critically ill patients. However, our patient population consisted of non-hospitalized patients with a milder form of the disease, which suggests that these findings are not only seen in patients with severe disease.

We also observed in our study that 13 (59.1%) of the 22 patients studied had small calcifications in the areas of the lungs with matched perfusion defects and mosaic hypoattenuation on their baseline scan (Table 1). All six of these patients who had follow-up studies revealed that these calcifications were persistent, as shown in Figs. 3 and 4. Although we are not certain, we suspect that these calcifications might be as a result of micro-infarcts following possible microthrombosis.

An expiratory chest CT is always needed to be able to identify air trapping on a lung CT, and the qualitative assessment of air trapping is subjective [8]. Our study has shown

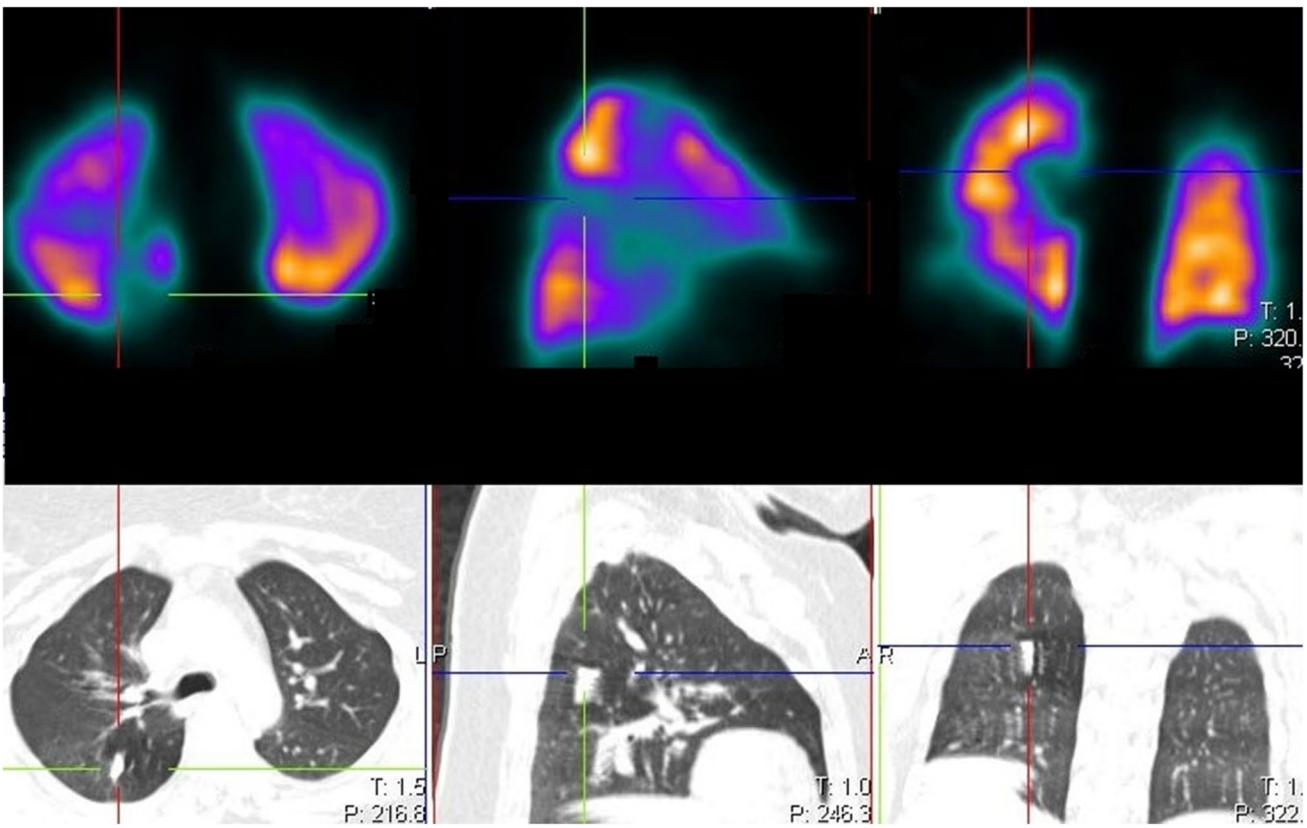

Fig. 4 Perfusion SPECT (above) and CT (below) of the same patient in Fig. 2 a, performed 1 year after the baseline study, showing persistence of the defect, despite being on anticoagulation therapy for 6 months. Note that the calcification is still present

some of the advantages a VQ SPECT/CT study has over a CT only study in evaluating these patients. An example is that it has the ability to clearly demonstrate ventilation and perfusion abnormalities easily, and the corresponding mosaic hypoattenuation in a single study. Another advantage it has over a diagnostic CT study is that it would be preferred as a follow-up tool in these patients if needed, due to its lower radiation dose.

Another important finding in our research was that therapeutic anticoagulation had no effect in improving the perfusion defects, as seen in all the patients (63.6%) who were on therapeutic anticoagulation. This is likely in keeping with the literature, where a multicenter autopsy study confirmed the presence of microthrombi in the pulmonary capillaries despite the fact that patients where on anticoagulation therapy [10]. Usually, lung perfusion defects due to pulmonary embolism improve over time in patients on therapeutic anticoagulation, as presented in Fig. 5.

Functional imaging with VQ SPECT is a well-validated imaging modality for the diagnosis of PE [11, 12]. Using the accepted European guidelines, at least one large segmental or two subsegmental mismatched perfusion defects meet the criteria for the diagnosis of PE [11]. Some of the patients in our study population had an initial perfusion only SPECT/CT study as ventilation was not routinely investigated very early on in the pandemic due to safety reasons. This led to an increase in false positive studies for PE as some of these defects were large, wedged-shaped, and associated with no obvious parenchymal lung changes on CT. It was only in hindsight, when we noticed on follow-up studies that these defects were persistent and matched, that we were able to appreciate the subtle mosaic hypoattenuation on CT. This observation is important as it buttresses the point that the ventilation aspect of the study is crucial in reducing the number of false positive studies, especially during the COVID-19 era. If a perfusion only study is done, segmental defects observed should be correlated with a CT and not an X-ray to look out for subtle mosaic hypoattenuated areas that could be associated with post-COVID-19 complications not necessarily attributable to PE. However, we must note that there are quite a number of lung abnormalities that could present with mosaic hypoattenuation on CT, which include lung parenchymal infiltrates in the form of ground glass opacities, small airway disease, and vascular abnormalities such as pulmonary

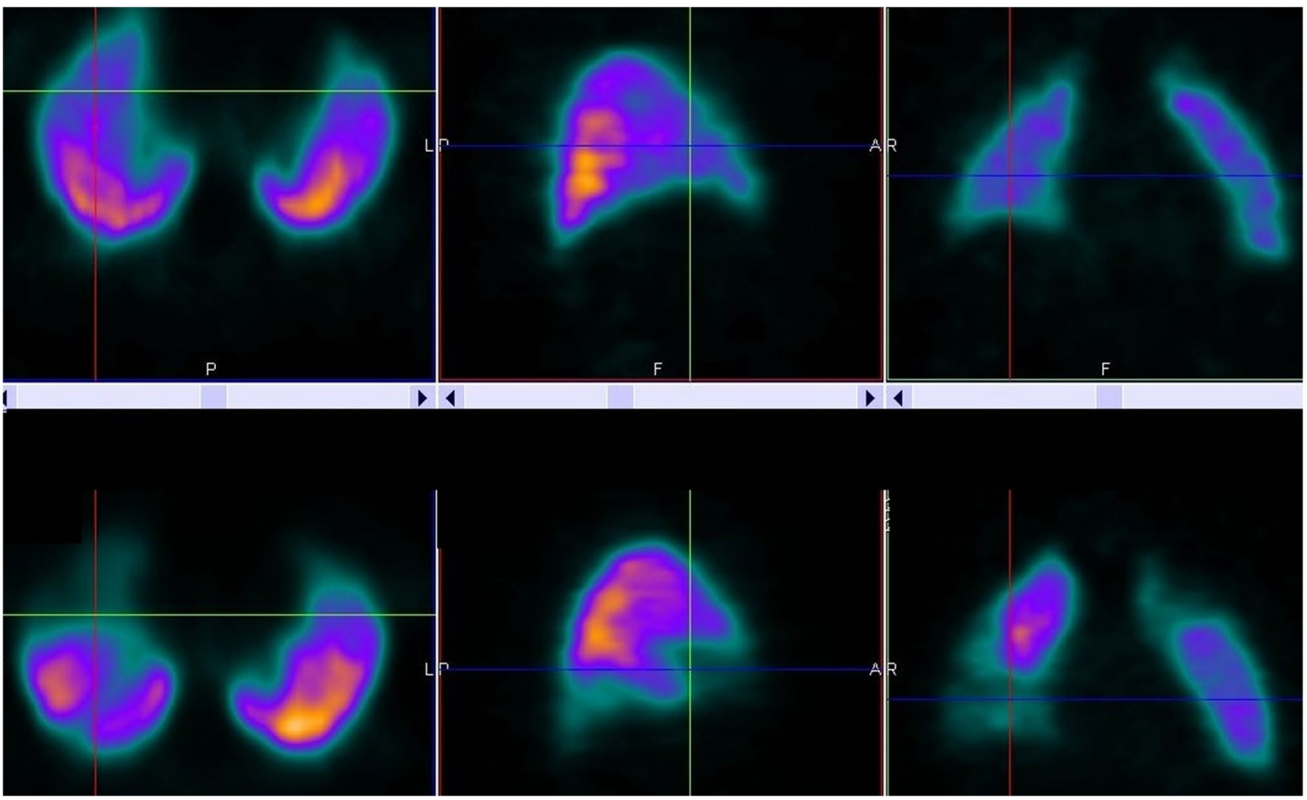

Fig. 5 Perfusion SPECT images of a 15 year old female, with systemic lupus erythematosus, who presented with unexplained resting tachycardia and shortness of breath and a diagnosis of pulmonary embolism was made on a VQ SPECT/CT. The images below are the baseline study, showing large perfusion defects in the apical posterior segment of the left upper lobe and medial and lateral segments of the right middle lobe. The images above performed 6 months after initiation of therapeutic anticoagulation shows complete resolution of all the defects

hypertension and PE [13–15]. This means that in a perfusion only study, the presence of a large perfusion defect, with corresponding mosaic attenuation on CT, could also be in keeping with PE. It is therefore imperative that the ventilation aspect of the study should be performed, as it obviously increases the diagnostic accuracy of the study.

An important limitation of our study is the fact that no evidence is available that our patient population did not have these lung changes prior to COVID-19. However, this is unlikely to be the case, as this particular pattern had not been seen in our facility prior to the pandemic.

Conclusion

Our findings highlight the importance of a VQ SPECT/CT study in the identification and follow-up of patients with COVID-19 mosaic hypoperfusion. If in the future there happens to be some form of effective treatment that can be administered for this complication, a VQ SPECT/CT study without a doubt will be a very effective and valuable investigation in assessing treatment response in these patients. One positive lesson that nuclear medicine physicians can learn from the COVID-19 pandemic is that VQ SPECT/CT is probably the best option for the evaluation of patients with suspected PE.

Acknowledgements With their permission, the authors would like to acknowledge all the nuclear medicine radiographers and nurses at the Department of Nuclear Medicine, University of The Free State.

Author Contribution The study was designed by Evbuomwan Osayande. Material preparation and data collection were performed by Evbuomwan Osayande, Endres Walter, Tebeila Tebatso, and Engelbrecht Gerrit. The first draft of the manuscript was written by Evbuomwan Osayande, and all the authors commented on the previous versions of the manuscript. All the authors read and approved the final manuscript.

Data Availability Contact the corresponding author for data requests.

Declarations

Ethical Approval and Consent to Participate The study was approved by the institutional review board from the University of The Free State Health Sciences Research Ethics Committee (UFS-HSD2021/1575), and the requirement for written consent was waived by the institutional review board as this was a retrospective study. All the procedures performed in studies involving human participants were in accordance with the Helsinki declaration, as revised in 2013 and its later amendments.

Consent for Publication Not applicable, as this was a retrospective study.

Competing Interests Evbuomwan Osayande, Endres Walter, Tebeila Tebatso, and Engelbrecht Gerrit declare that they have no competing interests.

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