Functional Alterations Due to COVID-19 Lung Lesions—Lessons From a Multicenter V/Q Scan-Based Registry

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Purpose: In coronavirus disease 2019 (COVID-19) patients, clinical manifestations as well as chest CT lesions are variable. Lung scintigraphy allows to assess and compare the regional distribution of ventilation and perfusion throughout the lungs. Our main objective was to describe ventilation and perfusion injury by type of chest CT lesions of COVID-19 infection using V/Q SPECT/CT imaging.

Patients and Methods: We explored a national registry including V/Q SPECT/CT performed during a proven acute SARS-CoV-2 infection. Chest CT findings of COVID-19 disease were classified in 3 elementary lesions: ground-glass opacities, crazy-paving (CP), and consolidation. For each type of chest CT lesions, a semiquantitative evaluation of ventilation and perfusion was visually performed using a 5-point scale score (0 = normal to 4 = absent function).

Results: V/Q SPECT/CT was performed in 145 patients recruited in 9 nuclear medicine departments. Parenchymal lesions were visible in 126 patients (86.9%). Ground-glass opacities were visible in 33 patients (22.8%) and were responsible for minimal perfusion impairment (perfusion score [mean ± SD], 0.9 ± 0.6) and moderate ventilation impairment (ventilation score, 1.7 ± 1); CP was visible in 43 patients (29.7%) and caused moderate perfusion impairment (2.1 ± 1.1) and moderate-to-severe ventilation impairment (2.5 ± 1.1); consolidation was visible in 89 patients (61.4%) and was associated with moderate perfusion impairment (2.1 ± 1) and severe ventilation impairment (3.0 ± 0.9).

Conclusions: In COVID-19 patients assessed with V/Q SPECT/CT, a large proportion demonstrated parenchymal lung lesions on CT, responsible for ventilation and perfusion injury. COVID-19–related pulmonary lesions were, in order of frequency and functional impairment, consolidations, CP, and ground-glass opacity, with typically a reverse mismatched or matched pattern.

Key Words: ventilation perfusion scintigraphy, SPECT, COVID-19, SARS-CoV-2

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2.[1] Clinical manifestations of this disease are variable and range from incidental finding in asymptomatic patient to acute respiratory injury.[2] CT is frequently performed during this infection to evaluate lung lesions extent or to look for complication such as pulmonary embolism (PE). Morphological lung alterations caused by COVID-19 disease are now well described[3] and seem to be variable from a patient to another but also in the same patient with possible temporal evolution.[4,5] Most observed lesions are ground-glass opacities (GGOs), crazy-paving (CP) lesions, or pulmonary consolidations. Younger adults more commonly have GGOs, whereas extensive/multilobar involvement with CP or consolidations is prevalent in the older population and in patients with severe disease.[6,7] However, although a high extent of lung lesion is correlated with a worse prognosis,[8] there are currently no imaging biomarkers able to predict CT evolution of lesions and clinical outcomes at the early stage of the disease.

Although chest CT findings of COVID-19 disease are well known, their functional consequences are far less so. Metabolic or functional imaging modalities are not routinely used to predict or assess the severity of the infection. At the beginning of the pandemic, the best approach for performing lung ventilation/perfusion (V/Q) scan was an active source of debate, which may partly explain its low use in COVID-19 patients. However, improved pulmonary function evaluation may potentially improve assessment, treatment, and follow-up of COVID-19 patients. V/Q scan seems as a tool of choice for a functional and noninvasive evaluation of regional lung function.[9] SPECT/CT may allow both to identify parenchymal COVID-19 lung lesions on CT and to locally evaluate the repercussions on ventilation and lung perfusion. To date, there are only sparse data on the direct impact of lung lesions observed during the infection on ventilation and pulmonary perfusion.[10–12]

The main objective of this work was to describe and compare ventilation and perfusion injury by type of chest CT lesions of COVID-19 infection using V/Q SPECT/CT imaging.

PATIENTS AND METHODS

Design and Patient Selection

This study is a retrospective central analysis of V/Q SPECT/CT scans included in a national registry powered by pulmonary working group on lung scintigraphy. The national registry collected lung scans performed in patients with confirmed COVID-19 infection (based on RT-PCR or antigen test) for suspected acute pulmonary embolism between March 2020 and April 2021. The protocol was approved by the nuclear medicine research ethics committee (CEMEN 2021-01). Informed consent was obtained from all participants. Description of the registry and collection of data were detailed in a previous work.[13]

V/Q SPECT/CT Central Review

In each center, lung scans were performed on hybrid gamma cameras able to perform low dose CT. Lung perfusion was performed after administration of ^{99m}Tc-labeled human albumin (^{99m}Tc-MAA). Ventilation was performed after inhalation ^{99m}Tc-Technegas or krypton gas (^{81m}Kr) according to local facilities.[13]

A centralized retrospective review of V/Q SPECT/CT scans was performed by a physician blinded to clinical information. Low-dose chest CT scans, performed during the SPECT/CT acquisition, were analyzed according to the Radiological Society of North America Expert Consensus Statement on reporting chest CT findings related to COVID-19,[4] to identify lesions and specify their extent. Three type of predominating elementary lesions were identified during COVID-19 infection and classified as follows[14]:

- GGO defined as an area of increased attenuation in the lung on CT with preserved bronchial and vascular markings.
- Crazy-paving lesions defined as increased density of lung parenchyma, with a ground-glass appearance, superimposed on a reticular thickening of the interlobular and intralobular septa.
- Consolidation, which refers to filling of the pulmonary tree with material that attenuates x-rays more than the surrounding lung parenchyma.

The overall extent (<10%; 10%–25%; 25%–50%; 50%–75%; >75%) and predominant location (subpleural, intermediate, or perihilar) of lesions were visually assess.

For each type of CT lesions, a qualitative evaluation of perfusion and ventilation was visually performed. Ventilation and perfusion were independently graded using a 5-point score based on a visual grading scale compared with normal uptake on healthy area (see Fig. 1: 0 = normal function, 1 = mild impairment, 2 = moderate impairment, 3 = severe impairment, 4 = absent function). This visual grading scale was adapted from the visual index proposed by Meyer et al[15] to quantify the pulmonary vascular

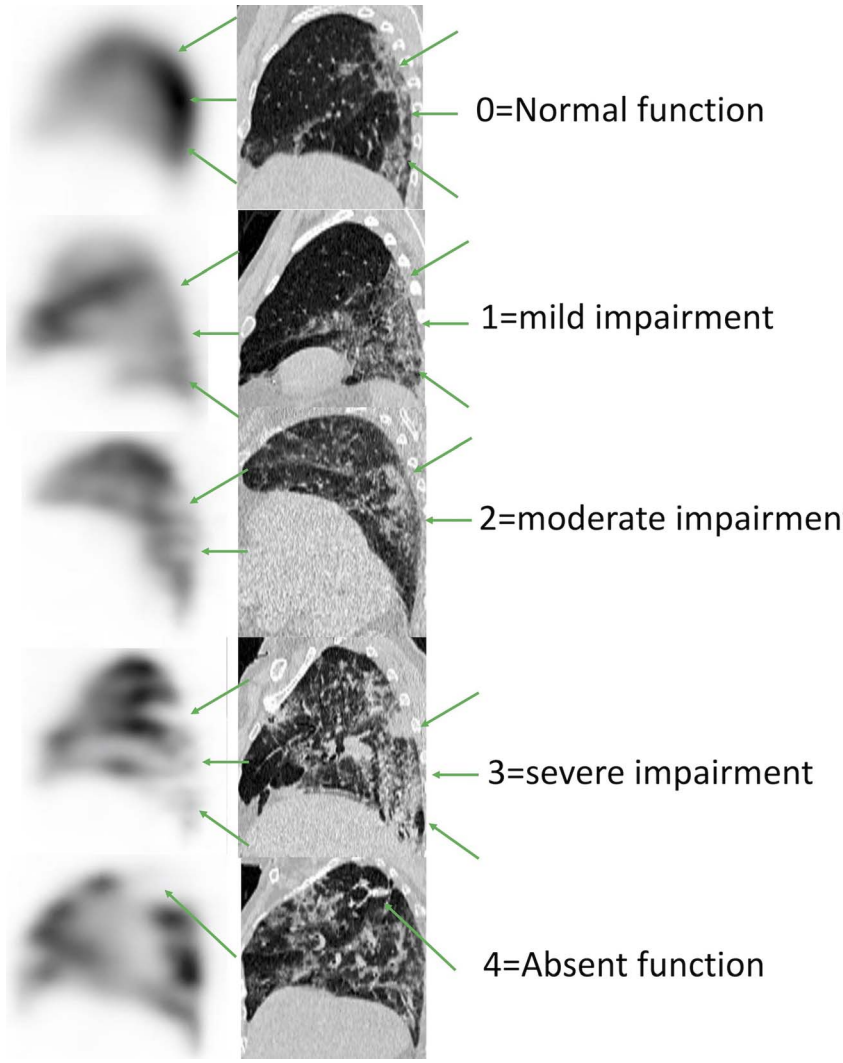

FIGURE 1. Description of the 5-point scale used for ventilation and perfusion semiquantitative evaluation. When CT lesions were visible, perfusion and ventilation were independently evaluated using visual score. Score 0 corresponds to a normal function, 1 to a mild impairment, 2 to a moderate impairment, 3 to a severe impairment, 4 to an absent function. Images are related to pulmonary perfusion scoring related to CT lesions visible on lower lobe (green arrows).

obstruction score. In patients with heterogeneous pattern of ventilation or perfusion for a type of CT lesion, the most representative score was recorded. Lung ventilation and/or perfusion were not analyzed in areas without chest CT lesions of COVID-19 disease, as there are many non–COVID-19 pulmonary conditions that may cause functional alterations on V/Q imaging (eg, pulmonary embolism, chronic obstructive pulmonary disease, asthma, non–COVID-19 pulmonary infection).

Analysis and graphical representation of data were performed using R Studio (Version 1.3.1093).

RESULTS

Of the 183 COVID-19 patients included in the national registry, 145 patients who underwent a complete scans were performed in 9 nuclear medicine departments. Demographic data as well as the main results of the central review are summarized in Table 1. Pulmonary lung lesions related to COVID-19 disease were visible on the low-dose CT in 126/145 patients (86.9%), and 38/145 patients (26.2%) presented with an association of 2 or 3 type of lesions. Lesions were most often bilateral (84.9%). Predominant distribution was subpleural (63.4%), peribronchovascular (9.2%), or mixed topography (22.1%). The lesions were extended to 1% to 10%, 11% to 25%, 26% to 50%, 51% to 75%, and >75% of lung parenchyma in 41/145 (28.3%), 50/145 (34.5%), 28/145 (19.3%), 6/145 (4.1%), and 1/145 (0.7%) patient, respectively. In analysis per patient, 118 of the 145 patients (81.4%) presented perfusion anomalies and 122 (84.1%) presented ventilation anomalies caused by at least 1 type of COVID-19–related lung lesion. Analysis by lesion revealed the presence of GGO in 33/145 patients (22.8%), CP in 43/145 patients (29.7%), and consolidation in 89/145 patients (61.4%). An associative representation of ventilation and perfusion impairment was proposed in Figure 2.

Ground-glass opacities (Fig. 3) were responsible for minimal perfusion impairment (perfusion score [mean ± SD], 0.9 ± 0.6) and moderate ventilation impairment (ventilation score, 1.7 ± 1.0). These lesions were responsible for mismatched, matched, and reverse mismatched defects in 2/33 (6%), 11/33 (33%), and 20/33 (61%) patients, respectively. Crazy-paving lesions (Fig. 4) were responsible for moderate perfusion impairment (perfusion score, 2.1 ± 1.1) and moderate-to-severe ventilation impairment (ventilation score, 2.4 ± 1.1). These lesions were responsible for mismatch, match, and reverse mismatch, respectively, in 6/43 (14%), 18/43 (42%), and 19/43 (44%) patients. Consolidations (Fig. 5) were responsible for moderate perfusion impairment (perfusion score, 2.1 ± 1.0) and severe ventilation impairment (ventilation score,

TABLE 1. Description of the Population Explored With V/Q SPECT/CT for PE Suspicion During Confirmed COVID-19 Infection

	V/Q SPECT/CT	
	n = 145	
Characteristics		
Male, n (%)	67	(46.2)
Age, mean (SD)	71	(17)
Lesions, n (%)	126	(86.9)
GGOs, n (%)	33	(22.8)
Perfusion alteration score, mean (SD)	0.85	(0.62)
Ventilation alteration score, mean (SD)	1.67	(1.02)
CP, n (%)	43	(29.7)
Perfusion alteration score, mean (SD)	2.12	(1.07)
Ventilation alteration score, mean (SD)	2.44	(1.08)
Consolidation, n (%)	89	(61.4)
Perfusion alteration score, mean (SD)	2.04	(1.05)
Ventilation alteration score, mean (SD)	2.97	(0.93)
Lesion extension (expressed in % of total lung parenchyma), n (%)		
Absence of visible lesions	19	(13.1)
<10%	41	(28.3)
11% to 25%	50	(34.5)
26% to 50%	28	(19.3)
51% to 75%	6	(4.1)
>75%	1	(0.7)
Location, n (%)		
Subpleural	85	(67.5)
Intermediate	29	(23.0)
Perihilar	12	(9.5)
Anomalies visible on CT, n (%)		
Chronic lung lesions (ie, emphysema and/or fibrosis lesions)	32	(22.1)
Pleural effusion	29	(20.0)
Pericardial effusion	5	(3.5)
Mediastinal adenomegalies	13	(9.0)
Cardiomegaly	32	(22.1)

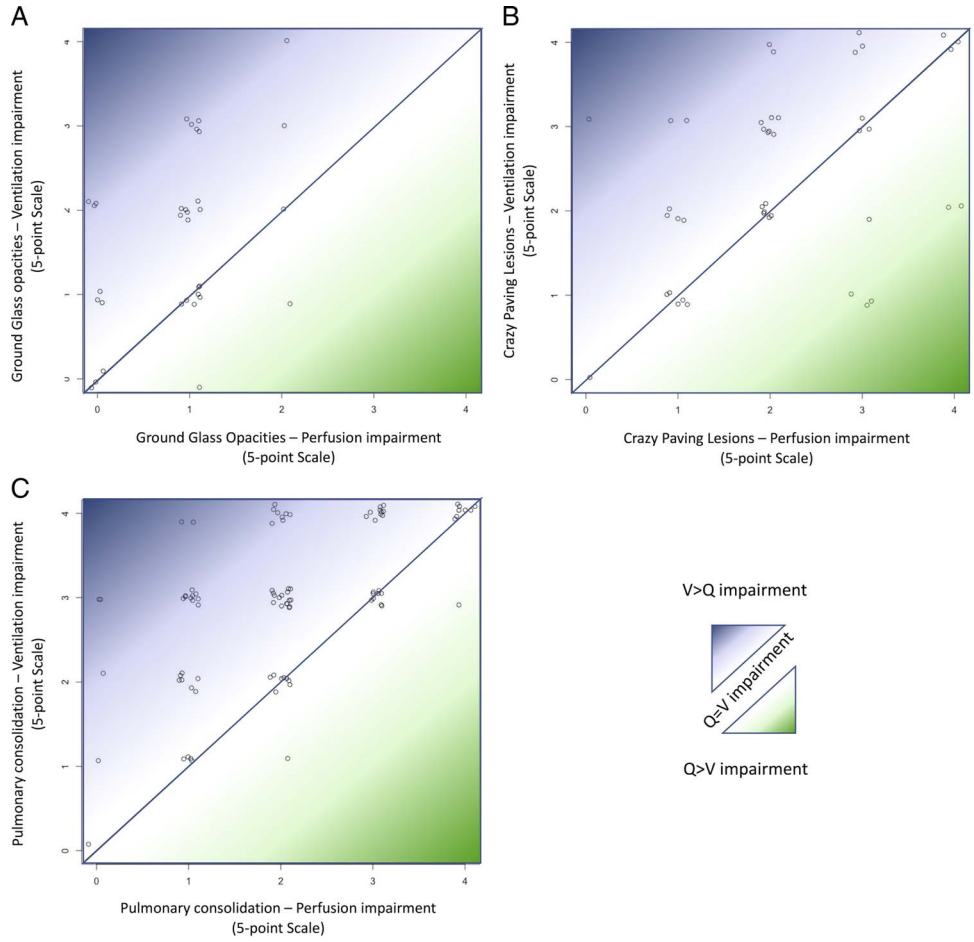

FIGURE 2. Representation of ventilation and pulmonary perfusion alteration associated with (**A**) GGOs, (**B**) CP, and (**C**) consolidations visualized in patients during COVID-19 infection. Ventilation and perfusion were independently scored using 5-point scale (0 = normal function to 4 = complete amputation of the function) when pulmonary lesion was visible on CT. Green area reflect V/Q mismatch (ie, Q alteration superior to V alteration), blue area reflect reverse mismatch (ie, V alteration superior than Q alterations), and blue line correspond to match anomalies.

3.0 ± 0.9). These lesions were responsible for mismatch, match, and reverse mismatch, respectively, in 2/89 (2%), 30/89 (34%), and 57/89 (64%) patients.

Mismatched lung alteration (ie, injury predominating in perfusion) was found in 10 patients, including 2 patients (6%) with GGO, 6 (14%) with CP, and 2 (2%) with consolidations, respectively. Of these 10 patients, the V/Q SPECT/CT scan was previously interpreted as negative for PE by the 2 independent readers in 9 patients because of the non–wedge-shaped pattern and the presence of chest CT findings of COVID-19 lesions. The last patient had perfusion mismatched defects both in areas with and without chest CT findings of COVID-19 disease and was considered for having PE.

DISCUSSION

In this multicenter series of COVID-19 patients assessed with V/Q SPECT/CT imaging for suspected acute PE, a large proportion (86.9%) had parenchymal lung lesions on CT including in order of frequency consolidation, CP, or GGO. Most of CT lesions were associated with ventilation and perfusion alterations, with typically a reverse mismatched or a matched pattern. However, a wide heterogeneity in the severity of lung perfusion and ventilation alteration was observed within each type of chest CT finding of COVID-19 lesion.

Ground-glass opacities were observed in 22.8% of patient in our cohort. They are described to represent 44% of patient with COVID-19 infection in CT series.[6] Ground-glass opacities are the most common imaging manifestations at 0 to 4 days[16–18] and have been described to reflect pulmonary edema with hyaline membrane formation.[19] These lesions were typically responsible for minimal perfusion impairment and moderate ventilation impairment. Crazy-paving was visible in 29.7% of patient in our cohort, as compared with 19.5% of patient with COVID-19 infection in CT series.[6] Crazy-paving has been described to reflect temporal evolution of GGO at 5 to 8 days.[16–18] We typically observed a moderate perfusion impairment and a moderate-to-severe ventilation impairment in these lesions. Finally, consolidations were observed in the majority of patient of our cohort (61.4%). It seems to reflect the final evolution of lesions and peaks between day 9 and 13 after the initial onset of symptoms.[16–18] In CT series, these lesions could be found isolated (24.2%) or associated with GGO (44.4%). Consolidations were related with a moderate perfusion impairment and severe ventilation impairment with, in some cases, total local amputation of ventilation

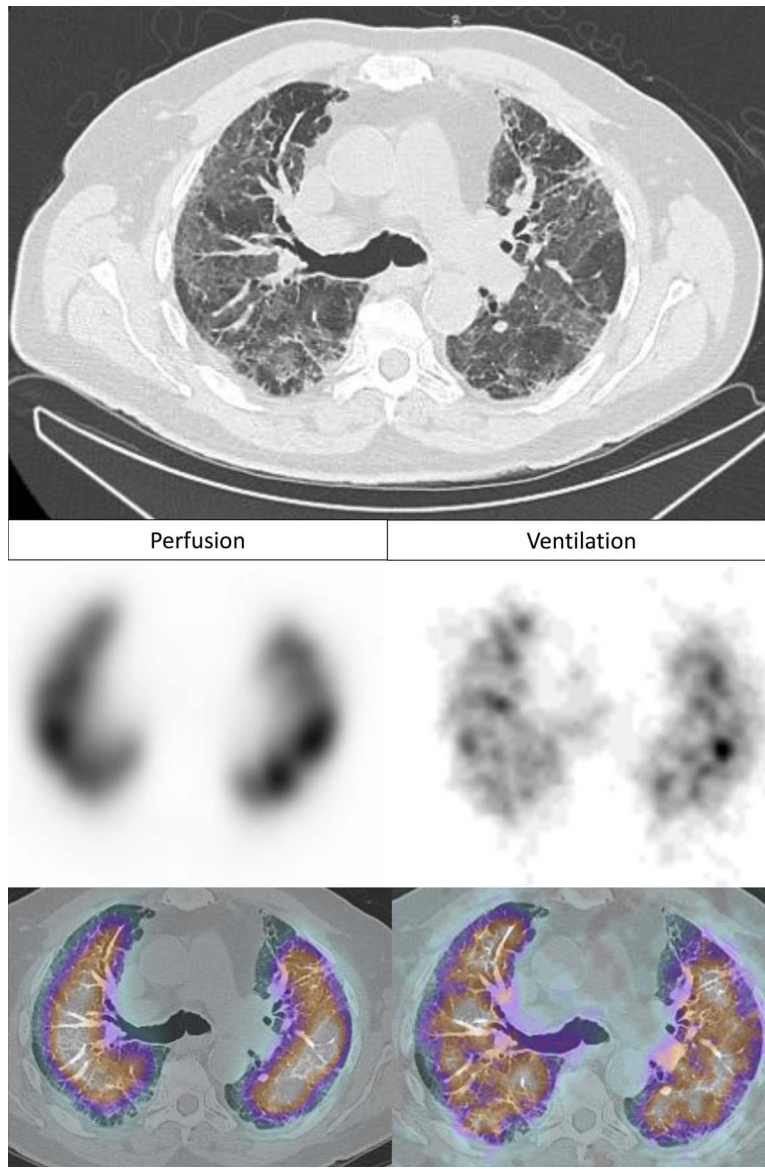

FIGURE 3. Illustration of GGOs visible during COVID-19 on V/Q SPECT/CT. Ground-glass opacities were visible on CT with bilateral and mixed topography (both subpleural and peribronchovascular distribution). Lesions were not responsible for a significant ventilation or perfusion impairment.

and perfusion. Differences observed between our V/Q SPECT/CT series and chest CT series could be partly explained by the temporal evolution of the lesions. As CT imaging is usually the first-line imaging test in COVID-19 patients, we could hypothesize that V/Q SPECT/CT scans were performed at a later stage of the disease or in case of complications, which could explain the lower incidence of GGO and similar rate of consolidations. Unfortunately, the time between the beginning of the infection and the SPECT/CT acquisition was not collected in the national registry.

Although large trends in lung functional consequences of COVID-19 lesions could be identified, an important result of our study is the wide heterogeneity of V/Q SPECT patterns for each type of chest CT finding of COVID-19 disease, ranging from normal lung function to major ventilation and/or perfusion alteration. In other words, V/Q SPECT imaging provides different information compared with CT imaging, which supports the concept of combining the morphological and functional approaches for lung function assessment in COVID-19 patients. This also supports the preferential use of V/Q SPECT/CT imaging rather than planar acquisition in COVID-19 patients.

Further studies are now needed to assess the clinical significance and the prognostic value of lung function alterations. In particular, it would be of interest to assess whether functional impairment is predictive of early complication, including microangiopathy and procoagulant state, or long-term disease. Indeed, SARS-CoV-2 survivors have been reported to experience long-term complications, such as lung pain, dyspnea, impaired exercise capacity, and persistent lung lesions, identified as long COVID-19.[20] Physiopathology related with this evolution is still unclear and possibly related with pulmonary parenchymal or vascular sequelae after the

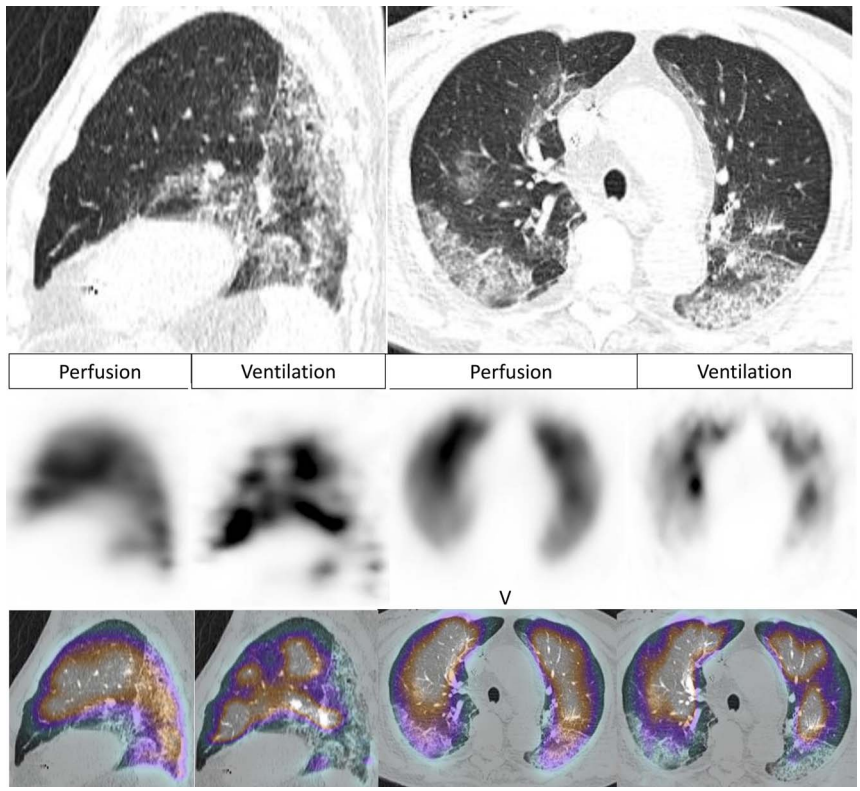

FIGURE 4. Illustration of CP visible during COVID-19 on V/Q SPECT/CT. Crazy-paving lesions predominate in posterior regions with bilateral and subpleural topography. These lesions caused mild impairment of perfusion and severe impairment of ventilation.

infection. Similar to pulmonary embolism sequels evaluations,[21,22] V/Q SPECT/CT may also be an interesting tool in the follow-up of COVID-19 patients.[23]

Our study has some limitation. First, as the main outcome was based on imaging findings, we did not correlate V/Q SPECT/CT findings with clinical characteristics, neither with the time from the beginning of patients' infection to the examinations with V/Q SPECT/CT or clinical outcomes. Second, as quantification with SPECT is still delicate, a visual evaluation of ventilation and perfusion impairment was performed. However, visual analysis was conducted using a standardized score based on a visual grading scale, and quantification was adapted from the index proposed by Meyer et al,[15] which is considered as the reference to quantify the pulmonary vascular obstruction score. Third, this evaluation was performed by only 1 nuclear medicine physician, and we did not assess the intraobserver agreement. Fourth, it is likely that this study refers to the beta/gamma variants that were dominants in our regions in the time frame of the study. Results may be slightly different with other variants, such as the current omicron variant. Fifth, we did not perform V/Q assessment in areas without COVID-19 abnormalities, as V/Q dysfunction in these areas may result from various pulmonary conditions (PE, asthma, chronic obstructive pulmonary disease). Accordingly, we could not assess whether COVID-19 disease may cause lung V/Q defects in areas without chest CT findings of COVID-19 disease. According to the European Association of Nuclear Medicine guidelines for lung scintigraphy[9] or the French Society of Nuclear Medicine guideline for lung scintigraphy protocols,[24] the CT scans were performed as a low-dose CT scan during continuous shallow breathing. Accordingly, the CT scans do not fulfill quality criteria to be diagnostic. However, optimization of acquisition and reconstruction parameters could enhance the diagnostic performance of the CT scans. Furthermore, CP, GGO, and consolidations can be found in many different entities and are not specific from COVID-19 infection. However, in our cohort of patient with proven infection, their presence was most likely related to the infection.

CONCLUSIONS

A large proportion of COVID-19 patients assessed with V/Q SPECT/CT imaging for suspected acute PE show parenchymal lung lesions on CT, with a frequent impact on ventilation and/or perfusion. COVID-19–related pulmonary lesions were, in order of frequency and functional impairment, consolidation, CP, and GGO, with typically a reverse mismatched or a matched pattern.

However, a wide heterogeneity in the severity of lung perfusion and ventilation alteration was observed, supporting the potential interest of combining the morphological and functional approach with V/Q SPECT/CT imaging for the assessment of COVID-19 patients. Further studies are now needed to assess the clinical significance and prognostic value of lung functional impairment.

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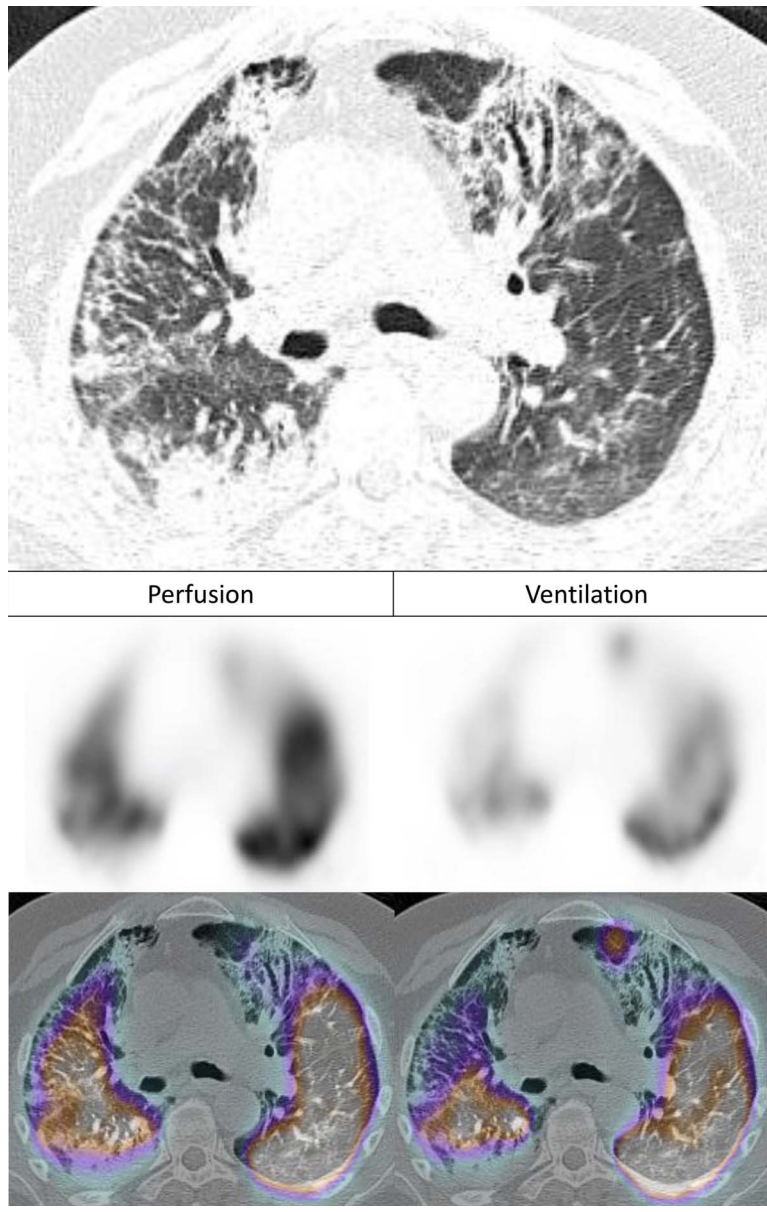

FIGURE 5. Illustration of consolidation visible during COVID-19 on V/Q SPECT/CT. Consolidations were visible in the anterior part of the 2 upper lobes and in the right lower lobe. We observed a severe alteration of lung perfusion with complete amputation of ventilation in these areas.

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