Original Article

The diagnostic accuracy of perfusion-only scan in the diagnosis of pulmonary embolism in the era of COVID-19: A single-center study of 434 patients

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Submission: 09-02-2023 Revised: 25-02-2023 Accepted: 09-03-2023 Published: 16-05-2023

Abstract:

INTRODUCTION: There is a paucity of data in the literature regarding the diagnostic accuracy of perfusion (Q)-only studies in the absence of ventilation images. This study aims to assess the diagnostic accuracy of Q-only imaging in the pandemic era.

METHODS: Patients who underwent Q-only imaging for pulmonary embolism between March 2020 and February 2021 were analyzed. Patients who underwent lung quantification analysis were excluded. Q-only test results were reported as per modified PIOPED II criteria and single positron emission tomography/computed tomography (SPECT/CT) imaging was performed as needed. Patients were considered concordant or discordant by correlating the Q-only results with CT angiogram (CTA) or clinical diagnosis made through chart review. The diagnostic accuracy was calculated after excluding intermediate probability and nondiagnostic studies.

RESULTS: Four hundred and thirty-four patients were identified. One hundred and twenty-eight patients (29.4%) underwent ultrasound Doppler, 37 patients (8.5%) underwent CTA, and 16 patients (3.6%) underwent both. After excluding patients with intermediate probability or nondiagnostic studies and who did not have follow-up (a total of 87 patients [20%]), 347 patients were enrolled in the final analysis. The combined planar and SPECT/CT sensitivity and specificity were 85.4% (72.2%–93.9% confidence interval [CI]) and 98.7% (96.9%–98.6% CI), respectively. The positive predictive value (PPV) of the Q-only imaging was 89.1% (77.3%–95.1% CI) and the negative predictive value (NPV) was 98.2% (96.4%–99% CI). The sensitivity with SPECT/CT reached 100% (CI: 71.5%–100%) with a specificity of 92.3% (CI: 64%–99.8%). The PPV was 85.7% (CI: 62.1%–95.6%) and the NPV was 100%.

CONCLUSION: Q-only imaging provides clinically acceptable results. The sensitivity of the Q-only scan is increased when coupled with SPECT/CT.

Keywords:

Pulmonary embolism, scintigraphy, ventilation/perfusion

Soon after the WHO declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a pandemic, concerns were raised regarding the safety of aerosolizing procedures when performing ventilation/perfusion (V/Q) scans, which prompted the Society of Nuclear Medicine and Molecular Imaging to release a statement on March 19, 2020 to cease the ventilation portion of V/Q studies.[1] Following this statement, many institutions elected to

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Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.atm_42_23

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How to cite this article: Cengiz TB, Abdelrahman A, Rohren SA, Doucette J, Ghesani M. The diagnostic accuracy of perfusion-only scan in the diagnosis of pulmonary embolism in the era of COVID-19: A single-center study of 434 patients. Ann Thorac Med 2023;18:199-205.

perform perfusion-only (Q-only) studies in conjunction with a chest X-ray (CXR), which was used as a surrogate for the ventilation assessment.[2] While this prompt action may have potentially decreased the potential spread of COVID-19 during V/Q studies in the hospital setting, it also led to concerns about compromised diagnostic accuracy of Q-only imaging for suspected pulmonary embolism (PE).

The Q-only imaging provides valuable clinical information regarding the presence of perfusion defects; however, the main drawback is its high false positivity rate.[3] A study done in 2015 demonstrated that the sensitivity of Q-only imaging is 73% without single positron emission tomography/computed tomography (SPECT/CT), with a specificity of 43%.[4] This shortcoming of the Q-only imaging is amplified in the era of COVID-19, not only the inherent increase in pneumonia-related homeostatic vasoconstriction but also the increased incidence of thromboembolic events in the setting of SARS-CoV-2.[5,6]

In this study, we aimed to investigate the sensitivity, specificity, and other diagnostic attributes of Q-only imaging in PE evaluation. Secondarily, we hypothesized that the utilization of SPECT/CT along with Q-only scintigraphy might increase the diagnostic accuracy for PE compared to planar imaging alone.

Methods

Study design and population characteristics

This is a single-center retrospective study. We included all patients above 18 years of age who underwent Q-only imaging including both inpatient and outpatient, for the suspicion of PE between March 2020 and February 2021. Patients who underwent evaluation for suspected chronic thromboembolic disease as an etiology of pulmonary hypertension were also included in the study. Patients who underwent lung quantification analysis for presurgical planning were also excluded from the study. Institutional review board approval was obtained.

Image acquisition

A standard dose of 2 mCi (74-111 MBq) of Tc99m macroaggregated albumin was injected intravenously. Planar images were taken in 6 standard positions: anterior, posterior, right anterior oblique, left posterior oblique, right lateral, left lateral, right posterior oblique, and lateral anterior oblique. The image matrix was set to 256 × 256 pixels with a magnification of about 1.3. Counts per image were about 300–400 thousand. SPECT/CT of the chest was performed as needed in patients with perfusion defects on planar images.

Data collection

Q-only test results were reported as per modified PIOPED II criteria. Patients were divided into 4 groups: low, intermediate, high probability, and nondiagnostic study. Patients with intermediate probability and nondiagnostic studies were excluded from the final analysis. All patients underwent an anatomical imaging of the chest within 24 h to Q-only imaging in the forms of CXR or computed tomography (CT). Chart reviews were conducted for lower extremity ultrasound (US) Doppler and computed tomography angiogram (CTA) studies within the same admission or 30 days from the Q-only imaging. Suboptimal PE studies were not included in the cohort and thus were not used to evaluate concordance or discordance. Patients who did not have any follow-up on EPIC or immediate discharge after Q-only imaging were not included in the final concordance analysis.

Evaluation of pulmonary scintigraphy and concordance analysis

Patients' charts were queried to include the PE diagnosis. Patients were marked as "concordant" or "discordant" with the Q-only imaging based on CTA results (when present) or depending on the clinical course leading to the most likely diagnosis of PE. The diagnosis of PE was made if a CTA study demonstrated evidence of PE or ruled out if CTA on the same admission did not show PE. After excluding patients who had undergone CTAs, the rest of the patients who had admissions or follow-up visits within 7 days of imaging were stratified.

The clinical diagnosis of PE was established despite a negative imaging study if at least one of the following conditions were met:

- Initiation of anticoagulation following the Q-only study
- Positive US of lower extremities with PE with PE is the most likely clinical diagnosis
- Resolution of the symptoms after intervention or commencement of anticoagulation.

False-positive clinical results included studies that are reported as high probability with the later imaging or workup showing another cause for the explanation of symptoms.

False negative cases were determined if the patients had persistent symptoms despite optimal medical care or evidence of diffuse thromboembolic states throughout their admission (i.e. disseminated intravascular coagulation).

Concordance analysis was carried out by three authors (TBC, AA, and SR); a Q-only study (without a deterministic CTA) was marked as PE positive or negative when at least 2 of the 3 authors agreed to rule in the diagnosis or ruled out in similar fashion. All patient factors were considered when reaching a clinical conclusion, including US Doppler findings and D-dimer levels. A positive US Doppler was not considered enough to rule in PE.

Statistical analysis

Sensitivity and specificity of the readings were computed based on the concordance and discordance analysis. A separate analysis was conducted for the patients who underwent SPECT/CT imaging in a similar fashion. Positive predictive value (PPV) and negative predictive value (NPV) were also calculated. Other demographic variables were compared including D-dimer levels and pretest probability for PE (Well's criteria) for low, intermediate, and high probability groups through one-way analysis of variance.

Results

A total of 457 patients underwent perfusion imaging; after excluding 23 patients who underwent perfusion quantification, 434 patients were included in the cohort (247 patients [56.9%] female). Thirty-three patients (3.4%) did not have sufficient follow-up after the imaging. After excluding patients with intermediate probability (42 patients, 9.7%) and nondiagnostic studies (12 patients, 2.7%), 347 patients were included in the final analysis. Figure 1 shows the flowchart depicting the final patient cohort and distribution of patients with imaging and clinical diagnoses.

The mean age was 66.1 ± 16 years. CXR results yielded normal findings (69.3%) and the rest of the CXRs demonstrated consolidations in 32 patients (7.3%), atelectatic/emphysematous changes in 59 patients (13.5%), and pleural effusion in 42 patients (9.6%). Two hundred and eighty-four patients (65.4%) had a low pretest probability for PE per Wells' criteria, 119 patients (27.4%) had intermediate probability, and 31 (7.1%) had a high probability of PE. Average D-dimer closest to the Q-only imaging was 3.17 ± 3.6 with 153 patients (35.2%) missing information. The most common presenting symptoms were dyspnea (47.2%), leg swelling (31.1%), and chest pain (21.7%). Forty-five patients (10.3%) were diagnosed with PE in the whole cohort. Patient demographics were outlined in Table 1.

One hundred and twenty-eight patients (29.4%) underwent US Doppler (time interval to US 2.1 ± 5.3 days), 37 patients (8.5%) underwent CTA (time interval to CTA 7.1 ± 9.3 days), and 16 patients (3.6%) underwent both imaging studies. Fourteen out of 128 US Doppler scans were positive (10.9%) for deep-vein thrombosis (DVT). Of these, 6 (42.6%) were reported as high probability, 2 (14.8%) were reported as intermediate probability, and 6 (42.6%) were reported as low probability. There were twelve patients (10.2%) with PE in the subgroup of patients who had a negative US for DVT.

Forty-four patients (10.1%) had high posttest probability, 42 patients (9.6%) had intermediate probability, and 336 patients (77.4%) had low probability for PE. Twelve studies (2.7%) were reported as nondiagnostic. Thirty-two patients (7.3%) underwent SPECT/CT

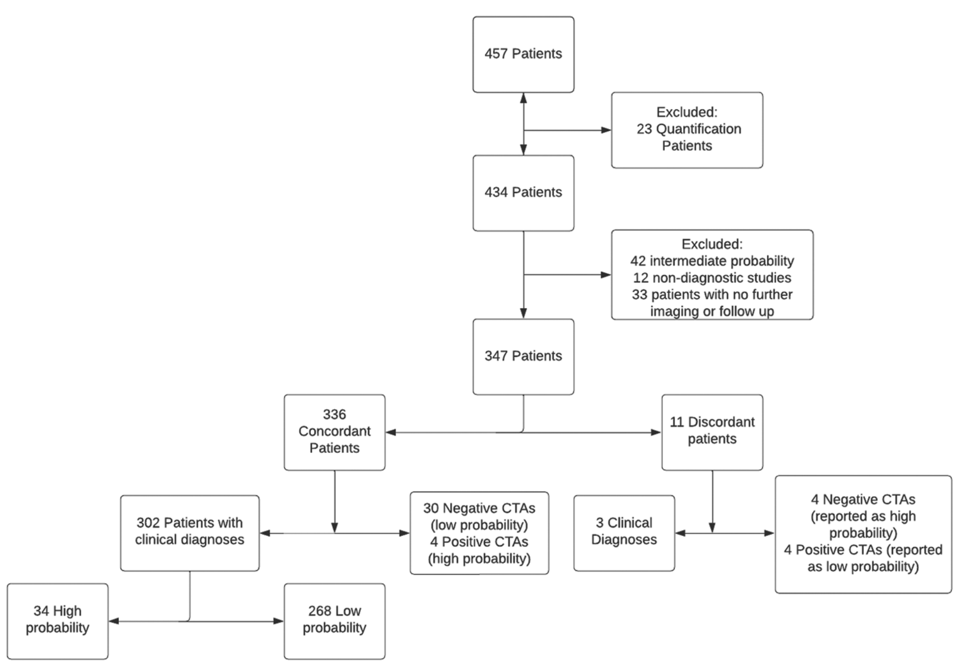

Figure 1: Flowchart of patients with details of concordant and discordant results

imaging. Forty patients (9.2%) did not have any further imaging after Q-only scan evaluating for PE or sufficient clinical follow-up to reach a diagnosis.

Three hundred and thirty-six patients (96.8%) had concordant results with CTA or with the diagnosis made after chart review. Of these who had concordant results, 38 were reported as high probability for PE and 298 were reported as low probability for PE. Patients with discordant results were seen in 5 high probability patients (false positive) and in 6 low-probability patients (false negative). Four patients with false-positive Q-only scans had negative CTA studies for PE; similarly, four patients with false-negative results had positive CTAs for PE despite being reported as low probability. Table 2 depicts the correlation with imaging findings and posttest probabilities.

Table 1: Patient demographics

Variables	Value, *n* (%)
Age (years), mean±SD	66.2±16.6
Gender	
Male	187 (43.1)
Female	247 (56.9)
Presenting symptom	
Dyspnea	205 (47.2)
Leg swelling	134 (31.1)
Chest pain	95 (21.7)
Chest X-ray findings	
Normal	301 (69.3)
Consolidations	32 (7.3)
Atelectatic/emphysematous	59 (13.5)
Pleural effusion	42 (9.6)
Wells score for PE	
Low PE likelihood	284 (65.4)
Intermediate PE likelihood	119 (27.4)
High PE likelihood	31 (7.2)
D-dimer levels for wells score	
Low PE likelihood	3.12±3.84*
Intermediate PE likelihood	3.83±4.35*
High PE likelihood	6.15±6.87*
Pulmonary embolism diagnosis	
PE present	45 (10.3)
PE absent	389 (89.7)
COVID positivity (%)	
PE present	2.2
PE absent	6.9

*One-way ANOVA *P*=0.0121. SD=Standard deviation, PE=Pulmonary embolism, ANOVA=Analysis of variance

The overall sensitivity of Q-only imaging was 86.3% (confidence interval [CI]: 72.6%–94.8%), and the specificity was 98.1% (CI: 95.9%–99.3%). The PPV of Q-only imaging was 86.3% (CI: 73.9%–93.4%) and NPV was 98.1% (CI: 94.3%–98.3%). The diagnostic accuracy was 96.7% (CI: 94.3%–98.3%). The negative likelihood ratio of the Q-only imaging was 0.14 (CI: 0.06–0.29) and the positive likelihood ratio was 46.4 (CI: 20.8–103.3). The imaging characteristics of the whole cohort are outlined in Table 3.

After the exclusion of four patients with intermediate probability, the patients who underwent SPECT/CTs (*n* = 26) after planar Q-only imaging had one discordant case in the high probability group: one patient with a negative CTA on the same day as Q-only imaging. The overall sensitivity with SPECT/CT reached 100% (CI: 71.5%–100%) with a specificity of 92.3% (CI: 64%–99.8%). The PPV was 85.7% (CI: 62.1%–95.6%) and the NPV was 100%. Table 4 shows the results of the SPECT/CT subgroup. Figure 2 demonstrates an example of advantages of using SPECT/CT in patients with COVID-19 pneumonia.

Thirty patients (6.9%) tested positive for COVID-19 either before or during the admission for Q-only scan. Of these, 2 were reported as high, 4 were intermediate, and 24 were low probability for PE. All these patients had concordant results; both patients with high probability had undergone concomitant SPECT/CTs for the final diagnosis.

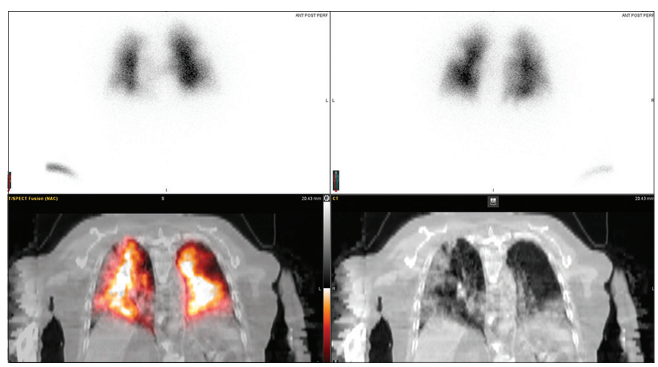

Figure 2: Planar and SPECT/CT images of a COVID-positive patient. Multiple perfusion defects, some of which correlate with ground-glass opacities seen on low-dose CT correlate. The left upper lobe defect corresponds to a “mismatched” area as there is no anatomic correlation on low-dose CT of the chest. SPECT/CT = Single positron emission tomography/computed tomography

Table 2: Correlation of pulmonary scintigraphy results with other imaging findings

Number of patients	High probability (*n*=44), *n* (%)	Intermediate probability (*n*=42), *n* (%)	Low probability (*n*=336), *n* (%)	Nondiagnostic (*n*=12), *n* (%)
CT angiography (+)	4 (9.0)	3 (7.1)	4 (1.2)	0
CT angiography (–)	4 (9.0)	9 (21.4)	30 (8.9)	1 (8.3)
Ultrasound Doppler (+)	6 (13.6)	2 (4.8)	6 (1.8)	0
Ultrasound Doppler (–)	9 (20.5)	18 (42.8)	85 (25.2)	2 (16.6)

CT=Computed tomography

Table 3: Results of Q-only scintigraphy including planar and single photon emission tomography/computed tomography combined (*n*=347)

	Percentage	CI (%)
Sensitivity	86.3	72.6–94.8
Specificity	98.1	95.9–99.3
PPV	86.3	73.9–93.4
NPV	98.1	94.3–98.3

CI=Confidence interval, PPV=Positive predictive value, NPV=Negative predictive value

Table 4: Single photon emission tomography/computed tomography results (*n*=26)

	Percentage	CI (%)
Sensitivity	100	71.5–100
Specificity	92.3	64–99.8
PPV	91.7	62.6–98.6
NPV	100	N/A

CI=Confidence interval, PPV=Positive predictive value, NPV=Negative predictive value, N/A=Not available

Discussion

In this study, our group analyzed over 400 patients who underwent Q-only imaging with or without a positive COVID polymerase chain reaction at the time of the study. Our results demonstrated that the overall sensitivity of the Q-only imaging is clinically comparable to V/Q scintigraphy, especially when coupled with SPECT/CT. The clinical implications of this study might lead to a safer practice by eliminating the necessity of ventilation images in patients with risk of aerosol spread, not only confined to active SARS-CoV-2 infection. The present study also allowed clinicians to safely consider Q-only imaging for patients who are not able to perform a ventilation study due to various issues (i.e. sedation, unable to follow commands) for PE imaging.

Soon after the recognition of severe acute respiratory syndrome caused by the novel coronavirus (SARS-CoV-2), the changes in hemostasis in patients affected by SARS-CoV-2 also became evident with a significant increase in the incidence of venous thromboembolism (VTE) and PE.[7,8] A study performed on COVID-19 patients in 2 Dutch hospital intensive care units demonstrated that 27% of the patients had VTE, and of those with proven VTE, 81% had experienced PE.[9] This exponential increase in clinical suspicion for DVT and PE has prompted a greater need for imaging studies evaluating PE. V/Q scintigraphy serves as a feasible alternate to CTPA for the diagnosis of PE and is commonly used in the setting of acute kidney injury, which was also a common complication in SARS-CoV-2 patients.[10-12] The constellation of these clinical changes and omitted ventilation studies have made Q-only scintigraphy a common method of evaluating patients for PE shortly after the pandemic began.

The diagnostic accuracy of Q-only scintigraphy has been studied previously.[13] One major confounder after the COVID-19 outbreak affecting the accuracy of Q-only imaging is that the pulmonary reflections of viral pneumonia.[14] It is predictable that already-questionable specificity of this method could decrease in light of active viral pneumonia-related changes in the lungs. While there are some attempts to clarify the role of Q-only or hybrid imaging (with SPECT/CT or low-dose CT), it remains elusive as to whether Q-only imaging is a reliable method of assessing PE during and after the pandemic.[15,16] The present study incorporates a meticulous pretest probability analysis of the patients to improve the insufficient specificity of the Q-only scintigraphy, which is of greater importance, especially in the oncologic patient populations.[16,17]

The initial reasoning behind the Q-only scintigraphy was to decrease the radiation dose delivered to each patient, and this effect was more prominent as the elimination of ventilation scan resulted in a significant decrease in radiation delivered to breast tissue.[13] Sostman *et al*. outlined the diagnostic accuracy of the Q-only scintigraphy combined with CXR on 889 patients who had undergone Q-only imaging and the concordance with the digital subtraction angiography, CTPA, or high Well's score (>6).[13] The application of modified PIOPED II criteria in Q-only imaging yielded sensitivity (84.9%) and specificity (92.7%) in their cohort which was comparable to our study results with 85.4% sensitivity and 98.7% specificity. However, the main drawback for Q-only imaging was the rate of nondiagnostic readings up to 20.6%, and the authors noted that younger age with a normal CXR might result in fewer nondiagnostic results. One might expect to see more abnormal CXRs in the era of SARS-CoV-2, and thus, this may lead to a greater number of nondiagnostic readings, yet our study noted only 2.3% nondiagnostic scans. This difference may be explained by a greater number of in-hospital imaging studies before Q-only scans (CT chest, serial CXR preceding the Q-only imaging) explaining the defects or abnormalities seen on the Q-only imaging or the utilization of SPECT/CT. It is expected to see a greater degree of confidence identifying lesions that could cause false-positive results on pulmonary scintigraphy with meticulous investigation of pulmonary, or nonpulmonary causes of patients' symptoms before nuclear medicine imaging during COVID-19 era. Another factor decreasing the rate of nondiagnostic studies was the increasing knowledge regarding Q-only imaging since the index study in 2008 and improved perception of images based on the growing evidence on V/Q imaging. All these factors could contribute to the increased specificity seen in this study, compared to the rest of the literature. Overall, the excellent NPV of the Q-only scintigraphy in the setting of normal CXR serves as a valuable option to rule out

PE, as the discussion regarding the dispensability of the ventilation scan is still being debated.[18,19]

The clinical aspects of Q-only imaging after the declaration of COVID-19 pandemic by the World Health Organization have been evaluated in the literature for patients with proven SARS-CoV-2 infection. One study from Memorial Sloan Kettering Cancer Center that evaluated 6 patients undergoing Q-only imaging and SPECT/CT with high pretest probability for PE showed a high posttest probability (67%) with significant anatomic correlations seen on SPECT/CT not only limited to ground-glass opacities.[20] Another study evaluating the low-risk patients for PE per Well's criteria showed that even when the pretest probability is low, the presence of perfusion defect on Q-only imaging remains high (41.7%) for patients with mild-to-moderate course of SARS-CoV-2.[21] Mahaletchumy reported 100% NPV for Q-only imaging while over-diagnosing PE in 13 out of 36 patients in their cohort with a similar study design including not only image-based (CT, US Doppler) confirmation but also clinical follow-up.[22] Mazurek *et al*. investigated 84 patients with planar, SPECT, and SPECT/CT in the pre-COVID era and showed that the sensitivity increases with the implementation of SPECT and SPECT/CT from 73% to 88% and 100%, respectively, along with specificity.[4] Figure 3 demonstrates an example of a patient who was reported as high probability based on the wedge-shaped defect; a diagnostic CT scan performed that 20 days later demonstrated a cavitary lesion which could have been seen on SPECT/CT imaging, if it had been performed. Overall, there is growing evidence in predicting the posttest probability of perfusion defects on Q-only imaging in conjunction with SPECT/CT.

In our study, we also demonstrated that rising D-Dimer levels correlate with rising pretest probability similar to the pre-COVID era, which promotes the use of D-dimer in the general population despite the pandemic. However, the specificity of D-dimer for PE in the setting of active COVID-19 is yet to be vetted.[21,23]

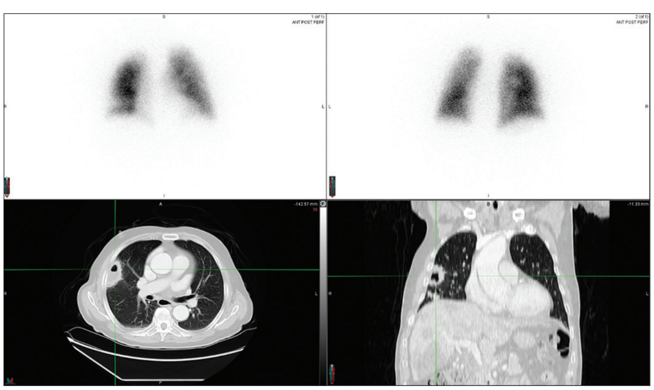

Figure 3: Images of a false-positive Q-only imaging study with planar anterior and posterior images demonstrating a wedge-shaped defect in the right middle lobe which was reported as high probability study. A diagnostic CT scan performed 20 days later demonstrated a cavitary lesion which yielded malignant cells on biopsy. CT = Computed tomography

There are a few limitations to our study, inherent to its retrospective design. Our study does not include a set variable evaluating the presence of PE by gold or best available standard method to determine whether the Q-only results were concordant or discordant. A fraction of patients underwent CTA (55/434, 12.7%) and the rest of the patients were analyzed through electronic chart review to determine if the clinic picture reflected any evidence of PE. Hence, our concordance or discordance in most of the patients was based on presumed clinical evidence of PE. We also excluded the patients with intermediate probability for PE to make the final assessment for clinical concordance less granular given that it might be controversial to assign concordance to intermediate probability scan. Secondarily, the use of SPECT/CT was limited to select patients at only one hospital, causing many patients to undergo planar Q-only images without the touted advantages of the SPECT/CT. Patients who underwent SPECT/CT imaging after evaluation of the planar images are subject to selection bias, and hence, the overall sensitivity and specificity might be overestimated. The number of patients who underwent SPECT/CTs is also limited (overall 30 patients), which poses another challenge when comparing it to the planar imaging results. One other aspect differentiating of our study from the literature is the relatively high specificity, contrary to the expected confounders inherent to viral pneumonia. Obviously, the increased specificity compared to the rest of the literature might be attributable to the retrospectively assessed scans with multiple prior imaging studies and a thorough evaluation of the pretest probability. Nonetheless, our group analyzed the patient electronic medical charts and ancillary imaging to aid the diagnosis of PE along with laboratory values and risk stratification based on pretest probability through Wells' score. Apart from the initial study that analyzed modified PIOPED II criteria, our study population contains the greatest number of patients investigating Q-only pulmonary scintigraphy. While there are some studies in the literature investigating the role of Q-only imaging in patients with SARS-CoV-2 infection, our study includes a patient population that encompasses patients with or without COVID-19 pneumonia. As the COVID-19 pandemic evolves, our study might reflect the most reliable risk stratification in terms of PE evaluation since prior investigations could not account for the above-mentioned changes intrinsic to SARS-CoV-2 infection.

Conclusion

Summary sentence

The overall sensitivity of the Q-only imaging is clinically comparable to V/Q scintigraphy, especially when coupled with SPECT/CT, even in the COVID-19 era. This study promotes Q-only imaging for patients who are not able to perform a ventilation (i.e. sedation, unable to follow commands) studies.

Take home points

- The present study demonstrates that Q-only pulmonary scintigraphy is a reliable method in the era of COVID-19 with a potential increase in sensitivity and specificity, especially when coupled with SPECT/CT
- The rate of nondiagnostic studies has decreased since the index PIOPED study evaluating the feasibility of Q-only scintigraphy
- Q-only study has further applications in patients with an active COVID-19 infection, pregnancy and for patients who cannot follow commands to perform ventilation portion.

Acknowledgment

This study was approved by the Institutional Review Board.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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