

Lung perfusion scan findings and clinical predictors of pulmonary embolism in hospitalized COVID-19 patients: A cross-sectional analysis

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ABSTRACT

Introduction: Pulmonary embolism (PE) is a complication of COVID-19 requiring timely diagnosis. This study evaluated lung perfusion scintigraphic findings and their association with Wells clinical probability in patients with COVID-19 and suspected PE.

Methods: This retrospective cross-sectional study included 48 hospitalized patients with confirmed COVID-19 and suspected PE who underwent lung perfusion scintigraphy. Demographic characteristics, symptoms, Wells probability, D-dimer levels, and scintigraphic findings were extracted from records. Perfusion scintigraphy was performed without ventilation imaging and interpreted with chest radiography using modified PIOPED II criteria for perfusion-only imaging. Findings were categorized as PE present, PE absent, or nondiagnostic. Factors associated with PE-present findings were evaluated by Firth penalized logistic regression.

Results: Among 48 patients, 30 (62.5%) were women, mean age 65.9 ± 22.0 years. Dyspnea (75.0%) and cough (70.8%) were most common. Twenty-five patients (52.1%) had low Wells probability (<4), and 23 (47.9%) had high probability (≥ 4). PE-present findings occurred in 14 patients (29.2%), PE-absent findings in 21 (43.8%), and nondiagnostic findings in 13 (27.1%). High Wells probability was strongly associated with PE-present findings (aOR, 16.77; 95% CI, 3.37–166.82; $P < 0.001$), whereas age and sex were not independently associated.

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Conclusion: Lung perfusion scintigraphy interpreted with chest radiography may provide useful diagnostic information in selected patients with COVID-19 and suspected PE, particularly when CTPA is unsuitable. The association with Wells probability supports clinical pretest assessment when interpreting perfusion-only studies. However, scintigraphic classifications should be considered supportive rather than definitive evidence of PE, particularly without a consistent reference standard.

Keywords: Lung perfusion scintigraphy; Pulmonary embolism; COVID-19; Wells score; PIOPED II

INTRODUCTION

The thrombogenic potential of SARS-CoV-2 infection is well established [1]. COVID-19, particularly in severe cases, can cause substantial respiratory complications requiring hospitalization and intensive care [2]. In hospitalized patients, systemic inflammation, endothelial dysfunction, hypercoagulability, and prolonged immobility increase the risk of venous thromboembolism (VTE), including PE [3]. Despite anticoagulant prophylaxis, VTE and PE remain important complications of COVID-19, particularly among critically ill patients [4]. The increased risk of PE in this population underscores the importance of appropriate clinical assessment and timely diagnostic evaluation [5]. Clinical prediction tools, including the Wells score, provide an estimate of the pretest probability of PE but do not establish the diagnosis [6]. Computed tomography pulmonary angiography (CTPA) is an important diagnostic reference standard for acute PE; however, its use may be limited in selected patients because of iodinated contrast exposure, renal impairment, radiation considerations, or other clinical circumstances [7]. Lung scintigraphy therefore remains a useful alternative in appropriately selected patients. Conventional ventilation/perfusion scintigraphy has historically used probability-based interpretation systems, including the PIOPED and modified PIOPED II criteria. In the absence of ventilation imaging, the modified PIOPED II approach allows interpretation of perfusion scintigraphy together with chest radiography. In their study, final examinations were classified as PE present, PE absent, or nondiagnostic [8]. Under this approach, findings highly suggestive of PE are classified as PE present, normal or very-low-probability findings as PE absent, and findings that do not meet either category as nondiagnostic [8, 9]. During the COVID-19 pandemic, perfusion-only imaging gained practical relevance because avoiding ventilation imaging can reduce the potential for aerosol-generating procedures [10]. However, COVID-19 itself may cause pulmonary vascular and microvascular abnormalities that can affect pulmonary perfusion, making interpretation more challenging. Therefore, perfusion scintigraphic findings should be interpreted in conjunction with chest radiographic and clinical findings. The present study aimed to evaluate lung perfusion scintigraphic findings in hospitalized patients with COVID-19 referred for suspected PE and to investigate their association with demographic and clinical characteristics, particularly the Wells clinical probability score.

METHODS

Study design and population

This retrospective cross-sectional study was conducted at Farshchian Heart Hospital, Hamadan, Iran. The study population comprised patients with confirmed COVID-19 who were suspected of having PE and were referred for lung perfusion scintigraphy between March 20, 2020, and December 31, 2021. COVID-19 was considered confirmed based on diagnostic

criteria documented in the medical records, including reverse-transcription polymerase chain reaction (RT-PCR) or characteristic chest computed tomography (CT) findings.

Inclusion criteria: Patients were eligible if they met all of the following criteria:

1. Confirmed COVID-19 based on RT-PCR or chest CT findings.
2. Clinical suspicion of PE based on symptoms and/or clinical assessment.
3. Availability of a Wells clinical probability score.
4. Availability of interpretable lung perfusion scintigraphy and corresponding chest radiography.

Exclusion criteria: Patients were excluded because of:

1. Incomplete medical records, including missing demographic, laboratory, or imaging data.
2. A documented history of PE or chronic thromboembolic pulmonary disease predating the COVID-19 diagnosis.
3. Any other predefined condition that prevented completion or reliable interpretation of the lung perfusion examination.

Pregnancy was not an exclusion criterion. Pregnant patients were included when lung perfusion scintigraphy was selected as an alternative imaging approach to CTPA because of concerns regarding radiation exposure associated with CTPA during pregnancy.

Data collection

Demographic characteristics, clinical symptoms, Wells clinical probability score, serum D-dimer levels, COVID-19 diagnostic method, indication for lung perfusion scintigraphy, and imaging findings were extracted from medical records using a structured data-collection form.

Lung perfusion scintigraphy and image interpretation

Lung perfusion scintigraphy was performed without ventilation imaging. The perfusion images were interpreted in conjunction with the corresponding chest radiographs using the modified PIOPED II approach described by Sostman et al. [11]. Under this approach, perfusion defects were assessed in relation to the corresponding chest radiographic findings. Findings considered highly suggestive of PE were classified as PE present. Normal or very-low-probability findings were classified as PE absent, whereas findings that did not meet the criteria for either PE present or PE absent were classified as nondiagnostic. All lung perfusion scintigraphy examinations and corresponding chest radiographs were interpreted by one experienced nuclear medicine specialist using the predefined interpretation criteria. Inter-observer agreement was not assessed because the examinations were interpreted by a single reader.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA), and R software, version 4.5.0. Continuous variables were assessed for distribution and are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables are presented as frequencies and percentages. For comparisons among the three-lung perfusion scintigraphy classification groups (PE present, PE absent, and nondiagnostic), continuous variables were compared using one-way analysis of variance (ANOVA) for normally distributed data or the Kruskal–Wallis test for non-normally distributed data. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. To evaluate factors associated with PE-present scintigraphic findings, multivariable Firth penalized logistic regression analysis was performed using the `logistf` package in R. The outcome was dichotomized as PE-present scintigraphic findings versus non-PE-present findings, with PE-absent and nondiagnostic

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examinations combined as the reference category. Firth penalized logistic regression was selected to reduce small-sample bias and address potential quasi-complete separation given the limited number of PE-present events ($n=14$). The model included age, sex, and Wells clinical probability as independent variables. Wells clinical probability was dichotomized as low (<4) versus high (≥ 4). Results are presented as adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs). Given the limited sample size and number of PE-present events, the regression estimates were considered exploratory, and the relatively wide confidence intervals should be interpreted cautiously. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

RESULTS

Patient characteristics

During the study period, 83 hospitalized patients with COVID-19 were referred for lung perfusion scintigraphy because of suspected pulmonary embolism (PE). Of these, 48 patients met the predefined eligibility criteria and were included in the final analysis, while 35 patients were excluded. Among the excluded patients, 28 (80.0%) had incomplete medical records, 5 (14.3%) had a history of PE before COVID-19 diagnosis, and 2 (5.7%) had contraindications to undergoing lung perfusion scintigraphy. Among the 48 included patients, the indications for lung perfusion scintigraphy were contrast intolerance in 40 patients (83.3%) and pregnancy in 8 patients (16.7%). In pregnant patients, perfusion scintigraphy was selected as an alternative imaging approach because of concerns regarding radiation exposure associated with CTPA during pregnancy. COVID-19 was diagnosed by chest CT in 29 patients (60.4%) and by RT-PCR in 19 patients (39.6%). The study population comprised 30 women (62.5%) and 18 men (37.5%). The mean age was 65.9 ± 22.0 years, and the median age was 71.5 years (IQR, 54.0–83.3 years). Dyspnea was reported in 36 patients (75.0%) and cough in 34 patients (70.8%), while palpitation and chest pain were reported in 6 (12.5%) and 4 (8.3%) patients, respectively. According to the Wells clinical probability score, 25 patients (52.1%) had a low clinical probability (<4), whereas 23 patients (47.9%) had a high clinical probability (≥ 4). The demographic and clinical characteristics of the study population are summarized in Table 1.

Lung perfusion scintigraphy findings

Lung perfusion scintigraphy was interpreted in conjunction with the corresponding chest radiographic findings using the modified PIOPED II approach [8]. Based on the final scintigraphic interpretation, 14 patients (29.2%) were classified as having PE-present findings, 21 patients (43.8%) as having PE-absent findings, and 13 patients (27.1%) as having nondiagnostic examinations (Table 1). The distribution of demographic characteristics, D-dimer levels, sex, and Wells clinical probability across the three scintigraphic classification groups is presented in Table 2. Age differed significantly among the PE-present, PE-absent, and nondiagnostic groups ($P=0.013$). The mean age was 77.07 ± 11.39 years in the PE-present group, 56.00 ± 25.55 years in the PE-absent group, and 70.08 ± 18.47 years in the nondiagnostic group. D-dimer levels did not differ significantly among the three groups ($P=0.162$), and no statistically significant difference was observed in sex distribution ($P=0.220$). A significant association was observed between Wells clinical probability and final scintigraphic classification ($P<0.001$) (Table 3). Among patients with PE-present findings, 13 of 14 patients (92.9%) had a high Wells clinical probability (≥ 4), whereas 1 patient (7.1%) had a low clinical probability (<4). In the PE-absent group, 2 patients (9.5%) had a high Wells clinical probability and 19 (90.5%) had a low clinical probability. In the nondiagnostic group, 8 patients (61.5%) had a high clinical probability and 5 (38.5%) had a low clinical probability.

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Multivariable analysis

To further evaluate factors associated with PE-present scintigraphic findings, a multivariable Firth penalized logistic regression model was performed. PE-present findings were considered the outcome, whereas PE-absent and nondiagnostic findings were combined as the non-PE-present reference category. The model included age, sex, and Wells clinical probability. High Wells clinical probability was strongly associated with PE-present scintigraphic findings (aOR, 16.77; 95% CI, 3.37–166.82; $P < 0.001$). Age was not significantly associated with PE-present findings after adjustment for the other variables (aOR, 1.03; 95% CI, 0.99–1.09; $P = 0.130$). Similarly, male sex was not significantly associated with PE-present findings compared with female sex (aOR, 1.91; 95% CI, 0.40–9.91; $P = 0.414$). The results of the multivariable analysis are presented in Table 4. Given the relatively small number of PE-present cases ($n = 14$), the multivariable findings should be considered exploratory, particularly in view of the wide confidence intervals.

DISCUSSION

COVID-19 is associated with a complex spectrum of thrombotic and pulmonary vascular abnormalities. Systemic inflammation, endothelial dysfunction, hypercoagulability, venous stasis, and both macrovascular thromboembolism and microvascular thrombosis may contribute to pulmonary vascular disease in affected patients [12–16]. These mechanisms are particularly relevant when interpreting pulmonary perfusion abnormalities because not every perfusion abnormality in a patient with COVID-19 necessarily represents conventional embolic occlusion. In this study, 48 hospitalized patients with COVID-19 and clinical suspicion of PE underwent lung perfusion scintigraphy. The examinations were interpreted in conjunction with corresponding chest radiographic findings using the modified PIOPED II approach described by Sostman et al [11]. Fourteen patients (29.2%) had PE-present findings, 21 (43.8%) had PE-absent findings, and 13 (27.1%) had nondiagnostic examinations. Thus, more than one-quarter of the examinations were nondiagnostic, emphasizing the importance of clinical correlation and the limitations of perfusion scintigraphy as a stand-alone diagnostic test in this population. The principal finding of this study was the strong association between Wells clinical probability and PE-present scintigraphic findings. Among patients with PE-present findings, 13 of 14 (92.9%) had a high Wells clinical probability, compared with 2 of 21 (9.5%) patients in the PE-absent group. This association remained statistically significant after adjustment for age and sex. In the multivariable Firth penalized logistic regression model, high Wells clinical probability was strongly associated with PE-present scintigraphic findings (aOR, 16.77; 95% CI, 3.37–166.82; $P < 0.001$). This finding should, however, be interpreted as an association between clinical pretest probability and scintigraphic classification rather than as evidence that the Wells score independently establishes the diagnosis of PE. The Wells score is a clinical prediction tool and is not a definitive diagnostic test. The wide confidence interval around the estimated odds ratio reflects the small number of PE-present cases and the uncertainty associated with estimating associations in a small dataset. Therefore, the magnitude of the observed association should be interpreted cautiously. Age differed significantly among the three scintigraphic groups in the unadjusted analysis ($P = 0.013$), patients with PE-present findings being older than those with PE-absent findings. However, age was not independently associated with PE-present findings after adjustment for Wells clinical probability and sex (aOR, 1.03; 95% CI, 0.99–1.09; $P = 0.130$). Thus, the unadjusted difference in age should not be interpreted as evidence that age is an independent predictor of PE-present findings in this cohort. Similarly, sex and D-dimer levels were not significantly associated with scintigraphic

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classification. In this study, perfusion findings were interpreted in conjunction with chest radiography using the modified PIOPED II approach in the absence of ventilation imaging. The final study classification was expressed as PE present, PE absent, or nondiagnostic. This approach allowed the perfusion findings to be considered together with the corresponding radiographic abnormalities and avoided interpreting perfusion defects in isolation. Perfusion scintigraphy without ventilation imaging may be useful in selected patients in whom CTPA is contraindicated or considered undesirable [17]. In the present cohort, contrast intolerance and pregnancy were the documented indications for referral for perfusion scintigraphy. In pregnant patients, perfusion scintigraphy was selected as an alternative imaging approach because of concerns regarding radiation exposure associated with CTPA during pregnancy [18-23]. However, this study does not establish that perfusion scintigraphy is diagnostically equivalent to CTPA. CTPA remains an important reference standard when clinically appropriate [24]. Another important consideration is the pathophysiology of COVID-19 itself. SARS-CoV-2 infection can cause endothelial injury, inflammation, microvascular thrombosis, and other pulmonary vascular abnormalities [25]. These mechanisms may produce perfusion abnormalities that cannot necessarily be distinguished from conventional thromboembolic disease by perfusion scintigraphy alone. Therefore, PE-present scintigraphic findings in patients with COVID-19 should be interpreted in conjunction with the clinical probability of PE and chest radiographic findings and should not automatically be considered definitive confirmation of thromboembolic PE. Likewise, the PE-absent category should not be interpreted as definitive exclusion of PE. In the present study, PE absent denotes a scintigraphic classification based on the predefined interpretation criteria and corresponding chest radiographic findings. In the absence of a consistent reference standard such as CTPA and systematic clinical follow-up, this classification should not be considered definitive exclusion of PE. Patients with persistent, discordant, or clinically high suspicion of PE may require additional diagnostic evaluation. The relatively high proportion of nondiagnostic examinations (27.1%) is also clinically relevant. It emphasizes that although the perfusion-only approach may provide useful information in selected patients, it cannot replace comprehensive clinical assessment or definitive imaging when additional evaluation is clinically indicated. Taken together, these findings suggest that combining clinical pretest probability with lung perfusion scintigraphic interpretation may provide useful information in selected hospitalized patients with COVID-19 who are suspected of having PE. However, the findings should be considered supportive rather than definitive, particularly in the absence of a consistent reference standard and systematic clinical follow-up. The strong association between high Wells clinical probability and PE-present scintigraphic findings is hypothesis-generating and should be confirmed in larger prospective studies.

Limitations

This study has several limitations. First, its retrospective, single-center design and small sample size (n=48), including only 14 PE-present cases, limit statistical power and generalizability. An a priori power calculation was not performed because all eligible patients during the predefined study period were included; therefore, the multivariable analysis should be considered exploratory. Second, a definitive reference standard such as CTPA was not available for all patients; thus, PE-present and PE-absent findings should not be considered definitive confirmation or exclusion of PE. Finally, COVID-19-related pulmonary microvascular abnormalities may contribute to perfusion defects, and subsequent clinical management was not standardized because of the retrospective design. Larger prospective studies with an appropriate reference standard are warranted.

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CONCLUSION

In hospitalized patients with COVID-19 and suspected PE, lung perfusion scintigraphy interpreted in conjunction with chest radiography demonstrated PE-present findings in 14 patients (29.2%), PE-absent findings in 21 (43.8%), and nondiagnostic findings in 13 (27.1%). High Wells clinical probability was strongly associated with PE-present scintigraphic findings, whereas age and sex were not independently associated with the outcome after multivariable adjustment. These findings suggest that clinical probability assessment may provide useful complementary information when interpreting perfusion scintigraphy in selected patients with COVID-19. However, given the small sample size, retrospective design, nondiagnostic examinations, and lack of a definitive reference standard in all patients, the scintigraphic classifications should not be considered equivalent to definitive confirmation or exclusion of PE. Larger prospective studies using an appropriate reference standard are required to establish the diagnostic role of perfusion scintigraphy in this population.

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Table 1. Demographic and clinical characteristics of the study population

	Characteristic	N=48
Age (years)	Mean $\pm$ SD	65.9 $\pm$ 22.0
	Median (IQR)	71.5 (54.0–83.3)
Sex, n (%)	Female	30 (62.5)
	Male	18 (37.5)
COVID-19 diagnosis, n (%)	CT	29 (60.4)
	RT-PCR	19 (39.6)
Indication for lung perfusion scintigraphy, n (%)	Contrast intolerance	40 (83.3)
	Pregnancy	8 (16.7)
Symptoms, n (%)	Dyspnea	36 (75.0)
	Cough	34 (70.8)
	Palpitation	6 (12.5)
	Chest pain	4 (8.3)
Wells clinical probability, n (%)	Low (<4)	25 (52.1)
	High ($\geq$ 4)	23 (47.9)
Final lung perfusion scintigraphy classification, n (%)	PE absent	21 (43.8)
	Nondiagnostic	13 (27.1)
	PE present	14 (29.2)

Abbreviations: CT, computed tomography; RT-PCR, reverse-transcription polymerase chain reaction; IQR, interquartile range; SD, standard deviation; PE, pulmonary embolism.

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Table 2. Association between lung perfusion scintigraphy findings and demographic characteristics and Wells clinical probability

Variable		Nondiagnostic (n=13)	PE absent (n=21)	PE present (n=14)	P value
Age, mean±SD	Years	70.08±18.47	56.00±25.55	77.07±11.39	0.013*
D-dimer, mean±SD	mg/L	1774.38±1226.40	1562.71±2110.59	1917.50±1112.03	0.162†
Sex, n (%)	Female	7 (53.8)	16 (76.2)	7 (50.0)	0.220‡
	Male	6 (46.2)	5 (23.8)	7 (50.0)	
Wells clinical probability, n (%)	Low (<4)	5 (38.5)	19 (90.5)	1 (7.1)	<0.001‡
	High (≥4)	8 (61.5)	2 (9.5)	13 (92.9)	

Values are presented as mean ± SD for continuous variables and count (percentage) for categorical variables. * ANOVA; † Kruskal–Wallis test; ‡ Pearson chi-square test.

Table 3. Distribution of Wells clinical probability according to final scintigraphic classification

Wells clinical probability	PE present	PE absent	Nondiagnostic
Low (<4), n (%)	1 (7.1)	19 (90.5)	5 (38.5)
High (≥4), n (%)	13 (92.9)	2 (9.5)	8 (61.5)

Table 4. Multivariable firth penalized logistic regression analysis of factors associated with PE-present scintigraphic findings

Variable	β	Adjusted OR	95% CI	P value
Age (years)	0.033	1.03	0.99–1.09	0.130
Male sex vs female sex	0.649	1.91	0.40–9.91	0.414
High Wells clinical probability vs low	2.820	16.77	3.37–166.82	<0.001

Model: Firth penalized logistic regression; outcome = PE-present scintigraphic findings. Reference categories: female sex and low Wells clinical probability.