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ORIGINAL RESEARCH

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Comparison of echocardiographic pulmonary flow Doppler markers in patients with massive or submassive acute pulmonary embolism and control group: A cross-sectional study

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Abstract

Background and Aims: Computed tomography angiography (CTA) is the gold standard for the diagnosis of massive (MPE) and submassive pulmonary embolism (SMPE). Ultrasound has not been accepted as a diagnostic tool. We aim to evaluate the pattern of pulmonary Doppler echocardiography in patients with pulmonary embolism (PE).

Methods: From 2020 to 2022, 30 patients with acute MPE or SMPE confirmed by CTA and normal pulmonary pressures were selected. A control group was created with 30 individuals without PE. All patients had an echocardiography Doppler study of the pulmonary flow with a focus on early systolic notching (ESN), McConnell's (MC) sign, Right ventricular outflow tract velocity time integral (RVOT VTI), segmental thickness variability (STV), right ventricular end-diastolic diameter (RVEDD), tricuspid regurgitation (TR) gradient, pulmonary artery pressure (PAP), and acceleration (AT) or ejection time (ET).

Results: ESN was identified in 96.6% of PE patients and 0% of the control group ($p < 0.001$). In comparison with the control group, STV ($p < 0.001$), RVOT VTI ($p < 0.001$), ET ($p = 0.04$), and AT ($p < 0.001$) values were lower in patients with PE while RVEDD, TR gradient, PAP, ESN, MC sign, and D-shape were higher ($p < 0.001$). Identification of the ESN pattern and AT/ET < 0.4 showed excellent predictive ability for MPE and SMPE with a sensitivity of 97.0% and 100%, specificity of 99.0% and 97%, and an area under the ROC curve of 0.967 (95% CI 0.914–1.00) and 0.933 (95% CI 0.844–1.00), respectively.

Conclusion: Doppler echocardiography with particular attention to ESN, may be a suitable noninvasive method for the diagnosis of MPE and SMPE. Further studies with more sample sizes are needed to confirm its diagnostic benefit.

KEYWORDS

echocardiography, massive pulmonary embolism, pulmonary artery doppler

1 | INTRODUCTION

Acute pulmonary embolism (PE) with shock or hypotension is a life-threatening condition requiring immediate diagnostic and treatment measures in accordance with international guidelines.[1,2] Mortality rates of massive embolism, sub-massive, and sub-segmental embolism have been reported up to 65%, 25%, and 1%, respectively.[3,4]

Computed tomographic angiography (CTA) and ventilation/perfusion scan are the most common noninvasive imaging techniques for diagnosing acute PE.[5] However, due to the high mortality associated with undiagnosed PE, acute PE must be classified promptly to ensure rapid initiation of anticoagulant therapy in appropriate cases and, conversely, to refrain from initiating such treatment when not indicated.[6,7]

Echocardiography has been used primarily to diagnose RV dysfunction (RVD) in patients with unstable condition due to its availability and low cost. Echocardiography can show the presence of a clot directly in the right ventricle or pulmonary artery.[8,9] Because trans-thoracic echocardiography (TTE) is one of the most accessible noninvasive imaging modalities, it is often used to diagnose acute shortness of breath, chest pain, and hemodynamic compensation.[10] In patients with PE, TTE can show not only RVD but also, in some cases, typical echocardiographic signs of acute PE, such as McConnell's (MC) and 60/60 signs. In addition, TTE can also show evidence of alternatives to the observed clinical picture, such as cardiac tamponade, left ventricular (LV) systolic dysfunction, and unexpected significant valvular lesions.[11] Therefore, Doppler echocardiography may be valuable in diagnosing massive PE cases.

Afonso et al. performed on 277 patients with suspected PE and evaluated the role of Doppler echocardiography in diagnosing massive and sub-massive embolism. According to this study, 92% of patients with massive and sub-massive embolism had early systolic notching (ESN) and other arterial Doppler parameters.[12]

This study aimed to evaluate the pattern of pulmonary blood flow in Doppler echocardiography of massive or sub-massive PE patients and compare it with the results of patients without PE.

2 | METHODS

2.1 | Study design and evaluation of outcome

The present cross-sectional study was conducted on patients with acute PE referred to our institution between 2020 and 2022. Patients with massive or sub-massive PE were chosen among acute PE patients.

The diagnostic criterion for PE in these patients was the presence of embolism on pulmonary CTA. Massive PE was diagnosed in patients with arterial hypotension and cardiogenic shock. Arterial hypotension is characterized as a systolic arterial pressure < 90 mmHg or a drop in systolic arterial pressure of at least 40 mmHg for at least 15 min. In addition, shock is recognized by tissue hypoperfusion and hypoxia, including an altered level of consciousness, oliguria, or cool, clammy extremities. In contrast, acute PE without systemic hypotension (systolic blood pressure > 90 mmHg) can be considered low-risk or submassive PE. Submassive PE was defined by the presence of RVD or myocardial necrosis.[13,14]

Patients with PE signs more than 14 days before diagnosis and patients with chronic thromboembolic hypertension were excluded from this study. An echocardiography specialist performed echocardiography in the early hours before starting treatment, less than 3 h after diagnosis.

Besides, the control group consists of patients with no past medical history especially dyspenea or lung diseases referred to our department's echocardiography ward.

2.2 | Evaluation of outcome

Patients of both groups underwent a cardiac Doppler echocardiography study with a focus on pulmonary flow patterns. The right ventricular end-diastolic diameter (RVEDD), segmental thickness variability (STV), tricuspid regurgitation (TR) gradient, pulmonary artery pressure (PAP), right ventricular outflow tract velocity time integral (RVOT VTI), right ventricular ejection time (RVET), acceleration time (AT), MC sign, D-shape septum, and ESN were recorded. Patients' demographics and clinical data were also collected. Group comparison of Doppler echocardiographic findings was performed.

In detail, RVET was obtained from the onset to the end of RVOT Doppler envelope. Furthermore, AT was assessed from the beginning of the flow to the peak flow velocity. Noteworthy, the marker should be placed at the peak first and then tracked back to the onset of flow, to detect time taken to peak velocity and not the propagation. RVOTVTI was measured by tracing the systolic RVOT pulsed-wave Doppler envelope.

The ESN pattern was represented as a sharp notch after a narrow spike in the RVOT Doppler envelope. In addition, MC sign was specified as akinesia of the mid free wall with apical sparing.[15–17]

2.3 | Calculation of sample size

The power (β) was set as 80%, and the significance level (α) was adjusted to 5%. According to a prior study[12] and the formula for comparing two means to obtain the difference of one unit in one variable (Deceleration time; DT), the estimated sample size for each group was 30.

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times \left(\sigma_1^2 + \sigma_2^2\right)}{(\mu 1 - \mu 2)^2}$$

Where $Z_{1-\frac{\alpha}{2}} = 1.96$, $Z_{1-\beta} = 0.84$, $\sigma_1 = 46$, $\sigma_2 = 44$, $\mu_1 = 186$, and $\mu_2 = 219$. In this regard, 60 patients were totally included in the current clinical study.

TABLE 1 Baseline characteristics of patients enrolled in the study.

Variables	PE (n = 30)	Control (n = 30)	p Value
Gender (n, %)			
Male	21 (70%)	18 (60%)	0.417[a]
Female	9 (30%)	12 (40%)	
Age (Years, Mean ± SD)	58.13 ± 14.28	44.9 ± 21.46	0.009[b]
SBP (mmHg, Mean ± SD)	102 ± 20.17	120 ± 14.01	0.001[b]
DBP (mmHg, Mean ± SD)	66 ± 14.46	71 ± 10.02	0.21[b]

Abbreviations: DBP, diastolic blood pressure; PE, Pulmonary embolism; SBP, Systolic blood pressure; SD, standard deviations.

[a]Comparing the PE and control groups using the χ^2 test;

[b]Comparing the PE and control groups using the Mann-Whitney test.

2.4 | Statistical analysis

The SPSS statistical program version.22 (SPSS Inc.) was used to analyze the data. Parametric data were expressed as Mean and standard deviations, whereas nonparametric outcomes were expressed as a number (n) with a percentage (%). Furthermore, the Student's t-test was utilized to compare continuous variables with parametric data, and the Mann–Whitney U test was used to compare nonparametric data, if applicable. The χ^2 or Fisher exact test evaluated the difference between categorical variables.

We also determined the diagnostic utility for prespecified echocardiographic parameters, such as notch-related parameters, RV dilation, and TR velocity. Optimal cutoffs for these echocardiographic values were considered the levels that minimized the square difference between sensitivity and specificity. The diagnostic ability of these markers was evaluated using probability statistics and ROC analysis. The significance level was considered p values less than 0.05.

3 | RESULTS

3.1 | Demographic results

The ratio of men to women was 70% to 30% in the PE group and 60% to 40% in the control group (p = 0.417, Table 1). The mean age was 58 ± 14.28 years in the PE group and 45 ± 21.46 years in the control group (p = 0.009, Table 1).

3.2 | Clinical findings of PE patients

Among 30 patients with PE, 19 (63.3%) received anticoagulant treatment, 7 (23.3%) received fibrinolytic treatment, and four (13.4%) received thrombectomy (Table 2). The clinical symptoms and electrocardiogram findings of PE patients are presented in Table 2. The most common complaints of PE patients were dyspnea (93.33%) and tachycardia (83.4%). According to electrocardiographic findings, the most common finding of PE patients was sinus tachycardia (96%, Table 2).

TABLE 2 Clinical findings of PE patients.

	Variable (n, %)	PE (n = 30)
Treatment	Thrombectomy	4 (13.4%)
	Fibrinolitic	7 (23.3%)
	Anticoagulant	19 (63.3%)
Symptoms	Chest pain	5 (16.67%)
	Syncope	9 (30.0%)
	Dyspnea	28 (93.33%)
	Tachycardia	25 (83.4%)
	LOC	3 (10%)
ECG Finfings	S1Q3T3	15 (50%)
	RBBB	11 (36%)
	Atrial fibrillation	1 (3.0%)
	Flutter	0 (0.0%)
	Sinus tachycardia	29 (96.0%)
	T inversion in precordial lead	14 (46.67%)

Abbreviations: ECG, electrocardiogram; LOC, loss of consciousness; PE, pulmonary embolism; RBBB, right bundle branch block.

3.3 | Echocardiographic results

The echocardiographic parameters of PE and control patients are illustrated in Table 3. Our results showed that STV (p < 0.001), RVOT VTI (p < 0.001), ET (p = 0.04), and AT (p < 0.001) in PE patients were significantly lower than the control group, while RVEDD, TR gradient, and PAP were notably higher than the control group (p < 0.001 for all cases, Table 3).

In addition, the most critical finding in PE patients was ESN, which was seen in 96.6% (Figure 1). In addition, MC sign and

TABLE 3 Echocardiographic results of PE and control patients.

Variable (Mean ± SD)	PE (n = 30)	Control (n = 30)	p Value
STV (cm)	9.90 ± 2.89	17.48 ± 26.04	<0.001[a]
TR gradient (mmHg)	47.93 ± 14.63	21 ± 4.51	<0.001[a]
RVEDD (cm)	4.36 ± 0.63	2.95 ± 0.31	<0.001[a]
RVOT VTI (cm)	10.04 ± 3.31	18.80 ± 4	<0.001[a]
RVET (ms)	261.57 ± 32.77	276.03 ± 6.88	0.04[a]
ET (ms)			
<273	20 (66.6%)	8 (26.6%)	0.002[b]
>273	10 (44.4%)	22 (73.4%)	
PAP (mmHg)	53.30 ± 14.33	26.07 ± 4.50	<0.001[a]
PAP (mmHg)			
<34	0 (0.0%)	29 (96.7%)	<0.001[b]
>34	30 (100%)	1 (3.3%)	
AT (ms)	57.23 ± 13.61	120.03 ± 29.49	<0.001[a]
AT (ms)			
<77	28 (93.3%)	2 (6.7%)	<0.001[b]
>77	2 (6.7%)	28 (93.3%)	
AT/ET	0.22 ± 0.06	0.43 ± 0.1	<0.001[a]
AT/ET			
<0.4	30 (100%)	0 (0.0%)	<0.001[b]
>0.4	0 (0.0%)	30 (100%)	
McConnell's sign (n, %)	22 (72.3%)	0 (0%)	<0.001[b]
D-SHAPE SEPTUM (n, %)	20 (66.6%)	0 (0%)	<0.001[b]
ESN (n, %)	29 (96.6%)	0 (0%)	<0.001[b]

Abbreviations: AT, acceleration time; ESN, early systolic notching; ET, ejection time; PAP, pulmonary artery pressure; PE, pulmonary embolism; RVEDD, right ventricular end-diastolic diameter; RVOTVTI, right ventricular outflow tract velocity time integral, SD, standard deviations; STV, segmental thickness variability; TR, tricuspid regurgitation.

[a]Comparing the PE and control groups using Mann–Whitney test.

[b]Comparing the PE and control groups using Fisher exact test.

D-shape septum were observed in 73% and 66% of PE patients, which can help to determine the severity of PE (Table 3). In addition, no ESN, MC sign, and D-shape was observed in control patients. We found that ESN, MC sign, and D-shape were significantly greater in PE patients than in the control group ($p < 0.001$ for all cases, Table 3).

Assessment of the ESN pattern, AT/ET < 0.4, and PAP > 34 mmHg on Doppler echocardiography showed excellent predictive ability for PE (Table 4 and Figure 2). The ESN pattern showed 97% sensitivity, 99% specificity, and an area under the ROC curve of 0.967 (95% CI 0.914–1.00). Furthermore, AT/ET < 0.4 showed 100% sensitivity, 97% specificity, and area under the ROC curve of 0.933 (95% CI 0.844–1.00). The PAP > 34 mmHg showed 96% sensitivity, 97% specificity, and an area under the ROC curve of 0.984 (95% CI 0.955–1.00). Moreover, the identification of MC sign had a sensitivity of 73.0%, specificity of 97%, and area under the ROC curve of 0.867 (95% CI 0.767–0.967, Table 4 and Figure 2).

4 | DISCUSSION

Echocardiography may be increasingly beneficial in diagnosing and treating acute PE. Although it is not the first diagnostic step, it can provide additional information for other diagnostic methods, has predictive value, and monitors the treatment, especially in cases where CTA is unavailable.[18] Occasionally, performing echocardiography for shortness of breath, chest pain, and HTN can accidentally detect PE. In addition, TTE can show a thrombus at the site of pulmonary artery branching, which is associated with

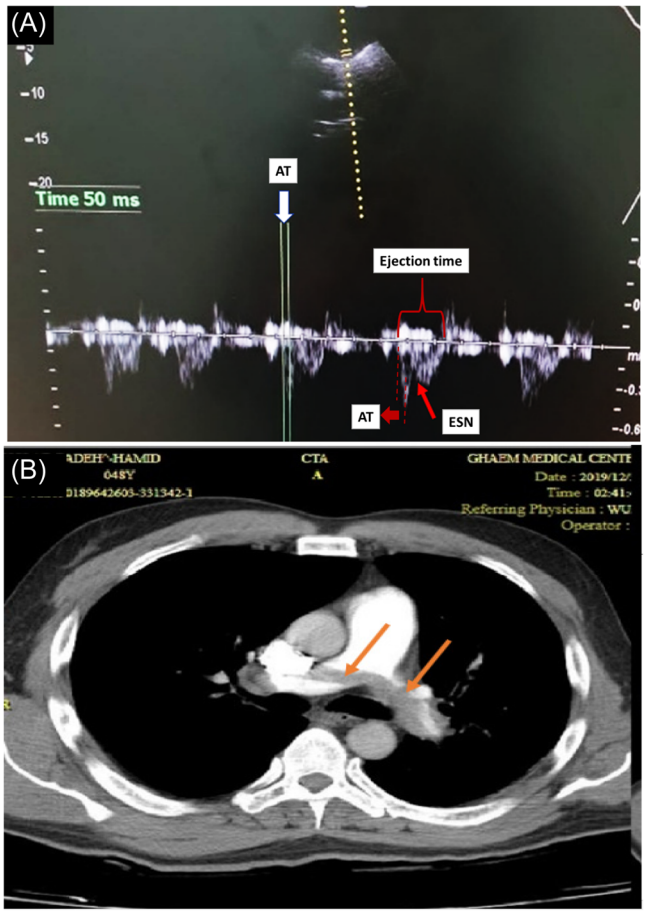

FIGURE 1 (A) Acceleration time (AT), ejection time (ET), Early systolic notching (ESN) in right ventricular outflow tract Doppler patterns; (B) Arrows show clot in left and right pulmonary artery.

high RVD and mortality. Although TEE can image the more terminal branches, it is seldom used as the first diagnostic modality for diagnosing PE.[19]

The present study included patients with suspected embolisms with massive or sub-massive PE confirmed by CTA. This study showed that a high percentage of PE patients (96.6%) had ESN symptoms, while no normal person (0.0%) had this symptom. Additionally, other pulmonary artery Doppler indices were also helpful in the diagnosis of massive or sub-massive PE. In this regard, we showed that the rate of RVOTVT, AT, and ET in patients with PE was significantly lower than in the control group. In contrast, the rates of RVEDD, PAP, and RV SIZE in patients with PE were notably higher than in the control group. Interestingly, identification of the ESN pattern, AT/ET < 0.4, and PAP > 34 mmHg on Doppler echocardiography showed excellent predictive ability for massive or sub-massive PE.

In line with our results, Afonso et al. examined the role of pulmonary artery Doppler in diagnosing mass and sub-massive PE. In this study, 277 patients underwent TTE in which ESN and MC sign, 60/60 sign, AT, ET, and RVOT were recorded. They noticed that 44% of patients had massive PE, 38% had sub-massive PE, and 39% were normal. Furthermore, ESN was identified in 92% of patients with massive and sub-massive PE, while in no normal patients (0.0%). They showed that the presence of ESN was associated with excellent predictive ability for massive and sub-massive PE, with a sensitivity of 92% (95% CI, 84%–97%), specificity of 99% (95% CI, 96%–100%), and area under the ROC curve of 0.96 (95% CI, 0.92–0.98). The detection of the ESN pattern was superior to the MC sign, the sign of 60.60, and AT < 87% in the diagnosis of mass and sub-massive PE.[12] Similarly,

TABLE 4 The sensitivity and specificity of echocardiographic markers compared to the standard CT pulmonary angiography test.

Variable	Sensitivity, %	Specificity, %	AUROC	Lower bound (95% CI)	Upper bound (95% CI)	*p* Value
McConnell's sign	73%	97%	0.867	0.767	0.967	<0.001
ESN pattern	97%	99%	0.967	0.914	1.00	<0.001
TR gradient > 31 (mmHg)	90%	100%	0.994	0.983	1.00	<0.001
RVEDD > 3.5 (cm)	93%	94%	0.988	0.969	1.00	<0.001
PAP > 34 (mmHg)	96%	97%	0.984	0.955	1.00	<0.001
AT < 89 (ms)	97%	94%	0.933	0.844	1.00	<0.001
AT/ET < 0.4	100%	97%	0.933	0.844	1.00	<0.001
RVET < 266 (ms)	67%	90%	0.718	0.57	0.866	0.004
RVOT VTI < 14.75 (cm)	87%	90%	0.955	0.908	1.00	<0.001
STV < 11.8 (cm)	80%	74%	0.815	0.704	0.92	<0.001

Abbreviations: AT, Acceleration time; AUROC, area under the ROC curve; CI, confidential interval; ET, Ejection time; ESN, early systolic notching; PAP, Pulmonary artery pressure; RVEDD, right ventricular end-diastolic diameter; RVOTVTI, Right ventricular outflow tract velocity time integral; STV, Segmental thickness variability; TR, Tricuspid regurgitation.

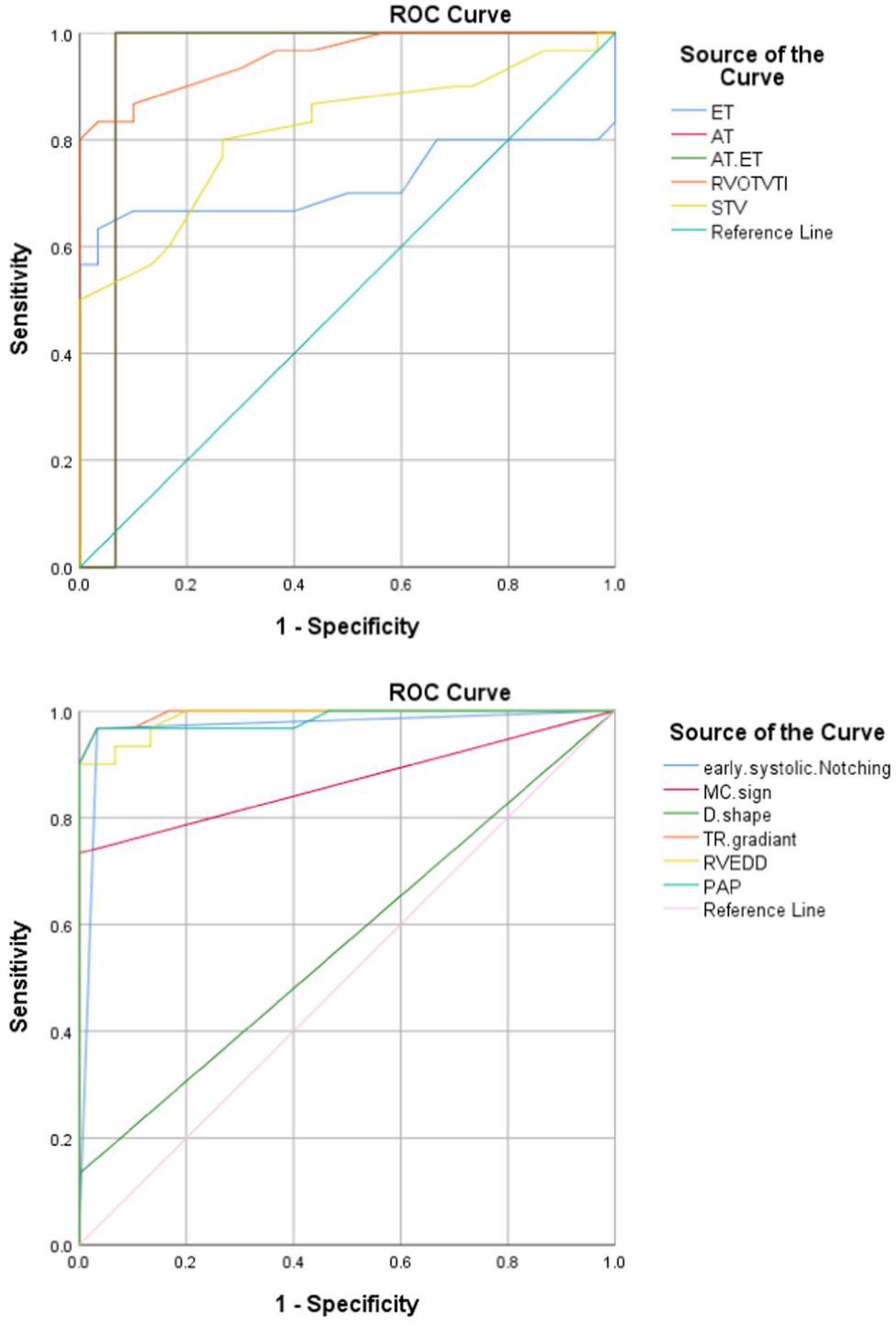

FIGURE 2 The ROC curve for evaluation of sensitivity and specificity of echocardiographic markers compared to the standard CT pulmonary angiography test. CT, Computed tomography.

Shah and coworkers determined 24 PE and 32 No PE patients. They found that ESN was observed in 75% of PE and 0% of No PE patients. Moreover, a 60/60 sign and right ventricle to left ventricle end-diastolic dimension ratio>0.9 were identified in 70.83% and 91.67% of PE and 6.25% and 25% of No PE patients. In addition, the ESN, 60/60 sign, and right ventricle to left ventricle end-diastolic dimension ratio>0.9 had sensitivities of 75%, 70.83%, and 91.67%, and specificities of 100%, 93.75%, and 75%, respectively. They suggested that ESN and 60/60 signs have excellent specificity while moderate sensitivity for diagnosing PE.[20] Lodato et al. demonstrated that the right ventricle to left ventricle end-diastolic dimension ratio > 0.7 accurately predicts PE with a sensitivity of 66% and specificity of 77%. In addition, MC sign had high specificity (96%) while low sensitivity (16%) for the

diagnosis of PE.[21] These studies may confirm our results regarding Doppler echocardiography, with particular attention to ESN may be a suitable and promising noninvasive method for diagnosing mass or sub-mass PE.

Fields and coworkers conducted a systematic review and meta-analysis study and reported that the right heart strain mark was the most commonly used sign with a sensitivity of 53% and a specificity of 83%. Additionally, other echocardiography markers such as TR, 60/60 sign, MC sign, and RVEDD were also identified in PE patients. This study suggested that echocardiography may be a suitable tool for diagnosing PE in critically ill patients in the emergency ward.[8] Similarly, Alerhand et al. also reviewed that echocardiographic results of right ventricular strain, including MC sign, TR, 60/60 sign, and ESN may correctly suggest and diagnose PE, can point toward a diagnosis of PE and thereby lead to earlier initiation of directed management.[22]

In contrast, Kurnicka et al. evaluated the value of some echocardiographic signs and markers in 511 patients with proven PE (281 females and 230 males). Finally, this study stated that about 70% of patients with PE did not have an abnormal observation in TTE.[11] Based on the findings of other studies, such as the article by Afonso et al., the statement that no finding was seen in 70% of patients is doubtful.[12] Similarly, Aslaner and coworkers evaluated 183 patients referred to 4 emergency centers for suspected PE undergoing CTA and underwent Doppler echocardiography. Among 183 patients, 96 (52.5%) had PE, and 87 (47.5%) did not have PE. Furthermore, ESN finding was observed in 34.4% of PE and 3.4% of No PE patients. The results showed that ESN had 34% sensitivity and 97% specificity for PE in all enrolled patients. In the analysis of subgroups with intermediate to high risk of PE disease, 69% sensitivity and 90% specificity was observed for the ESN pattern. They supported that ESN has low sensitivity and moderate to high specificity for detecting PE in all patients referred to the emergency department.[23]

Summarising the results, the findings of pulmonary artery Doppler findings are helpful in diagnosing PE and its severity.

5 | CONCLUSION

According to the findings of this study, pulmonary artery Doppler using transthoracic echocardiography may be a beneficial imaging technique for evaluating patients suspected of having a massive or sub-massive PE. In particular, the presence of ESN, which was significantly seen in patients with PE, can be used as a potential diagnostic method in the absence of imaging facilities or as the first imaging method. However, further studies with more sample sizes are needed to understand these results better.

AUTHOR CONTRIBUTIONS

Leila Bigdelu: Conceptualization; funding acquisition; investigation; methodology; supervision. **Mahdi Hasanzadeh Daloee**: Conceptualization; methodology; supervision. **Maryam Emadzadeh**: Data curation; formal analysis; software. **Leila Parsa**: Data curation; writing—original draft. **Mahnaz Najafi**: Data curation; investigation; writing—original draft. **Vafa Baradaran Rahimi**: Formal analysis; investigation; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was confirmed by the ethics committee of Mashhad University of Medical Sciences (approval code. IR.MUMS.fm.-REC.1399.172). All participants received and signed written informed consent before their inclusion in the study. All the authors gave consent for the publication of this study in the journal.

TRANSPARENCY STATEMENT

The lead author Mahnaz Najafi, Vafa Baradaran Rahimi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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