Article published online: 2023-01-16

Diagnostic Accuracy of a Bespoke Multiorgan Ultrasound Approach in Suspected Pulmonary Embolism

OPEN ACCESS

Authors

Casper Falster[1, 2, 3], Gro Egholm[4], Rune Wiig[2], Mikael Kjær Poulsen[4], Jacob Eifer Møller[4], Stefan Posth[5], Mikkel Brabrand[5], Christian Borbjerg Laursen[1, 2]

Affiliations

1 Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark
2 Odense Respiratory Research Unit (ODIN), Department of Clinical Research, University of Southern Denmark, Odense, Denmark
3 OPEN, Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark
4 Department of Cardiology, Odense University Hospital, Odense, Denmark
5 Department of Emergency Medicine, Odense University Hospital, Odense, Denmark

Key words

ultrasound, methods & techniques, echocardiography, embolization, embolism/thrombosis, themes

received 21.03.2022
accepted after revision 23.10.2022

Bibliography

Ultrasound Int Open 2022; 8: E59–E67
DOI 10.1055/a-1971-7454
ISSN 2199-7152

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Dr. Casper Falster
Odense University Hospital
Department of respiratory medicine
Kløvervænget 2
5000 Odense
Denmark
Tel.: +4560139562
casper.falster@rsyd.dk

ABSTRACT

Purpose The aims of this study were to prospectively assess the diagnostic accuracy of a bespoke multiorgan point-of-care ultrasound approach for suspected pulmonary embolism and evaluate if this model allows reduced referral to further radiation diagnostics while maintaining safety standards.

Materials and Methods Patients with suspected pulmonary embolism referred for CT pulmonary angiography or ventilation/perfusion scintigraphy were included as a convenience sample. All patients were subject to blinded ultrasound investigation with cardiac, lung, and deep venous ultrasound. The sensitivity and specificity of applied ultrasound signs and the hypothetical reduction in the need for further diagnostic workup were calculated.

Results 75 patients were prospectively enrolled. The Wells score was below 2 in 48 patients, between 2 and 6 in 24 patients, and above 6 in 3 patients. The prevalence of pulmonary embolism was 28 %. The most notable ultrasound signs were presence of a deep venous thrombus, at least two hypoechoic pleural-based lesions, the D-sign, the 60/60-sign, and a visible right ventricular thrombus which all had a specificity of 100 %. Additionally, a multiorgan ultrasound investigation with no findings compatible with pulmonary embolism yielded a sensitivity of 95.2 % (95 %CI: 76.2–99.9). CT or scintigraphy could be safely avoided in 70 % of cases (95 %CI: 63.0–83.1 %).

Conclusion The findings of our study suggest that implementation of a multiorgan ultrasound assessment in patients with suspected pulmonary embolism may safely reduce the need for CT or scintigraphy by confirming or dismissing the suspicion.

Introduction

Patients with pulmonary embolism (PE) may present with a heterogeneous array of symptoms. Dyspnea and chest pain are common but are easily confused with exacerbation of chronic obstructive pulmonary disorder (COPD), decompensated heart failure, or acute coronary syndrome [1, 2]. A combination of clinical scores, such as the Wells score, and measurement of D-dimer, as recommend by the European Society of Cardiology, the European respiratory Society, and the American College of Physicians, is useful for ruling out PE. However, in at least two thirds of patients, suspicion of PE cannot be excluded through this approach and additional radiation-based imaging tests are required [3–5]. Computed tomography pulmonary angiography (CTPA) and ventilation/perfusion scan (V/Q) are established diagnostic tests in suspected PE but are not always feasible. CTPA is relatively contraindicated in renal failure or contrast allergy and both modalities require intrahospital transportation and involvement of multiple staff members and expose the patient to radiation [6]. As recent studies report a prevalence of PE in patients referred to CTPA of 20–30 % in Europe and as low as 5–10 % in the United States, improvement of the clinical assessment of PE probability and refining of the selection of patients for radiation imaging are warranted [7, 8]. Use of point-of-care ultrasound (PoCUS) in the diagnostic algorithm could reduce the need for CTPA or V/Q scan by confirming or dismissing PE suspicion in selected cases [9]. It is noninvasive, can be performed bedside, and reduces time, radiation exposure, and costs [10]. Three PoCUS modalities utilized as a multiorgan approach have the potential to confirm or dismiss PE suspicion: Deep venous ultrasound allows visualization of a source thrombus, allowing confirmation of PE and adding valuable prognostic information [4, 11]; lung ultrasound can detect pleural infarctions, a downstream consequence of PE; and cardiac ultrasound allows the clinician to demonstrate the upstream hemodynamic consequence of pulmonary artery occlusion, namely signs of right ventricular (RV) pressure overload or even a visible thrombus [10, 12].

While several previous studies have evaluated the diagnostic accuracy of a PoCUS investigation, only three have utilized a multiorgan approach, encompassing heart, lung, and deep venous ultrasound [13–15]. To further the body of evidence and confirm the existing literature, we developed a bespoke multiorgan ultrasound approach, combining the ultrasound signs with the highest sensitivities and specificities, based on a recent meta-analysis on the diagnostic accuracy of ultrasound in suspected PE, including 70 descriptive studies [9]. Prospective validation of a bespoke approach via a diagnostic accuracy study is an important prerequisite for assessing its impact in a randomized controlled trial. The aims of this study were to prospectively describe the diagnostic accuracy of our multiorgan PoCUS approach, confirm the diagnostic accuracy of each separate included ultrasound sign as reported in previous literature, and to evaluate whether integration of this model could reduce referral to radiation diagnostics by ruling PE suspicion in or out, while maintaining safety standards.

Materials and Methods

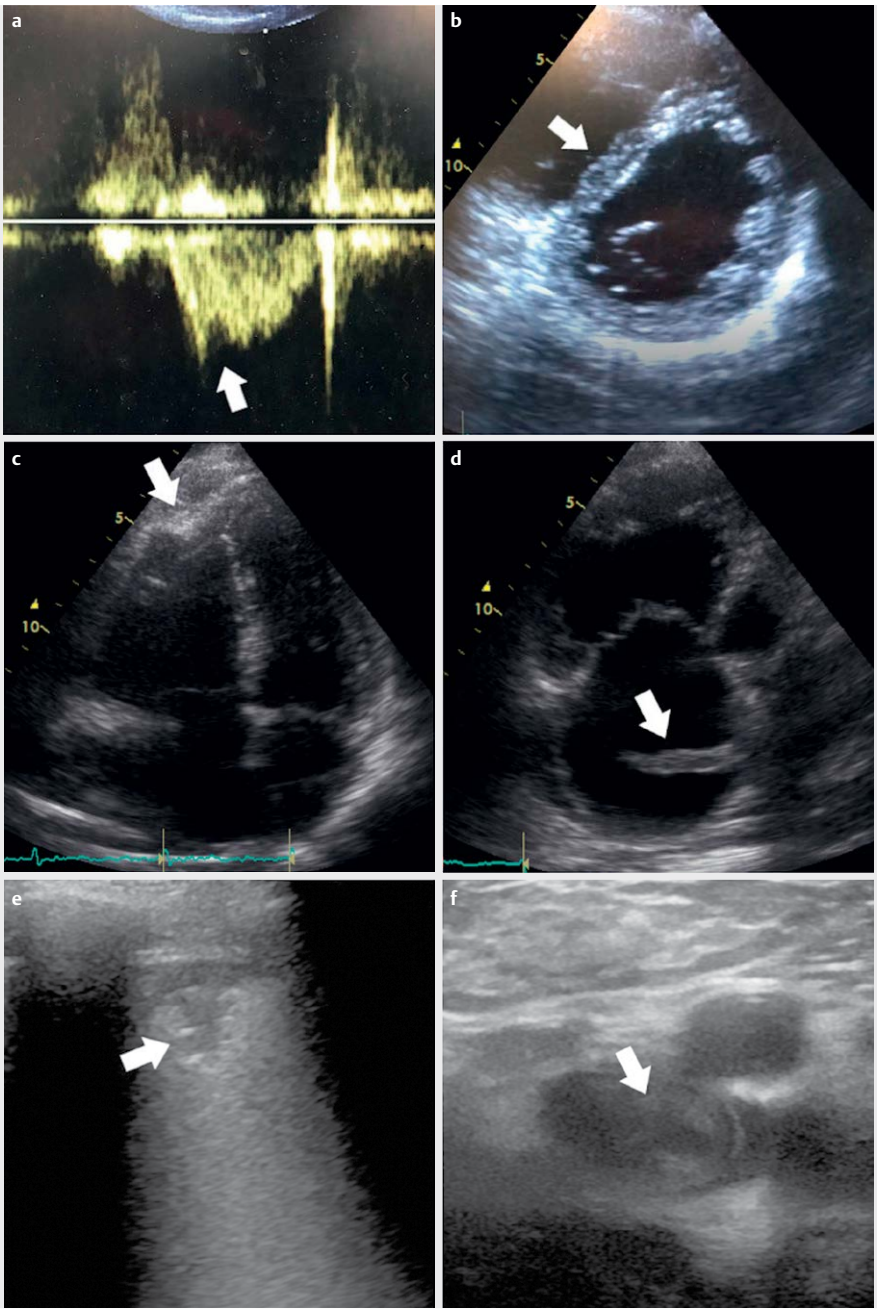
The study was a single-center prospective accuracy study, approved by the local scientific ethics committee. All aspects of this study have been conducted and reported in accordance with the Standard for Reporting of Diagnostic Accuracy (STARD) guidelines [16].

Patients were recruited during a period of 11 months in the emergency department (ED) of a university hospital with an annual census of 65,000 visits. The study cohort comprised adult patients in whom PE suspicion could not be dismissed based on initial clinical assessment and who were referred for diagnostic CTPA or V/Q scan. Study participants were enrolled as a convenience sample based on availability and accessibility. The initial diagnostic workup included the Wells score, electrocardiography, and blood sampling for highly sensitive D-dimer, in addition to a standard blood panel and arterial blood gas. Ultrasound was not part of the diagnostic algorithm prior to inclusion. Patients with mental disability, known contrast allergy, renal failure (s-creatinine > 200 µmol/L), or hemodynamic instability (two or more consecutive systolic blood pressure measurements < 90 mmHg) were not eligible for inclusion.

Multiorgan ultrasound

To validate the protocol as uniformly and systematically as possible, all multiorgan ultrasound investigations were performed within 24 hours of the final diagnostic test by the study's first author who was certified in deep venous and lung ultrasound in accordance with the National Society for Emergency Medicine guidelines and had completed more than 300 echocardiographic exams. If CTPA or V/Q had been conducted prior to inclusion, a colleague advised the patient before he or she was approached for inclusion and informed them not to disclose the result of the scan. A LOGIQ E9 (General Electric, Boston, Massachusetts, USA) was used for deep venous and lung ultrasound and a Vivid S5 (General Electric, Boston, Massachusetts, USA) for echocardiography. The first author was blinded to all clinical information and imaging other than visible signs. Ultrasound investigations were conducted in a standardized sequence: Echocardiography, lung, and deep venous.

Echocardiography was performed using a 1.5–4 MHz phased array probe with the patient in left lateral decubitus position with attached ECG leads. Parasternal, apical, and subxiphoid images were assessed for: The 60/60-sign (pulmonary valve acceleration time < 60ms in conjunction with a tricuspid valve regurgitation maximum flow rate < 60 mmHg), D-sign (abnormal septal flattening or bulging towards the left ventricle due to RV pressure overload), McConnell's sign (akinesia of the RV free wall with normal or hyperkinetic apical motion), intracardiac thrombi, basal RV end diastolic diameter (RVEDD)/left ventricular end diastolic diameter (LVEDD) ratio, left ventricular ejection fraction, valvular pathology, pericardial effusion and tricuspid annular plane systolic excursion (TAPSE) [4]. Lung ultrasound was performed with a 1–6 MHz curved array probe with the patient in the supine or sitting position. A focused protocol involving assessment of anterior, lateral, and posterior zones of each hemithorax was used. The protocol has been validated in several settings including for ED patients presenting with respiratory symptoms [17, 18]. The presence of well-demarcated pleural-based hypo-echoic lesions was noted in addition to lung sliding, pleural effusion, B-lines, and consolidations suggestive of pneumonia. Deep venous ultrasound was performed using a 4–15 MHz linear probe with the patient in the supine position. A protocol applied in several previous studies, comprising short-axis



▶ **Fig. 1** Examples of selected ultrasound used in the protocol for suspected pulmonary embolism. (**a**) Echocardiography showing early systolic notching (arrow) and a pulmonary valve acceleration time < 60ms demonstrated via pulsed wave doppler placed just distal to the pulmonary valve in the parasternal short axis view. (**b**) Echocardiography with a parasternal short axis view demonstrating the D-sign, comprising abnormal septal flattening or bulging towards the LV (arrow) due to RV pressure overload (**c**) Echocardiography with a modified apical four chamber view showing a basal RVEDD/LVEDD-ratio > 1 and the McConnell's sign, comprising distinctive akinesia of the RV free wall with normal or hyperkinetic apical motion (arrow). (**d**) Echocardiography with a modified apical four-chamber view showing a clearly dilated ventricle with a transit thrombus (arrow) lodged in a persisting oval foramen. (**e**) Lung ultrasound demonstrating a well-demarcated triangular hypoechoic consolidation (arrow). (**f**) Deep venous ultrasound showing a non-compressible hyperechoic formation in the femoral vein (arrow), compatible with a deep venous thrombus. All images are provided by study first author.

visualization and compression of the common and superficial femoral and popliteal veins, was utilized [13, 15, 19–24]. Absence of total vein compression or visible intravascular thrombi was considered diagnostic of a deep venous thrombus (DVT). Examples of selected ultrasound signs are available in ▶ **Fig. 1**.

The following multiorgan approach was formulated based on the recent meta-analysis:

1. *Clinical suspicion of PE confirmed in the case of ≥ 1 of the following ultrasound findings*
   1. Visible proximal deep venous thrombus

2. ≥ 2 hypoechoic pleural-based lesions with a diameter of ≥ 0.5 cm
3. Visible RV thrombus
4. 60/60-sign
5. McConnell's sign or D-sign present in both systole and diastole in the absence of known pulmonary hypertension (PH), interstitial lung disease (ILD), pulmonary valve stenosis, or COPD

2. *Further radiation-based diagnostic imaging required in the case of ≥ 1 of the following ultrasound findings:*
   1. 1 hypoechoic pleural-based lesion with a diameter of ≥ 0.5 cm
   2. Pleural effusion not explained by other cause
   3. Basal RVEDD/LVEDD > 1.0 or RV visibly larger than the LV
   4. TAPSE < 17 mm
   5. McConnell's or D-sign in the presence of known PH, ILD, pulmonary valve stenosis, or COPD

3. *Clinical suspicion of PE dismissed in the case of ≥ 1 of the following ultrasound findings:*
   1. No DVT, no pleural consolidation or effusion, no signs of RV strain or thrombus
   2. Obvious differential diagnosis demonstrated on ultrasound, i. e., pneumonia, pneumothorax, or newly discovered significant disease of the left ventricle

Reference standard and final diagnosis

CTPA and V/Q scan were used as reference standards. However, perfusion scintigraphy was considered sufficient for pregnant participants. All CTPAs were performed on a GE Revolution CT (GE Healthcare, Waukesha, Wisconsin, USA) and V/Q scans on a Discovery NM-CT 670 or Optima NM-CT 640 (General Electric, Boston, Massachusetts, USA). Interpreting radiologists and nuclear medicine physicians were blinded to ultrasound findings. In patients without PE, the final diagnosis was obtained through medical record audit at the end of the study period by two independent assessors. Any discrepancies were resolved by consensus discussion or final decision by the study's last author.

Statistical analysis

Statistical analyses were performed in GraphPad Prism 9.0.0. (GraphPad Software, San Diego, California USA). The diagnostic accuracy of ultrasound is presented as sensitivity, specificity, positive and negative predictive values (PPV and NPV) as well as accuracy. 95 % confidence intervals were calculated as Clopper-Pearson intervals for diagnostic accuracy and as Wilson score intervals for proportions. Normality was assessed using the Shapiro-Wilk test. Normally distributed data is presented as mean ± SD and compared with the Student's *t*-test. Non-normally distributed data is presented as median with interquartile range (Q1-Q3) and compared with a Mann-Whitney test. χ^2-test was used for comparing categorical data. A P-value < 0.05 was considered statistically significant.

Results

Patient population

During the study period, 86 patients were approached for inclusion. Ten did not wish to participate and one was excluded due to leaving the ED before CTPA was conducted. Thus, 75 patients were included for final analysis ▶ **Table. 1**. The median age was 65 years (Q1-Q3: 46–75) and 55 % were female. PE prevalence was 28 %. 50 patients were referred to CTPA with PE suspicion being confirmed in 15 (30 %), and 25 were referred to V/Q scan with PE being confirmed in 6 (24 %). The list of final diagnoses of all included patients was available in ▶ **Table. 2**. PE suspicion was confirmed in 6 (12.5 %) of 48 patients with a low probability Wells score of < 2. Of the 24 patients with an intermediate Wells score of 2–6, 14 (58 %) were diagnosed with PE, and of the three high-probability patients with a score > 6, one (33 %) had a PE ▶ **Fig. 2**.

Validation of protocol

Appropriate acoustic windows were achieved in all 75 patients. Ten patients had a multiorgan ultrasound compatible with the presence of PE, which was confirmed by CTPA or V/Q in all instances. PE was present in 1 (2.3 %) of 43 patients in whom PE suspicion was dismissed, and in 10 (45.5 %) of the 22 patients requiring further diagnostic imaging ▶ **Fig. 3**. Thus, 53 patients (76 %) were categorized as either PE confirmed or dismissed following PoCUS investigation. Of these, 52 (98 %, 95 %CI 90.1–99.7 %) were correctly allocated, while one patient with a Wells score of 6 and D-dimer of 5.1 mg/L (2 %, 95 %CI: 0.3–10.0 %) was falsely considered negative as the CTPA revealed multiple segmental emboli. As such, in 52 (70 %, 95 %CI: 63.0–83.1 %) of included patients, CTPA or V/Q could have been safely omitted.

Single-organ ultrasound findings

Echocardiography

PE was confirmed in all nine patients with echocardiographic findings compatible with PE diagnosis. Namely, the 60/60-sign observed in five patients, visible RV thrombus found in two patients, as well as the D-sign and McConnell's sign in the absence of PH, pulmonary valve stenosis, COPD, or ILD demonstrated in seven and five patients, respectively, all yielded a PPV of 100 %. TAPSE < 17 mm and dilated RV were less specific for PE, both yielding PPVs below 80 %.

Lung ultrasound

At least one hypoechoic pleural-based lesion was observed in 16 patients, with PE being diagnosed in 13. One patient had two pleural-based lesions and present PE, yielding a specificity of 100 % but low sensitivity of 4.8 % (95 %CI: 0.1–23.8). Pleural effusions, which may be observed in pleural infarctions, were seen in approximately half of patients with PE, resulting in a sensitivity of 52.4 % (95 %CI: 29.8–74.3). Four patients exhibited interstitial syndrome, compatible with an obvious differential diagnosis. Of these, none had PE.

Deep venous ultrasound

PE was present in all six patients with deep venous ultrasound compatible with the presence of DVT. Diagnostic characteristics of single- and multiorgan ultrasound signs when compared to CTPA or

▶ **Table 1** Characteristics of enrolled patients stratified by the presence of pulmonary embolism. Data are presented as n (%), mean ± SD, or median with associated interquartile range.

	All patients (n = 75)	Pulmonary embolism (n = 21)	No pulmonary embolism (n = 54)	p-value
Age (years)	65 (Q1-Q3: 46–75)	62 ± 15.0	65.5 (Q1-Q3: 43–77)	0.795
Female sex	41 (54.7)	10 (47.6)	31 (57.4)	0.585
Body mass index (kg/m²)	26.8 (Q1-Q3: 23.6–31.2)	26.4 (Q1-Q3: 24.1–31.4)	27.3 ± 5.1	0.992
Symptoms at presentation				
Dyspnea	66 (88.0)	18 (85.7)	48 (88.9)	0.704
Chest pain	30 (40.0)	7 (33.3)	23 (42.6)	0.462
Cough	16 (21.3)	6 (28.6)	10 (18.5)	0.340
Dizziness	7 (9.3)	3 (14.3)	4 (7.4)	0.358
Hemoptysis	6 (8.0)	3 (14.3)	3 (5.5)	0.211
Syncope	3 (4.0)	1 (4.8)	2 (3.7)	0.834
Calf pain	3 (4.0)	1 (4.8)	2 (3.7)	0.834
Vital signs				
Pulse (beats/min)	85 (Q1-Q3: 68.5–95.0)	82.9 ± 17.2	84.4 ± 18.9	0.748
Systolic blood pressure (mmHg)	140.1 ± 18.9	140.3 ± 21.1	140.0 ± 18.2	0.932
Diastolic blood pressure (mmHg)	84.6 ± 14.7	84.1 ± 16.6	84.8 ± 14.0	0.854
Oxygen saturation (%)	97.0 (Q1-Q3: 95.5–99.0)	96.3 ± 2.6	98.0 (Q1-Q3: 95.0–99.0)	0.285
Supplementary oxygen (n)	3 (4)	2 (9.5)	1 (1.9)	0.386
Supplementary oxygen (L/min)	4 (Q1-Q3: 2.5–8.0)	6 (Q1-Q3: 4.0–8.0)	2.5	–
Respiratory rate	16.0 (Q1-Q3: 16.0–20.0)	17.0 (Q1-Q3: 16.0–20.0)	16.0 (Q1-Q3: 16.0–20.0)	0.912
Temperature (C°)	36.8 (Q1-Q3: 36.5–37.2)	36.9 ± 0.6	36.8 (36.4–37.2)	0.984
Lab results and Wells score				
D-dimer (mg/L)	1.4 (Q1-Q3: 0.8–3–7)	6.5 (Q1-Q3: 2.0–8.9)	1.1 (Q1-Q3: 0.5–1.9)	< 0.001
Troponin T (ng/L)	11.0 (Q1-Q3: 5.0–19.5)	11.0 (Q1-Q3: 6.0–23.0)	10.5 (Q1-Q3: 5.0–18.0)	0.246
Wells score for pulmonary embolism	1.5 (Q1-Q3: 0.0–3.0)	3.5 ± 2.0	0.0 (Q1-Q3: 0.0–1.5)	< 0.001
Comorbidities				
Hypertension	25	8	17	0.298
No known	19	5	14	0.850
COPD	8	2	6	0.842
Asthma	6	1	5	0.519
Stroke	5	2	3	0.536
Type II diabetes	4	1	3	0.891
Previous cancer	3	1	2	0.834
Supraventricular tachycardia	3	0	3	–
Valvular disease	3	1	2	0.834
Ischemic heart disease	3	1	2	0.834
Obstructive sleep apnea	2	1	1	0.482

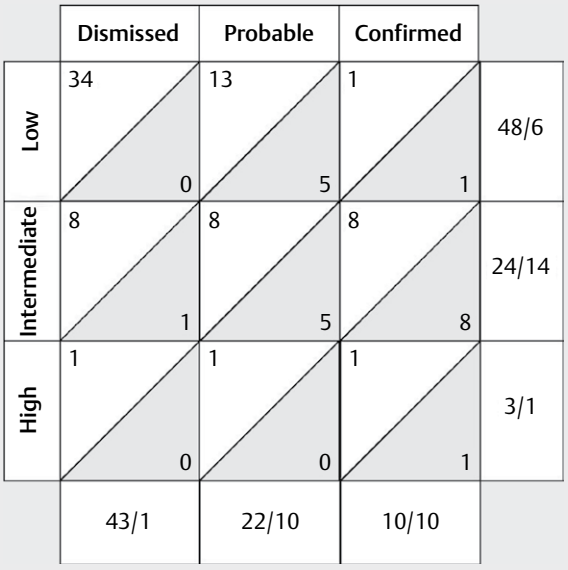
V/Q are presented in ▶ **Table. 3** and corresponding 2 × 2 tables are available in ▶ **Table. 4**.

Discussion

The findings of this study support that a multiorgan ultrasound approach, based on meta-analytic data, may be helpful in confirming and dismissing PE suspicion. Our results suggest that integration of this approach may reduce the need for CTPA or V/Q, while maintaining safety standards if pre-test probability is taken into consideration. This is particularly relevant in light of the rise in the availability of noninvasive radiation diagnostics, leading clinicians to suspect PE and initiate diagnostic workup more frequently than in the past. This is exemplified by the modest contemporary prevalence of PE in patients referred to CTPA of 20–30 % in Europe and 5–10 % in the United States, compared to approximately 50 % in the 1980s [7, 8]. In this study, PE prevalence was 28 %, suggesting a representative study population. Only three previous studies have

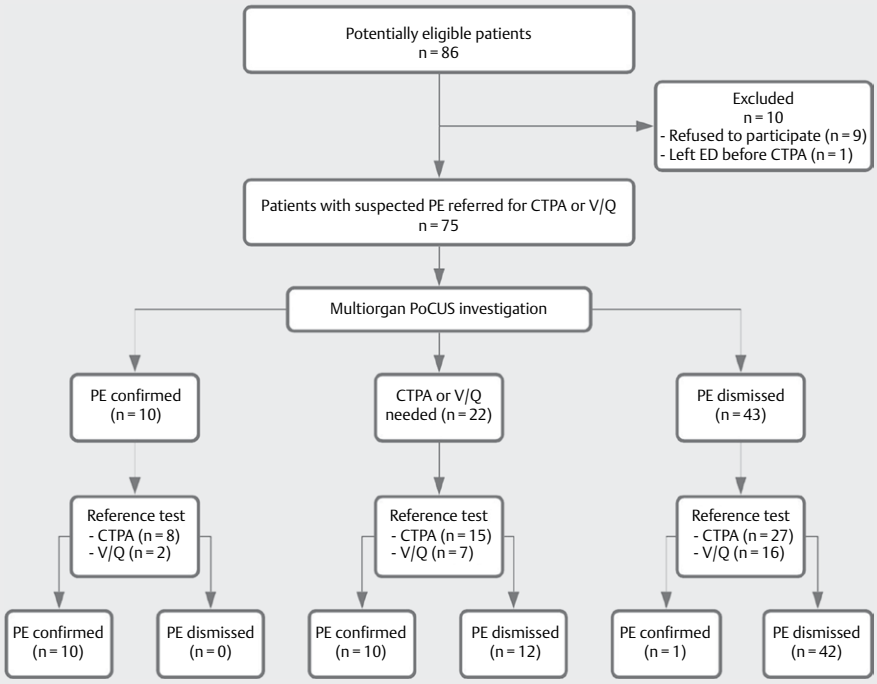
▶ **Table 2** Final diagnoses of included patients.

Final diagnosis	n
Pulmonary embolism	21
Psychogenic hyperventilation	4
Pneumonia	4
Infection	3
COPD with exacerbation	3
Muscular chest pain	3
Asthma with exacerbation	2
Sarcoidosis	2
Acute myocardial infarction	2
Pericardial effusion	1
Decompensated heart failure	1
Pregnancy related symptoms	1
Intrathoracic struma	1
Chronic pleural effusion	1
COVID sequelae	1
No acute pathology	25



▶ **Fig. 2** 3 × 3 table showing relationship between Wells' scores of low (< 2), intermediate (2–6) and high (> 6) probability, results of ultrasound investigation and number of confirmed pulmonary embolisms. Numbers in white triangles represent number of patients with a given combination of pre-test probability and ultrasound results. The number in the gray triangles represent number of patients diagnosed with pulmonary embolism.

reported on protocols utilizing a combined assessment of the heart, lungs, and deep veins of the lower extremities in suspected PE [13–15]. In 2014, Nazerian et. al. found a sensitivity of 90 % with a corresponding NPV of 95 % when employing a protocol dismissing PE suspicion in the absence of DVT, pleural-based lesions, RV dilation, or thrombus in 357 patients with an elevated D-dimer or Wells score > 4. Sensitivity increased to 100 % when an alternative diagnosis was present, suggesting a reduction of approximately 50 % in the need for CTPA [15]. Koenig and colleagues further explored multiorgan ultrasound in 2014, examining 96 patients referred for CTPA regardless of pre-test probability. In 55 % of cases, CTPA could be safely avoided since an alternative diagnosis or a DVT was detected [14]. Most recently, in 2017, Aktürk and colleagues applied a protocol identical to that of Nazerian in 92 patients with a moderate to high pre-test probability. They reported an almost identical sensitivity of 89.8 % but an NPV of only 79.2 %, since 66 % of the included patients were diagnosed with PE, in contrast to 31 % in the study by Nazerian et. al. In our study, absence of DVT, hypoechoic pleural-based lesions, pleural effusion and RV strain or thrombi yielded a sensitivity of 95.2 %. Also in line with previous findings, evidence of an alternative diagnosis was associated with a sensitivity of 100 %. As PE prevalence varies from 10 % in low-probability populations to 65 % in those with high probability, the variance in NPV highlights the importance of integrating the risk of the presence of PE when interpreting ultrasound findings [22]. In our study, no low-probability patients with a normal ultrasound examination had PE but one out of eight with intermediate probability did. As such, our study stresses that physicians utilizing multiorgan PoCUS for dismissing PE suspicion should not rely solely on ultrasound findings but should incorporate consideration of pre-test probability before ruling out PE. If this approach were applied to our ultrasound protocol, the false-negative patient with intermediate probability would be referred to further diagnostic imaging, as no other explanation for his dyspnea, Wells score of 6, and D-dimer of 5.1 mg/L could be determined. When considering the ability of our selected single-organ ultrasound signs to confirm PE suspicion, our findings support the results of a recent meta-analysis [9]. The presence of a DVT, at least two hypoechoic pleural lesions, D-sign, 60/60-sign, and a visible RV thrombus all had a specificity of 100 %, which also applied to the McConnell's sign in the absence of COPD, ILD, known PH, or pulmonary valve stenosis. We decided to incorporate these conditions for the D-sign and McConnell's sign, since, even though the McConnell's sign in particular is considered highly specific for PE, its presence has been described in other pathologies [23], as was also the case in our study where it was found in a case of COPD exacerbation. PE research often excludes patients with known illnesses which might affect findings during heart ultrasound. Our decision not to exclude these patients but rather incorporate possible consequences increases the generalizability [9]. The several ultrasound signs with high specificity raise the possibility that some PEs may be confirmed without further diagnostic workup. For this application, special precaution should be taken when interpreting cardiac ultrasound signs. While acknowledging a dilated RV is within the grasp of most physicians trained in cardiac ultrasound, detection of D-sign or McConnell's sign requires attention to the movement of distinct segments of the myocardium. However, a 2017 meta-analysis by Fields and colleagues has shown encouraging results in this regard by demonstrating diagnostic accuracies of D-sign and McConnell's sign on par with the collective literature when performed in an emergency setting [24]. We do believe, however, that



▶ **Fig. 3** Flow of participants through the study.

▶ **Table 3** Diagnostic accuracy of all ultrasound signs utilized in the protocol. *Regardless of presence of COPD, ILD, known PH, or pulmonary valve stenosis # Not considered diagnostic in the presence of COPD, ILS, known PH, or pulmonary valve stenosis.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Cardiac ultrasound					
D-sign	23.8 (8.2–47.2)	100 (93.4–100)	100 (100–100)	77.1 (72.7–81.1)	78.7 (67.7–87.3)
Right ventricular dilation (Basal RVEDD/LVEDD > 1.0 or RV > LV visibly)	38.1 (18.1–61.6)	94.4 (84.6–98.8)	72.7 (43.9–90.1)	79.7 (73.6–84.7)	78.7 (67.7–87.3)
McConnell's sign*	28.6 (11.3–52.2)	98.2 (90.1–100)	85.7 (43.4–97.9)	77.9 (72.9–82.3)	78.7 (67.7–87.3)
McConnell's sign#	28.6 (11.3–52.2)	100 (93.4–100)	100 (100–100)	78.3 (73.3–82.5)	80.0 (69.2–88.4)
TAPSE < 17 mm	9.5 (1.2–30.4)	96.3 (87.3–99.6)	50.0 (13.1–86.9)	73.2 (70.2–76.0)	72.0 (60.4–81.8)
60/60-sign	23.8 (8.2–47.2)	100 (93.4–100)	100 (100–100)	77.1 (72.7–81.1)	78.7 (67.7–87.3)
Visible right ventricular thrombus	9.5 (1.2–30.1)	100 (93.4–100)	100 (100–100)	74.0 (71.2–76.6)	74.7 (63.3–84.0)
Lung ultrasound					
≥ 1 hypoechoic pleural-based lesion with a diameter of ≥ 0.5 cm	61.9 (38.4–81.9)	94.4 (84.6–98.8)	81.2 (57.9–93.2)	86.44 (78.6–91.7)	85.3 (75.3–92.4)
≥ 2 hypoechoic pleural-based lesions with a diameter of ≥ 0.5 cm	4.8 (0.1–23.8)	100 (93.4–100)	100 (100–100)	73.0 (71.1–74.8)	73.3 (61.9–82.9)
Any unexplained pleural effusion	52.4 (29.8–74.3)	83.3 (70.1–92.1)	55.0 (37.2–71.6)	81.8 (73.9–87.7)	74.7 (63.3–84.0)
Deep venous ultrasound					
Bilateral compression of femoral and popliteal veins for DVT	28.6 (11.3–52.2)	100 (93.4–100)	100 (100–100)	78.3 (82.5)	80.0 (69.2–88.4)
Multiorgan ultrasound					
No deep venous thrombus, no hypoechoic pleural-based lesion or effusion, no signs of RV strain or thrombus	95.2 (76.2–99.9)	77.8 (64.4–88.0)	62.5 (50.1–73.5)	97.7 (86.1–99.7)	82.7 (72.2–90.4)
Obvious differential diagnosis based on ultrasound findings	100 (83.89–100)	7.41 (2.1–17.9)	29.6 (28.0–31.2)	100 (100–100)	33.3 (22.9–45.2)

▶ **Table 4** 2 × 2 tables of ultrasound findings TP = True positive, FP = False positive, FN = False negative, TN = True negative *Regardless of presence of COPD, ILS, known PH, or pulmonary valve stenosis # Not considered diagnostic in the presence of COPD, ILS, known PH, or pulmonary valve stenosis.

	TP	FP	FN	TN
Deep venous ultrasound				
Bilateral compression of femoral and popliteal veins for DVT	6	0	15	54
Lung ultrasound				
≥ 1 hypoechoic pleural-based lesion	13	3	8	51
≥ 2 hypoechoic pleural-based lesion	1	0	20	54
Any unexplained pleural effusion	11	9	10	45
Cardiac ultrasound				
D-sign	5	0	16	54
Right ventricular dilation	8	3	13	51
McConnell's sign*	6	1	15	53
McConnell's sign#	6	0	15	54
TAPSE < 17 mm	2	2	19	52
60/60-sign	5	0	16	54
Visible right ventricular thrombus	2	0	19	54
Multiorgan ultrasound				
No deep venous thrombus, no hypoechoic pleural-based lesion or effusion, no signs of RV strain or thrombus	20	12	1	42
Obvious differential diagnosis	21	50	0	4

the 60/60-sign, which requires experience with complicated Doppler measurements, should only be interpreted by or with the aid of a cardiologist. While several ultrasound signs show promise in confirming PE, patients at intermediate or high risk, who require hospital admission, should still receive final confirmation via CTPA or V/Q. It may be safe to discharge low risk patients with oral anticoagulative treatment and refer them to follow-up without further immediate diagnostic workup. As such, the aforementioned signs of cardiac strain may rarely allow omission of CTPA or V/Q as they are often associated with elevated troponin levels, resulting in an intermediate-high 30-day mortality risk, requiring admission for telemetric surveillance.

While the findings of this study are encouraging, some limitations should be considered. This study was designed to minimize the risk of bias in accordance with the STARD guideline [25] and Quality Assessment of Diagnostic Accuracy Studies-2 protocol (QUADAS-2) [26]. As such, radiologists and nuclear medicine physicians were blinded to interpretation of the ultrasound investigation when interpreting the reference test and vice versa. Also, the time interval between ultrasound examination and CTPA or V/Q was always less than 24 hours. While only employing a single reference standard would have reduced the risk of bias, both CTPA and V/Q were utilized due to a strong collaboration between the departments of emergency and nuclear medicine at our hospital where V/Q is often utilized in the case of suspicion of peripheral embolization. Especially the use of V/Q may have introduced bias as studies have suggested that the PPV of a high-probability V/Q is not sufficient to confirm PE in patients with low clinical probability [4]. Furthermore, while all V/Qs in our study yielded definite results, the clinical utility of V/Q is generally limited by a high number of inconclusive results. While convenience sampling is common in diagnostic accuracy research, the approach carries an inherent risk of selection bias, as it provides no guarantee that the recruited patients are truly representative of the ED cohort. Although most hemodynamically stable patients with PE are referred by their general practitioner during the daytime, caution should be taken when extrapolating these findings to a general emergency population. Furthermore, while the clinical characteristics of included patients with or without PE were mostly similar, they differed significantly in both Wells score and D-dimer. This implies that a proportion of the patients should not have been referred to CTPA or V/Q, and emphasizes that, in the real-life emergency setting, referral to radiation diagnostics is not always strictly based on guidelines. All ultrasound investigations were performed by the study's first author who was at an intermediate level in all ultrasound modalities. While using only one investigator reduces the external validity, using a sonographer with an intermediate skill level mirrors the average emergency physician more than an expert. Furthermore, as the aim of this study was to validate a bespoke ultrasound protocol, it was prioritized to conduct the protocol as uniformly as possible. Lastly, only 75 patients were included in this study, significantly less than the 357 in Nazerian et. al. and 92 and 96 patients in the studies by Aktürk and Koenig, respectively. As such, while our findings on diagnostic accuracy are generally on par with previous publications, the considerable uncertainty, as reflected by the broad confidence intervals due to the low number of included patients, is a strong limitation and should be considered when interpreting the results. However, this number was chosen for preliminary validation of a planned randomized controlled trial, randomizing 150 patients with suspected PE in a 1:1-ratio to either CTPA or V/Q as the control group or investigation with our PoCUS protocol. In conclusion, the findings of this prospective validation study support high diagnostic accuracy of a multiorgan ultrasound assessment in suspected PE based on meta-analytic data, and the results on diagnostic accuracy of each separate included ultrasound sign reinforce the evidence already provided in the literature. Implementation of this approach may safely reduce the need for CTPA or V/Q by confirming or dismissing the suspicion in selected patients.

Funding Information

Syddansk Universitet — http://dx.doi.org/10.13039/501100006356; Master Carpenter Jacobsen foundation — Odense Universitetshospital — http://dx.doi.org/10.13039/501100004196;

Conflict of Interest

Prof Jacob E Møller has received grants and personal fees from Abiomed, personal fees from Novartis, personal fees from Orion Pharma, and personal fees from Boeinger Ingelheim outside the submitted work. All remaining authors declare no competing interests.

References

[1] Laack TA, Goyal DG. Pulmonary embolism: an unsuspected killer. Emerg Med Clin North Am 2004; 22: 961–983

[2] Stein PD, Beemath A, Matta F et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med 2007; 120: 871–879

[3] Huisman MV. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006; 295: 172–179

[4] Konstantinides SV, Meyer G, Galié N et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020; 41: 543–603. doi: 10.1093/eurheartj/ehz405

[5] Raja AS, Greenberg JO, Qaseem A et al. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015; 163: 701

[6] Mathews JD, Forsythe AV, Brady Z et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 2013; 346: f2360–f2360

[7] Righini M, Robert-Ebadi H, Le Gal G. Diagnosis of acute pulmonary embolism. J Thromb Haemost 2017; 15: 1251–1261

[8] Le Gal G, Bounameaux H. Diagnosing pulmonary embolism: running after the decreasing prevalence of cases among suspected patients. J Thromb Haemost 2004; 2: 1244–1246

[9] Falster C, Jacobsen N, Coman KE et al. Diagnostic accuracy of focused deep venous, lung, cardiac and multiorgan ultrasound in suspected pulmonary embolism: a systematic review and meta-analysis. Thorax 2022; 77: 679–689. doi: 10.1136/thoraxjnl-2021-216838

[10] Moore CL, Copel JA. Point-of-Care Ultrasonography. N Engl J Med 2011; 364: 749–757

[11] Jiménez D, Aujesky D, Díaz G et al. Prognostic Significance of Deep Vein Thrombosis in Patients Presenting with Acute Symptomatic Pulmonary Embolism. American Thoracic Society 2012; 181: 983–991. doi:10.1164/rccm.200908-1204OC

[12] Laursen CB, Rahman NM, Volpicelli G. Thoracic Ultrasound. In: Thoracic Ultrasound. European Respiratory Society. 2018

[13] Aktürk UA, Koçak ND, Ernam D. The role of multi-organ ultrasonography for diagnosing non-massive pulmonary thromboembolism. Biomed Res 2017: 28: 8044–8049

[14] Koenig S, Chandra S, Alaverdian A et al. Ultrasound assessment of pulmonary embolism in patients receiving CT pulmonary angiography. Chest 2014: 145: 818–823

[15] Nazerian P, Vanni S, Volpicelli G et al. Accuracy of Point-of-Care Multiorgan Ultrasonography for the Diagnosis of Pulmonary Embolism. Chest 2014; 145: 950–957

[16] Cohen JF, Korevaar DA, Altman DG et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 2016; 6: e012799

[17] Laursen CB, Sloth E, Lassen AT et al. Point-of-care ultrasonography in patients admitted with respiratory symptoms: A single-blind, randomised controlled trial. Lancet Respir Med 2014; 2: 638–646

[18] Riishede M, Laursen CB, Teglbjærg LS et al. Diagnostic value of whole-body-focused ultrasonography in high-acuity patients in the emergency department: a prospective single-center cross-sectional study. Ultrasound J 2019; 11: 11. doi: 10.1186/s13089-019-0126-7

[19] Nazerian P, Volpicelli G, Gigli C et al. Diagnostic accuracy of focused cardiac and venous ultrasound examinations in patients with shock and suspected pulmonary embolism. Intern Emerg Med Italy 2018; 13: 567–574

[20] Nazerian P, Volpicelli G, Gigli C et al. Diagnostic Performance of Wells Score Combined With Point-of-care Lung and Venous Ultrasound in Suspected Pulmonary Embolism. Acad Emerg Med 2017: 24: 270–280

Dwyer KH, Rempell JS, Stone MB. Diagnosing centrally located pulmonary embolisms in the emergency department using point-of-care ultrasound. Am J Emerg Med 2018: 36: 1145–1150

[21] Ceriani E, Combescure C, Le Gal G et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost 2010; 8: 957–970

Walsh BM, Moore CL. McConnell's Sign Is Not Specific for Pulmonary Embolism: Case Report and Review of the Literature. J Emerg Med 2015; 49: 301–304

[22] Fields JM, Davis J, Girson L et al. Transthoracic Echocardiography for Diagnosing Pulmonary Embolism: A Systematic Review and Meta-Analysis. J Am Soc Echocardiogr 2017; 30: 714–723.e4. doi: 10.1016/j.echo.2017.03.004

[23] Bossuyt PM, Reitsma JB, Bruns DE et al. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015; 351: h5527. doi: 10.1136/bmj.h5527

[24] Whiting PF, Rutjes AWS, Westwood ME et al. Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529–536. doi: 10.7326/0003-4819-155-8-201110180-00009