Utility of ultrasound in the diagnostic work-up of suspected pulmonary embolism: an open-label multicentre randomized controlled trial (the PRIME study)

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Summary

Background Prevalence of pulmonary embolism (PE) in patients referred to diagnostic imaging is decreasing, indicating a need for improving patient selection. The aim of this study was to assess reduction in referral to diagnostic imaging by integrating a bespoke ultrasound protocol and describe associated failure rate and adverse events in patients with suspected PE.

Methods In a randomized open-label multicentre trial spanning June 18, 2021, through Feb 1, 2023, adult patients with suspected PE and 1) a Wells score of 0–6 and elevated age-adjusted D-dimer or 2) Wells score >6 were randomly assigned 1:1 to direct diagnostic imaging (controls) or focused lung, cardiac, and deep venous ultrasound by unblinded investigators. Ultrasound could: 1) dismiss PE if no signs of PE and low clinical suspicion or an alternate diagnosis, 2) confirm PE in case of visible venous thrombus, ≥2 subpleural infarctions, McConnell's, or D-sign, or 3) refer to diagnostic imaging if neither category was fulfilled or a patient with confirmed PE by ultrasound required admission. Primary endpoint was proportion of patients referred to diagnostic imaging. Outcome assessors were not blinded to group assignment. All included participants were included in safety analyses. The trial was registered at clinicaltrials.gov (NCT04882579).

Findings A total of 150 patients were recruited, of whom 73 were randomized to ultrasound. Among 77 controls referred to diagnostic imaging, 26 patients had PE confirmed. In the ultrasound group, 40 patients were referred to diagnostic imaging of whom 20 had PE, reducing referral for diagnostic imaging by 45.2% (95% CI: 34.3–56.6, $p < 0.0001$). Three further PEs were diagnosed by presence of a DVT. During 3-month follow-up, the number of patients who did not receive anticoagulation but was diagnosed with PE was two (4%; 95% CI: 1.1–13.5) and none (0%; 95% CI: 0.0–7.0) in the ultrasound and control group, respectively.

Interpretation Ultrasound substantially reduced referral to diagnostic imaging in suspected PE. Albeit with an unacceptable failure rate.

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Research in context

Evidence before this study

Recent years have brought several attempts at improving selection of patients with suspected pulmonary embolism for diagnostic imaging. Notable examples are the ADJUST-PE and PEGeD studies which showed that adjustable D-dimer cut-off levels based on age or pre-test probability reduce referral to diagnostic imaging while maintaining acceptable failure rates. To assess the utility of ultrasound in this regard, we searched MEDLINE, Embase, CINAHL, and Cochrane library for papers published from the inception to 02/07/2020 using variations of the terms: ultrasound AND pulmonary embolism AND diagnosis with no restrictions on language (Falster 2021, Thorax). We identified 70 descriptive studies reporting on diagnostic accuracies of several ultrasound signs to assess presence of pulmonary embolism. Some ultrasound signs were characterized by specificities >95% suggesting use in confirming the diagnosis, notable examples include the McConnell's sign, D-sign and presence of a deep venous thrombus. Further, a combination of lung, cardiac, and venous ultrasound devoid of any signs of subpleural infarctions, right ventricular strain, or deep venous thrombi had a sensitivity and specificity of approximately 90% and 85%, respectively, yielding a high negative predictive value in the context of a low pre-test probability. It was however still unclear if actual clinical utility could achieved under real clinical conditions, where physicians must rely on their ultrasound findings for clinical decision making rather than just describing them. Studies assessing real life efficacy and failure rate are an important prerequisite to actual implementation of ultrasound guided decision making in suspected pulmonary embolism.

Added value of this study

This study is the first randomized controlled trial examining efficacy of a bespoke multiorgan ultrasound investigation in patients with suspected pulmonary embolism. We show that our approach significantly reduces referral to diagnostic imaging under real life clinical conditions. However, while not powered to address this question with statistical significance, the failure rate, defined as proportion of participants who did not initially receive anticoagulation and were later objectively diagnosed with pulmonary embolism during the 3-month follow-up period, exceeded the acceptable threshold.

Implications of all the available evidence

While our study confirms that ultrasound substantially reduces referral to diagnostic imaging in suspected pulmonary embolism, we cannot recommend routine application of ultrasound for dismissing suspicion until further studies powered to assess failure rate of the approach is below an acceptable threshold. Conversely, our study further supports that some ultrasound signs are highly predictive of pulmonary embolism and may allow initiation of anticoagulation or even diagnose pulmonary embolism if diagnostic imaging is not feasible.

Introduction

Pulmonary embolism constitutes blockage of one or several branches of the pulmonary arterial vessels by an element originating elsewhere in the vasculature, most often a deep venous thrombus.[1] The condition is common and accounts for a substantial number of deaths from cardiovascular disease, surpassed only by heart attack and stroke.[2]

As the clinical presentation of pulmonary embolism is often unspecific, contemporary clinical guidelines recommend that in patients whose symptoms cannot be attributed to another cause, stratification into groups of expected prevalence should be conducted using clinical decision rules, such as the Wells or Revised Geneva score.[3] In instances of low or intermediate probability, a subsequent D-dimer measurement within normal reference range allows dismissal of pulmonary embolism suspicion. However, while most current assays have sensitivities of approximately 95%, interpretation of D-dimer is limited by low specificity.[4,5] In patients at or below 40 years of age, specificity is ≈60%, but in patients at or above 80 years of age or in the presence of comorbidities such as cancer, infection, or inflammatory disease, specificity decreases to ≈10%, resulting in a significant proportion of false positive results.[4,5] Consequently, only around 20% of patients referred to diagnostic imaging are diagnosed with pulmonary embolism in recent European studies.[6] Meta-analytic data suggests that ultrasound of the heart, lungs, and lower extremity veins may improve selection of patients for diagnostic imaging.[7] Cardiac ultrasound by demonstrating right ventricular strain, lung ultrasound by showing subpleural infarctions, and venous ultrasound may detect residual source thrombotic material. While a subset of single organ ultrasonographic findings are characterized by high specificity, overall sensitivity is

low. However, by applying a multiorgan approach in which multiple organs are assessed for signs of pulmonary embolism, meta-analytic data suggests that sensitivity increases notably, yielding a high negative predictive value in the presence of sufficiently low pre-test probability.[7] Indeed, descriptive studies integrating a multiorgan approach into clinical evaluation estimate a reduction in referral to CT pulmonary angiography of approximately 50% while maintaining acceptable safety standards.[8–10] The objective of the PRIME study was to evaluate whether the integrated use of a bespoke ultrasound protocol combining the most sensitive and specific ultrasound signs reduces referral of patients with suspected pulmonary embolism to diagnostic imaging in a real life setting and describe associated failure rate, defined as the proportion of missed pulmonary emboli diagnosed within three months following study enrolment, and adverse events.

Methods

Study design and participants

PRIME is an open-label multicentre randomized controlled trial, conducted at six Danish hospitals: One tertiary hospital with an annual emergency department census of 65,000 visits and five secondary hospitals with annual censuses between 33,000 and 55,000. The trial began recruitment on June 18, 2021, and reached its intended number of inclusions on the February 1, 2023. The study protocol (available in the Appendix) was approved by the institutional review board at all participating sites and the regional scientific ethics committee (registration number: S-20210027). A study timeline and a complete list of participating sites with associated period of patient inclusion as well as number of study investigators and their ultrasound experience is available in the Appendix. The trial population consisted of patients 18 years of age or older admitted to an emergency department in whom suspicion of pulmonary embolism could not be ruled out based on clinical assessment and who simultaneously fulfilled criteria for referral to diagnostic imaging (Wells score 0–6 and an elevated age-adjusted D-dimer or Wells score >6). Patients were not eligible for inclusion if they were pregnant, hemodynamically unstable (systolic blood pressure <90 mmHg for at least two consecutive measurements), had been subject to ultrasound prior to enrolment, diagnosed with a pulmonary embolism within six months, or had permanent mental disability. Participants were included by the study investigators and could comprise both patients of whom an investigator was the main physician involved in the diagnostic work-up or patients being assessed by another physician who contacted a present study investigator. Sex data was registered based on the unique personal identification number assigned to all Danish citizens. Written informed consent was obtained from all study participants.

Randomisation and masking

After accepting enrolment in the study, participants were randomized in a 1:1 ratio to receive a multiorgan ultrasound investigation (intervention) or referral to CT pulmonary angiography or lung scintigraphy (control). Randomization was performed using a web-based system utilizing permuted blocks of random numbers, ensuring that all participating centres allocated an equal number of patients in each study arm. The allocation sequence was generated by an affiliated biostatistician who was not otherwise involved in the trial. Upon completion of randomization, both the investigator and participating patient were aware about group allocation. Outcome assessors and those analysing the data were also not blinded to the result of randomization.

Procedures

Patients randomized to the control group underwent CT pulmonary angiography or lung scintigraphy in accordance with national and local department guidelines.[11] Those randomized to the ultrasound group were subject to multiorgan ultrasound examination of the heart, lungs, and lower extremity veins performed by an investigator certified in all three modalities in accordance with recommendations of the Danish society for emergency medicine[12] (Fig. 1). The examination was conducted in the following sequence.

1. Focused cardiac ultrasound

With the patient in the left lateral decubitus or supine position, a phased array probe was used for visualization of the parasternal long and short axis as well as the apical four chamber and subxiphoid view. The investigators emphasized detection of right ventricular strain (right ventricular dilation, D-sign (septal flattening or bulging towards the left ventricle), McConnell's sign (akinesia of the free right ventricular wall with a concomitant normokinetic or hyperkinetic right ventricular apex), tricuspid annular plane systolic excursion <17 mm, and visible thrombi) but also screened for reduced left ventricular systolic function, chamber enlargement, pericardial effusion, and valve pathology, as recommended by the European Society of Cardiology.[13]

2. Focused lung ultrasound

With the patient in a supine position for the anterior and lateral zones and sitting for the posterior zones, a convex or linear probe was utilized for visualization of the pleural line in 14 predefined zones; an approach described in the 2018 European Respiratory Society monograph on thoracic ultrasound which has been validated for assessing patients with respiratory failure in an emergency department setting.[14–16] In all zones, the investigator emphasized detection of subpleural

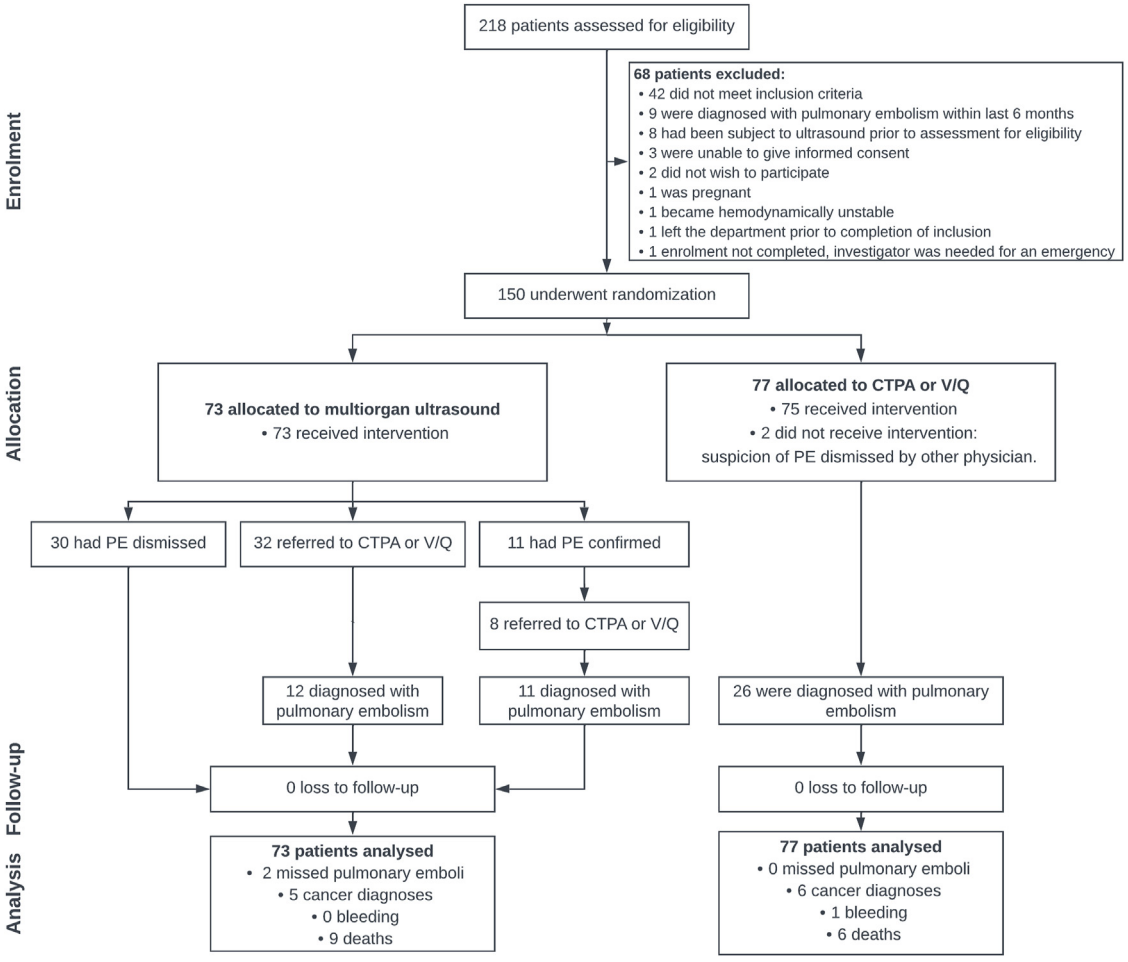

Fig. 1: Patient flow through the study.

lung consolidations representative of subpleural infarctions, but also assessed the presence or absence of lung sliding, B-lines, and pleural effusion. If the patient reported any chest pain, ultrasound was also performed at this location.

3. Lower extremity venous ultrasound

With the patient in a supine position, a linear probe was utilized for bilateral compression of the femoral and popliteal veins. If the linear probe was unable to adequately demonstrate a profoundly situated femoral vein, the curved probe could be used at the investigator's discretion. Starting at the inguinal region, the common femoral artery and vein were visualized in the short axis as landmarks. Subsequently, the probe was moved distally, demonstrating the joining of the great saphenous vein and the bifurcation of the common femoral artery while adding pressure to assess compressibility of the vein. Visualization and compression of the femoral vein continued along the thigh until it could no longer be demonstrated sufficiently. Lastly, both popliteal fossae were investigated, demonstrating the popliteal artery and vein, and compressing the latter. Deep vein thrombosis was defined as absence of total venous collapse during compression. This protocol is preferred by the Society of Radiologists in Ultrasound for ultrasonographic diagnosis of proximal deep venous thrombi when a complete duplex ultrasound is not feasible.[17]

Based on ultrasound findings (Fig. 2), patients were allocated into one of three categories (Table 1):

If pulmonary embolism was confirmed by ultrasound, the investigator estimated risk of mortality within 30 days by applying the simplified pulmonary embolism severity index score and registering presence of cardiac troponin level and right ventricular dysfunction as recommended by the European Society of Cardiology and the European Respiratory Society.[18] Patients estimated at intermediate-low or

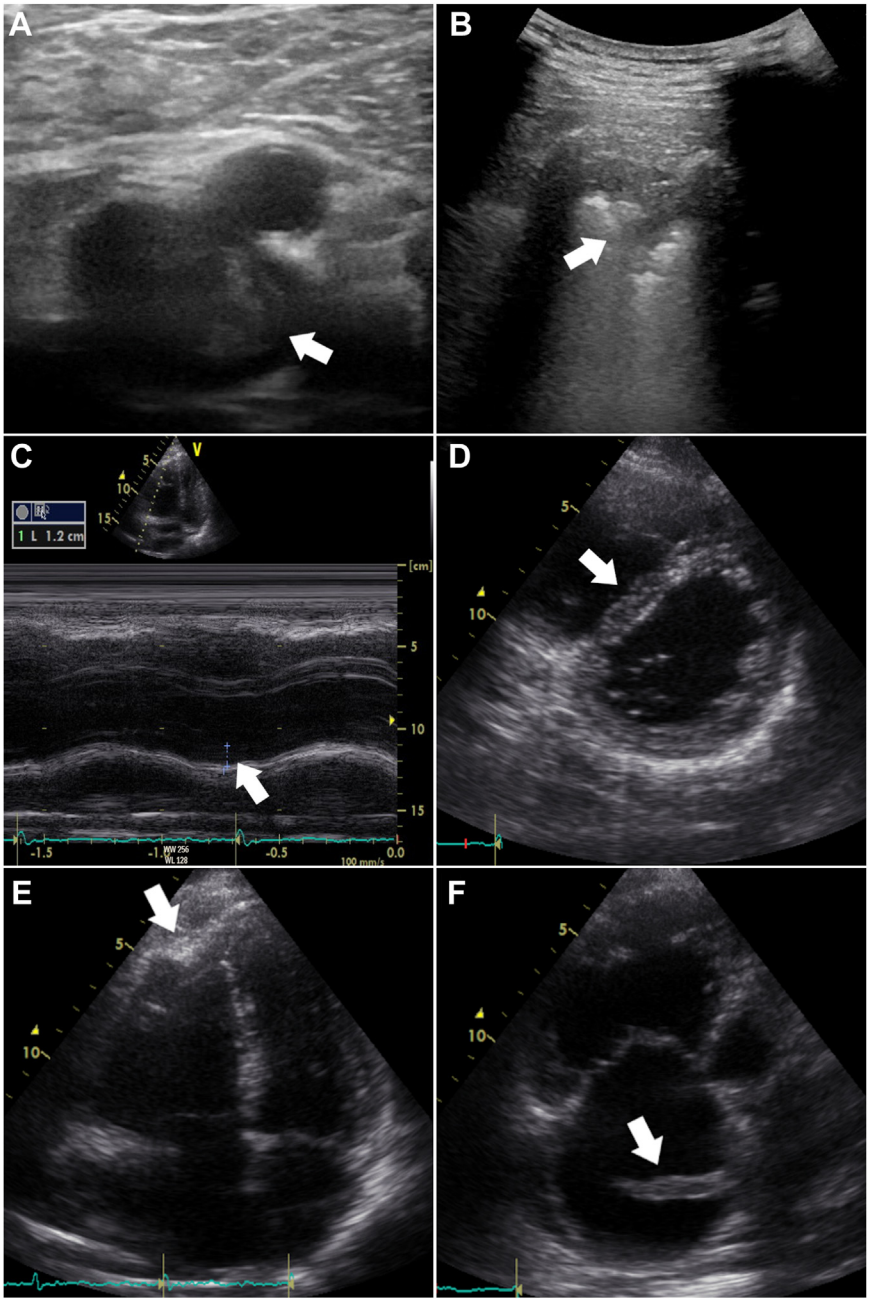

Fig. 2: Examples of ultrasound findings used in the protocol. A) Deep venous ultrasound showing a non-compressible isoechoic formation in the femoral vein (arrow), compatible with a deep venous thrombus. B) A typical wedge-shaped well-demarcated wedge-shaped lesion, representing a pleural infarction. C) Reduced tricuspid annular plane systolic excursion (TAPSE) measured by M-mode. D) The D-sign comprising septal flattening or bulging towards the left ventricle in both diastole and systole (arrow), representing right ventricular pressure overload in relation to present PE. E) The McConnell's sign, comprising akinesia of the free right ventricular wall with a concomitant normokinetic or hyperkinetic right ventricular apex (arrow). F) A visibly dilated right ventricle with a thrombus (arrow) lodged in a persisting oval foramen.

intermediate-high risk were admitted and referred for CT pulmonary angiography or lung scintigraphy to finally confirm diagnosis. Patients with low risk and no other cause for hospital admission, were treated with anticoagulative treatment in an outpatient setting without further diagnostic work-up. Consequently, only patients exhibiting a deep venous thrombus or at least two subpleural infarctions could avoid diagnostic imaging, as presence of right ventricular strain entails at least intermediate-low risk.

Allocation	Ultrasound findings
Pulmonary embolism confirmed	**≥ 1 the following:** • Proximal DVT • ≥ 2 hypoechoic subpleural consolidations with a diameter of ≥0.5 cm • Right ventricular thrombus • D-sign present in both systole and diastole or McConnell's sign in absence of known pulmonary hypertension, interstitial lung disease, pulmonary valve stenosis, or COPD
Pulmonary embolism dismissed	• No sign of DVT, no subpleural consolidation or effusion, no signs or right ventricular strain or thrombus and PE not most or equally likely diagnosis, or obvious differential diagnosis demonstrated by ultrasound, such as pneumonia, pneumothorax, or newly discovered significant disease of the left ventricle.
Need for diagnostic imaging	**≥ 1 the following:** • 1 hypoechoic subpleural consolidations with a diameter of ≥0.5 cm • Pleural effusion not explained by other cause. • Right ventricle visibly larger than left ventricle or basal ventricular diameter ratio >1. • TAPSE <17 mm • D-sign or McConnell's sign in presence of known pulmonary hypertension, interstitial lung disease, pulmonary valve stenosis, or COPD. • No DVT, no subpleural consolidation or effusion, no signs or right ventricular strain or thrombus, but PE most or equally likely diagnosis

DVT, deep venous thrombus; COPD, chronic obstructive pulmonary disorder; TAPSE, tricuspid annular plane systolic excursion.

Table 1: **Allocation of patients with suspected pulmonary embolism based on ultrasound findings.**

If suspicion of pulmonary embolism was dismissed by ultrasound investigation (no findings compatible with pulmonary embolism and pulmonary embolism not the most or equally diagnosis, or by demonstrating a differential diagnosis), the patient was either discharged or subject to further investigations if indicated. When discharged, these patients were instructed to contact a healthcare professional if no improvement or worsening of symptoms occurred within two weeks. If pulmonary embolism could be neither dismissed nor confirmed after ultrasound investigation, the patient was referred to CT pulmonary angiography or lung scintigraphy as standard practice.

Three months following inclusion, a review of electronic patient records of included patients was performed by two independent reviewers to determine incidence of secondary outcomes. All diagnostic work-up in relation to acute and chronic venous thromboembolism is handled by the public health care system in Denmark and is registered in the records which contain information on both in- and outpatient treatment. In cases of discrepancy, a decision was reached through consensus discussion or review by a third assessor. EPJ (Columna Clinical Information System, Systematic, Denmark) was used as electronic medical record system in all study sites except for Slagelse Hospital which used Sundhedsplatformen (Epic Systems, Wisconsin, United States).

Outcomes

The primary outcome measure of the trial was the proportion of patients referred to CT pulmonary angiography or lung scintigraphy following ultrasound investigation. Secondary exploratory outcome measures, after which the study was not powered, encompassed failure rate, adverse events, proportion of patients with pulmonary embolism diagnosed at enrolment, proportion of patients with alternate diagnoses provided by ultrasound, number of cancer diagnoses, and costs related to diagnostic work-up. Failure rate was defined as the proportion of missed pulmonary emboli, objectively diagnosed by a physician through use of CT pulmonary angiography or lung scintigraphy within three months following study enrolment. Adverse events encompassed a composite endpoint of major bleeding, readmission, or death within three months of study enrolment. Major bleeding was defined in accordance with the International Society on Thrombosis and Haemostasis as either fatal bleeding, symptomatic bleeding in critical area, drop in haemoglobin level of 1.24 mmol/L, or the need for two or more units of blood (either whole blood or erythrocytes).[19] Readmission was registered when the patient was referred to an emergency department for evaluation of any acute symptoms. Deaths were considered as caused by pulmonary embolism if it was confirmed by diagnostic imaging before death or was shown by autopsy. Ultrasound images were subject to central adjudication in all instances of missed pulmonary emboli. Expenditures associated with imaging modalities in relation to the diagnostic work-up was provided by the Danish Health Data Agency.[20]

Statistical analysis

A sample size of 120 patients was calculated to provide a 90% power with a significance level of 0.05 to detect an absolute reduction in number of referrals to CT pulmonary angiography or lung scintigraphy of 15% or more in the intervention group, as a smaller reduction was not considered clinically significant. It was decided to accommodate this number to a possible dropout rate of 25% due to loss-to-follow-up, withdrawal of consent, or patients leaving the emergency department prior to completion of all study procedures. As such, it was decided to enrol 150 patients in total.

Data analysis was conducted using GraphPad Prism 9.0.0 (GraphPad Software, San Diego, California USA). All enrolled patients were included in the analyses, applying an intention-to-treat approach.

Fisher's exact test was used for comparing proportion of patients referred to diagnostic imaging between groups. For secondary endpoints, normality was assessed using the Shapiro–Wilk test. Normally distributed data was presented as means with 95% confidence intervals and compared using students T-test. Non-normally distributed data was presented as medians with associated interquartile range and compared using Mann–Whitney U test. The chi square test was used for comparison of proportions except in instances where at least one cell contained frequencies below 5, in these cases, Fisher's exact test was used. Associated 95% confidence intervals were calculated as Wilson Score intervals. A two-sided significance level of 5% was used in all tests. No data monitoring committee was instated. The trial was registered at clinicaltrials.gov (NCT04882579).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 18, 2021, through Feb 1, 2023, 218 patients were assessed for eligibility of whom 150 were enrolled. Seventy-three patients were randomly assigned to ultrasound investigation and 77 patients to usual diagnostic imaging (Fig. 1). No exclusion or dropouts occurred at any stage following inclusion and no protocol crossover occurred. Baseline characteristics were similar between the two groups (Table 2). The median age of patients was 68 years, 50.6% were female, and the most common symptoms were dyspnoea (79.3%) and chest pain (44.7%). Median Wells score was 3 and median D-dimer was 1.99 mg/L. No adjustments were made based on study site due to notable difference in number of study inclusions, ranging from 9 to 76 (Appendix).

Complete multiorgan ultrasonographic assessment was feasible in all 73 patients of whom suspicion of pulmonary embolism was dismissed in 30. In 20 patients, the diagnosis was dismissed based on ultrasound screening devoid of right ventricular strain, subpleural consolidations, and deep venous thrombi. In 10 patients, ultrasound provided an alternative diagnosis to the patients' symptoms (data available in the Appendix). Pulmonary embolism was confirmed by ultrasound in 11 patients, most commonly by presence of a proximal deep venous thrombus, which was observed in nine patients. Eight of these patients had intermediate-low or -high 30-day mortality risk and were referred to CT pulmonary angiography or lung scintigraphy which

Characteristics	Ultrasound investigation (N = 73)	Standard care (N = 77)
Female sex	38 (52.1%)	38 (49.4%)
Age at randomization (years)	71 (57.5–79)	66 (56–77)
BMI (kg/m^2)	26.3 (23.1–29.3)	27.7 (24.7–30.8)
Active smoker	10 (13.7%)	13 (16.9%)
Previous smoker	30 (41.1%)	27 (35.1%)
Pack years	24 (15–40.8)	30 (11.5–45)
Symptoms at presentation		
Dyspnoea	59 (80.8%)	60 (77.9%)
Chest pain	32 (43.8%)	35 (45.5%)
Cough	21 (28.8%)	25 (32.5%)
Lower extremity swelling	14 (19.2%)	20 (26.0%)
Lower extremity pain	16 (21.9%)	17 (22.1%)
Syncope	3 (4.1%)	6 (7.8%)
Haemoptysis	3 (4.1%)	1 (1.3%)
Vital parameters at presentation		
Heart rate (beats/min)	85 (72–102)	88 (72.5–105.5)
Systolic blood pressure (mmHg)	137 (120–151)	140 (123–160.5)
Diastolic blood pressure (mmHg)	79 (70.5–89.5)	82 (71–91)
Arterial oxygen saturation (%)	96 (94–98)	97 (95–98)
Supplementary oxygen (n)	18 (24.7%)	20 (26.0%)
Supplementary oxygen level (L/min)	2 (1–4)	2 (2–3)
Respiratory rate (breaths/min)	20 (17.5–24)	18 (16–21)
Temperature (C°)	36.9 (36.6–37.3)	37 (36.6–37.3)
Biochemistry and clinical score		
Wells' score	3 (1.5–4.5)	3 (1.5–6)
D-dimer (mg/L)	1.7 (1.2–4.6)	2.1 (1.1–5.6)
Troponin T (ng/L)	13 (8.5–31)	11 (8–31)
Past medical history		
Hypertension	30 (41.1%)	21 (27.3%)
Chronic obstructive pulmonary disorder	13 (17.8%)	7 (9.1%)
Ischemic heart disease	11 (15.1%)	9 (11.7%)
Diabetes mellitus	9 (12.3%)	8 (10.4%)
Asthma	9 (12.3%)	7 (9.1%)
Atrial fibrillation or flutter	7 (9.6%)	6 (7.8%)
Previous stroke	6 (8.2%)	6 (7.8%)
Previous cancer	7 (9.6%)	5 (6.5%)
Active cancer	5 (6.8%)	4 (5.2%)
Heart failure	4 (5.5%)	2 (2.6%)
Previous pulmonary embolism	1 (1.4%)	3 (3.9%)
Previous deep venous thrombus	2 (2.7%)	2 (2.6%)
Pulmonary hypertension	2 (2.7%)	2 (2.6%)
Chronic kidney failure	2 (2.7%)	2 (2.6%)
Interstitial lung disease	2 (2.7%)	1 (1.3%)
Relevant medication		
Acetylsalicylic acid	28 (38.4%)	31 (40.3%)
P2Y12-inhibitors	8 (11.0%)	10 (13.0%)
Direct oral anticoagulation	3 (4.1%)	6 (7.8%)
Vitamin K antagonist	2 (2.7%)	2 (2.6%)
Low molecular weight heparin	3 (4.1%)	0 (0.0%)
Progesterone	3 (4.1%)	2 (2.6%)

Data are n (%) or median (IQR). BMI, body-mass index.

Table 2: **Baseline characteristics of the study population.**

confirmed pulmonary embolism in all instances. Lastly, 32 patients were referred to diagnostic imaging as ultrasound could neither confirm nor dismiss suspicion of pulmonary embolism of whom 12 had the diagnosis confirmed.

Of the 77 patients referred to diagnostic imaging in the control group, CT pulmonary angiography or lung scintigraphy was performed on 75. Protocol deviation occurred in two patients as clinical suspicion of pulmonary embolism was dismissed by a physician involved in the diagnostic work-up following study enrolment. In the ultrasound group, 40 out of 73 patients underwent CT pulmonary angiography or lung scintigraphy. Consequently, a significant absolute reduction in referral to diagnostic imaging of 45.2% was observed in the ultrasound group (95% confidence interval [CI], 34.3–56.6; $p < 0.001$) (Table 3). Subsequent post-hoc sensitivity analyses, adjusting for centre as the stratification variable, supported robustness of these findings (Appendix).

At enrolment, pulmonary embolism was diagnosed in 23 of the 73 patients randomized to ultrasound (31.5%) and in 26 of the 77 patients (33.8%) in the control group. Of the 50 patients in the ultrasound group who did not receive anticoagulation, two patients had pulmonary embolism confirmed during the 3-month follow-up period, corresponding to a failure rate of 4.0% (95% CI: 1.1–13.5). Both these patients were among the 30 who had pulmonary embolism dismissed by ultrasound alone and did not undergo diagnostic imaging, yielding a failure rate of 6.7% (95% CI: 1.9–21.3) in this sub-population. The first patient was characterized by a Wells score of 0 and a D-dimer of 0.98 mg/L. The second patient had a Wells score of 1.5 and a D-dimer of 4.6 mg/L. Both were diagnosed with pneumonia following initial clinical work-up. Further elaboration on the clinical course of these patients is available in the Appendix. None of the 51 patients in the control group who did not receive anticoagulation were diagnosed with pulmonary embolism during the follow-up period (0%; 95% CI: 0.0–7.0).

Adverse events were registered in 32 patients in the ultrasound group (43.8%, 95% CI: 33.1–55.2) and 22 patients in the control group (22.6%, 95% CI: 19.7–38.7) during the follow-up period, corresponding to a hazard ratio of 1.53 (95% CI: 0.99–2.38). No patients in the ultrasound group experienced bleeding complications during follow-up (0%, 95% CI: 0.0–5.0), whereas one patient (1.3%, 95% CI: 0.2–7.0) in the control group had a lower gastrointestinal bleeding (hazard ratio 0.35, 95% CI: 0.01–8.49). Referral to an emergency department for evaluation occurred in 26 patients in the ultrasound group (35.6%, 95% CI: 24.6–46.6) and 19 patients in the control group (24.7%, 95% CI: 16.4–35.4) (hazard ratio 1.44, 95% CI: 0.88–2.37). Nine patients (12.3%, 95% CI: 6.6–21.8) died during the follow-up period in the ultrasound group and six (7.8%, 95% CI: 3.6–16.0) died in the control group (hazard ratio 1.58, 95% CI: 0.59–4.22). No patients died because of a missed pulmonary embolism.

Five patients (6.8%, 95% CI: 3.0–15.1) in the ultrasound group received a cancer diagnosis during follow-up, as was the case for six patients (7.8%, 95% CI: 3.6–16.0) in the control group (hazard ratio 0.88, 95% CI: 0.28–2.76). An overview of types of cancer and causes of death and readmission is available in the Appendix. An overview of all study endpoints is available in (Table 3).

Contemporary expenses associated with conduction of a single CT pulmonary angiography in Denmark amounts to € 346.56. Thus, a reduction in referral to diagnostic imaging of 45.2% would correspond to an overall saving of approximately € 156.6 per patient. The application of ultrasound in the intervention group is not associated with additional expenses according to the Danish Health Data Agency.[20] No other significant

	Intervention group (n = 73)	Control group (n = 77)
Reduced referral to diagnostic imaging, %	45.2 (34.3–56.6)	N/A
Failure rate, %	4.0 (1.1–13.5)	0.0 (0.0–7.0)
Adverse events, %	43.8 (33.1–55.2)	22.6 (19.7–38.7)
Bleeding, %	0 (0.0–5.0)	1.3 (0.2–7.0)
Readmission, %	35.6 (24.6–46.6)	24.7 (16.4–35.4)
Death, %	12.3 (6.6–21.8)	7.8 (3.6–16.0)
Alternative diagnosis by ultrasound, %	13.7 (7.6–23.4)	N/A
Median time to initiation of treatment, minutes	46 (70–144)	57 (76–186)
Discharge without admission, %	54.8 (43.2–65.7)	49.4 (38.5–60.3)
Admission to internal medicine ward, %	24.7 (16.2–35.6)	27.3 (18.6–38.1)
Admission to cardiology ward, %	16.4 (9.7–26.6)	23.4 (15.3–34.0)
Admission to intensive care unit, %	2.7 (0.7–9.5)	0.0 (0.0–0.5)
Cancer diagnosis, %	6.8 (3.0–15.1)	7.8 (3.6–16.0)

N/A: Not applicable. Data are presented as % with 95% confidence intervals or median with associated interquartile range.

Table 3: **Overview of study outcomes.**

differences were observed between groups in relation to diagnostic work-up and hospital stay.

Discussion

This study is the first randomized pragmatic trial in which physicians apply ultrasound in dismissing or confirming suspicion of pulmonary embolism, given a sufficiently low or high clinical probability. The findings support that integration of multiorgan ultrasound in the diagnostic work-up of suspected pulmonary embolism can reduce referral to diagnostic imaging, however, while not powered to definitely answer this question, the associated failure rate in the present study is unacceptably high. Consequently, studies adequately powered to assess safety, or modifications to the present protocol aimed at improving sensitivity, are highly warranted.

Attempting to improve selection of patients for diagnostic imaging is not uncommon within the field of pulmonary embolism diagnostics. Noteworthy examples include the YEARS-study where patients with suspected pulmonary embolism were assessed for presence of three items: clinical signs of deep venous thrombosis, haemoptysis, and pulmonary embolism as the most likely diagnosis. If none were present, D-dimer cutoff was increased to 1000 μg/L. Consequently, the study reported a reduction of 14% in referral to CT pulmonary angiography with an associated failure rate of 0.6% (95% CI: 0.4–1.0).[21] Most recently, the 2019 PEGeD-study assessed an approach allowing dismissal of pulmonary embolism suspicion in patients with a Wells' score of 0–4 and concomitant D-dimer <1.0 mg/L.[22] This approach reduced referral to diagnostic imaging by 17% with no instances of symptomatic venous thromboembolism in the 3-month follow-up period.

While the reduced referral to diagnostic imaging of 45.2% (95% CI: 34.3–56.6) in our study was notably higher, it was accompanied by an equally higher 3-month failure rate of 4.0% in the entire intervention group and 6.7% among patients with pulmonary embolism dismissed by ultrasound alone. The study was not powered for assessment of failure rate and no acceptable threshold was defined. The contemporary approach to determination of acceptable failure rate originates from The International Society on Thrombosis and Haemostasis which proposed an equation for determining an acceptable failure rate, taking into account the prevalence of the study population.[6] Applying the prevalence of 33.7% in this study's control group to the equation, 1.82 + 0.00528 x prevalence, yields an acceptable failure rate of 2.0%, thus numerically lower than the failure rate of the intervention group in the present study.

Considering the two patients with missed pulmonary embolism, one had a D-dimer of 0.98 mg/L and a Wells' score of 0, a combination similar to 1285 patients in the PEGeD-study of whom none had pulmonary embolism during follow-up.[22] Consequently, this patient was characterized by very low probability of pulmonary embolism regardless of ultrasonographic findings. Subsequent central adjudication revealed that the patient had an unremarkable chest x-ray and an arterial blood gas with an oxygen saturation of 89%, a combination which some physicians would arguably deem suggestive of pulmonary embolism, yielding a Wells score of 3. This highlights an important pitfall of our approach, namely that not only interpretation of ultrasound findings varies between physicians, but so does assessment of pre-test probability.[23,24]

The other patient which exhibited a Wells' score of 1.5 and a D-dimer of 4.6 mg/L was diagnosed with pneumonia due to ultrasound findings of air bronchograms and no signs of right ventricular strain, subpleural infarctions, or deep venous thrombi. These findings were subsequently confirmed by central adjudication. The efficacy of ultrasound in offering alternative diagnoses in emergency situations has been previously assessed. In a 2014 study, Laursen and colleagues integrated multiorgan ultrasound into the diagnostic work-up of 160 patients with dyspnoea.[15] Their findings revealed a significant 24.3% absolute increase in accurate presumptive diagnoses (95% CI: 15.0–33.1) and demonstrated a median time use of 12 min for assessment of the heart, lungs, and deep veins. Subsequently, Weile and colleagues conducted a study involving 403 unselected emergency department patients, demonstrating that ultrasound led to a modification in clinical management for 17.6% of cases.[25]

It is noteworthy that all participants in the present trial had undergone an initial diagnostic work-up that failed to provide a definite explanation for their symptoms other than pulmonary embolism. In this context, ultrasound offered alternative diagnoses in 13.7% of cases (95% CI: 7.6–23.4), which is encouraging. However, it is important to highlight that the overall course following study enrolment was similar between groups, encompassing time to initiation of treatment, allocation, and occurrence of adverse events.

A strength of this study is the randomized controlled design. Including a control group allows approximation of the background prevalence while minimizing confounding by evenly distributing prognostic factors and reducing risk of selection bias. However, the study still harbours important limitations which should be considered when interpreting the results. An important aspect and possible safety concern is that the proposed ultrasound approach does not integrate D-dimer level when allocating patients, only pre-test probability and ultrasound findings. The main rationale behind this decision was that D-dimer level has been shown to correlate with pulmonary arterial obstruction and by extension right ventricular strain and dilation, which would have been acknowledged by ultrasound and thus resulted in referral to diagnostic imaging.[26–28] However,

as D-dimer level has also been demonstrated to correlate with positive likelihood ratio of pulmonary embolism, especially when above 2.5 mg/L.[29] Integrating this level as a safety threshold should be considered in future studies.

Another possible source of bias is the rate at which the 150 patients were enrolled. As the inclusion period spanned approximately 19 months, recruitment across the six participating sites was significantly slower than in for instance the PEGeD-study which included approximately 70 patients per month across nine sites.[22] While a novel approach to interpretation of D-dimer level does not require any tailored training, making potential study investigators, and thereby opportunities for inclusion, abundant, the risk of selection bias in the present study should be considered. As only few physicians were certified in cardiac, lung, and deep venous ultrasound at time of study initiation, all study investigations were performed by 13 dedicated physicians across six hospitals. Thus, while all investigators consecutively assessed patients for eligibility while present in the emergency department, it is unlikely that all possible participants were considered for study inclusion. However, to which degree cannot be determined as the total number of patients referred to diagnostic imaging on suspicion of pulmonary embolism during the study period is not available. Nevertheless, when comparing the present study participants with those of a large scale descriptive study on 2408 patients with suspected pulmonary embolism, clinical characteristics such symptoms at presentation, Wells score, and D-dimer level are similar, suggesting a representative population.[30]

Further, as interpretation of ultrasonographic findings is associated with moderate interrater variability, universal application of such an approach harbours an important risk of misinterpreted findings.[23] This underscores the importance of sufficient competency prior to clinical use. Contemporary educational research recommends theoretical and practical courses, supervised clinical training, and subsequent evidence-based competency assessment rather than sheer number of completed scans or years of experience, as these parameters do not reliably reflect actual competency of the physician.[31] Naturally, even though all study investigators were certified in all three ultrasound modalities in accordance with recommendations of the Danish Society for Emergency Medicine, it should be acknowledged that competencies vary between physicians, making the validity of findings less reliable than for instance dichotomous interpretation of D-dimer level.

While the proposed ultrasound protocol reduces referral to diagnostic imaging, the actual failure rate remains to be determined prior to clinical implementation. A possible study setup aimed at reducing failure rate would comprise a population of patients with a Wells' score below 2, corresponding to a pre-test probability of approximately 6% in whom an ultrasound investigation devoid of subpleural infarctions, right ventricular strain, and deep venous thrombi would yield a negative predictive value of approximately 99.3%.[7,32] In accordance with the recent recommendation from the International Society on Thrombosis and Hemostasis, this would correspond to an acceptable failure rate of 1.85%.[6] As D-dimer level impacts likelihood ratio, the patient population could be specified further by limiting the level to a maximum of 2500 µg/L. This would at most double the pre-test probability from 0.7% to 1.4% thus remaining below the acceptable failure rate.[29] While the ultrasound approach encompasses assessment for deep venous thrombus, including the diagnosis of this condition within three months of study inclusion to the failure rate would increase comparability to similar studies on the topic.

Lastly, acknowledging that ultrasonographic confirmation of pulmonary embolism alleviated the need for diagnostic imaging in only three patients, removing the possibility of confirming pulmonary embolism, rendering the approach dichotomous and thus more accessible, should be considered.

In conclusion, integration of a bespoke multiorgan protocol in patients with suspected pulmonary embolism reduces referral to diagnostic imaging. However, while not powered to definitely answer this question, the estimated failure rate is unacceptably high. Our findings suggest that future studies, adequately powered to determine failure rate, should limit the study population to low-probability patients in order to increase the negative predictive value.

Contributors

The study was conceptualized by Casper Falster, Christian B. Laursen, Mikkel Brabrand, Stefan Posth, Mikael Kjær Poulsen, and Jacob Møller. The study design and practical considerations were agreed upon by all authors. Data collection was done by Casper Falster, Mads Damgaard Mørkenborg, Mikkel Thrane, Jesper Clausen, Michael Arvig, Kristoffer Brockhattingen, Peter Biesenbach, Lasse Paludan Bentsen, Stefan Posth, Rune Wiig Nielsen and Thi Anh Nhi Huynh. Data was verified by Casper Falster, Rune Wiig Nielsen, and Christian B. Laursen. Analysis and writing of initial manuscript draft was done by Casper Falster. All authors have read and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Qualified researchers from an appropriate institution may request access to individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices). Upon approval of a data sharing request by the regional legal body, information necessary to address the research question will be provided under the terms of a signed data sharing agreement. Requests should be submitted to casper.falster@rsyd.dk.

Declaration of interests

Casper Falster has received personal fees from AstraZenica for a presentation on thoracic ultrasound and Bristol-Myers Squibb for a presentation on pulmonary embolism. Prof Jacob E Møller has received institutional research grants from Abiomed and Novo Nordisk, speaker fees from Abbott and Boehringer Ingelheim, travel support from Abiomed, has participated in a data safety monitoring and advisory

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100941.

References

1 Hull RD, Hirsh J, Carter CJ, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med*. 1983;98:891–899.
2 Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379:1835–1846.
3 Falster C, Hellfritzsch M, Gaist TA, et al. Comparison of international guideline recommendations for the diagnosis of pulmonary embolism. *Lancet Haematol*. 2023. https://doi.org/10.1016/S2352-3026(23)00181-3.
4 Linkins LA, Takach Lapner S. Review of D-dimer testing: good, bad, and ugly. *Int J Lab Hematol*. 2017;39:98–103.
5 Righini M, Goehring C, Bounameaux H. Effects of age on the performance of common diagnostic tests for pulmonary embolism. *Am J Med*. 2000;109:357–361.
6 Dronkers CEA, van der Hulle T, Le Gal G, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15:1040–1043.
7 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*. 2021;77. thoraxjnl-2021-216838.
8 Koenig S, Chandra S, Alaverdian A, Dibello C, Mayo PH, Narasimhan M. Ultrasound assessment of pulmonary embolism in patients receiving CT pulmonary angiography. *Chest*. 2014;145:818–823.
9 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.
10 Casper Falster A, Egholm G, Wiig R, et al. Diagnostic accuracy of a bespoke multiorgan ultrasound approach in suspected pulmonary embolism. *Ultrasound Int Open*. 2022;8:E59–E67.
11 Bonde AN, Andersen A, Schultz J, et al. Treatment guideline | Pulmonary embolism and deep venous thrombus. https://nbv.cardio.dk/lungeemboli. Accessed August 26, 2023.
12 Laursen CB, Nielsen K, Riishede M, et al. A framework for implementation, education, research and clinical use of ultrasound in emergency departments by the Danish Society for Emergency Medicine. *Scand J Trauma Resusc Emerg Med*. 2014;22. https://doi.org/10.1186/1757-7241-22-25.
13 Neskovic AN, Edvardsen T, Galderisi M, et al. Focus cardiac ultrasound: the European association of cardiovascular imaging viewpoint. *Eur Heart J Cardiovasc Imaging*. 2014;15:956–960.
14 Laursen CB, Rahman NM, Volpicelli G. *Thoracic ultrasound (monograph)*. European Respiratory Society; 2018. https://doi.org/10.1183/2312508x.erm7918.
15 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.
16 Laursen CB, Sloth E, Lambrechtsen J, et al. Focused sonography of the heart, lungs, and deep veins identifies missed life-threatening conditions in admitted patients with acute respiratory symptoms. *Chest*. 2013;144:1868–1875.
17 Needleman L, Cronan JJ, Lilly MP, et al. Ultrasound for lower extremity deep venous thrombosis: multidisciplinary recommendations from the society of radiologists in ultrasound consensus conference. *Circulation*. 2018;137:1505–1515.
18 Konstantinides SV, Meyer G, Bueno H, 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.
19 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.
20 Health finance - Danish health data agency. https://sundhedsdatastyrelsen.dk/da/english/health_finance. Accessed April 10, 2024.
21 van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet (London, England)*. 2017;390:289–297.
22 Kearon C, de Wit K, Parpia S, et al. Diagnosis of pulmonary embolism with d -dimer adjusted to clinical probability. *N Engl J Med*. 2019;381:2125–2134.
23 Knackstedt C, Bekkers SCAM, Schummers G, et al. Fully automated versus standard tracking of left ventricular ejection fraction and longitudinal strain: the FAST-EFs multicenter study. *J Am Coll Cardiol*. 2015;66:1456–1466.
24 Wolf SJ, McCubbin TR, Feldhaus KM, Faragher JP, Adcock DM. Prospective validation of wells criteria in the evaluation of patients with suspected pulmonary embolism. *Ann Emerg Med*. 2004;44:503–510.
25 Weile J, Frederiksen CA, Laursen CB, Graumann O, Sloth E, Kirkegaard H. Point-of-care ultrasound induced changes in management of unselected patients in the emergency department - a prospective single-blinded observational trial. *Scand J Trauma Resusc Emerg Med*. 2020;28. https://doi.org/10.1186/S13049-020-00740-X.
26 Ghanima W, Abdelnoor M, Holmen LO, Nielssen BE, Ross S, Sandset PM. D-dimer level is associated with the extent of pulmonary embolism. *Thromb Res*. 2007;120:281–288.
27 Geissenberger F, Schwarz F, Probst M, et al. D-dimer predicts disease severity but not long-term prognosis in acute pulmonary embolism. *Clin Appl Thromb*. 2019;25. https://doi.org/10.1177/1076029619863495.
28 Ji YQ, Sun B, Juggessur-Mungur KS, Li ZY, Zhang ZH. Correlation of D-dimer level with the radiological severity indexes of pulmonary embolism on computed tomography pulmonary angiography. *Chin Med J (Engl)*. 2014;127:2025–2029.
29 Kohn MA, Klok FA, van Es N. D-Dimer interval likelihood ratios for pulmonary embolism. *Acad Emerg Med*. 2017;24:832–837.
30 Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (multicenter emergency medicine pulmonary embolism in the real world registry). *J Am Coll Cardiol*. 2011;57:700–706.
31 Pietersen PI, Bhatnagar R, Rahman NM, et al. Evidence-based training and certification: the ERS thoracic ultrasound training programme. *Breathe*. 2023;19. https://doi.org/10.1183/20734735.0053-2023.
32 Ceriani E, Combescure C, Gal G Le, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8:957–970.