CHEST

Original Research

PULMONARY PROCEDURES

Accuracy of Point-of-Care Multiorgan Ultrasonography for the Diagnosis of Pulmonary Embolism

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Background: **Presenting signs and symptoms of pulmonary embolism (PE) are nonspecific, favoring a large use of second-line diagnostic tests such as multidetector CT pulmonary angiography (MCTPA), thus exposing patients to high-dose radiation and to potential serious complications. We investigated the diagnostic performance of multiorgan ultrasonography (lung, heart, and leg vein ultrasonography) and whether multiorgan ultrasonography combined to Wells score and D-dimer could safely reduce MCTPA tests.**

Methods: **Consecutive adult patients suspected of PE and with a Wells score > 4 or a positive D-dimer result were prospectively enrolled in three EDs. Final diagnosis was obtained with MCTPA. Multiorgan ultrasonography was performed before MCTPA and considered diagnostic for PE if one or more subpleural infarcts, right ventricular dilatation, or DVT was detected. If multiorgan ultrasonography was negative for PE, an alternative ultrasonography diagnosis was sought. Accuracies of each single-organ and multiorgan ultrasonography were calculated.**

Results: **PE was diagnosed in 110 of 357 enrolled patients (30.8%). Multiorgan ultrasonography yielded a sensitivity of 90% and a specificity of 86.2%, lung ultrasonography 60.9% and 95.9%, heart ultrasonography 32.7% and 90.9%, and vein ultrasonography 52.7% and 97.6%, respectively. Among the 132 patients (37%) with multiorgan ultrasonography negative for PE plus an alternative ultrasonographic diagnosis or plus a negative D-dimer result, no patients received PE as a final diagnosis.**

Conclusions: **Multiorgan ultrasonography is more sensitive than single-organ ultrasonography, increases the accuracy of clinical pretest probability estimation in patients with suspected PE, and may safely reduce the MCTPA burden.**

Trial registry: **ClinicalTrials.gov; No.: NCT01635257; URL: www.clinicaltrials.gov**

CHEST 2014; 145(5):950–957

Abbreviations: MCTPA = multidetector CT pulmonary angiography; PE = pulmonary embolism

Pulmonary embolism (PE) is a heterogeneous condition that should be always suspected in patients with dyspnea, chest pain, syncope, shock/hypotension, or cardiac arrest without an alternative obvious cause.[1] PE can be safely ruled out in patients with low pretest probability associated with a negative D-dimer test result.[2-5] Conversely, patients showing high pretest probability or high D-dimer level should undergo further diagnostic testing.

In recent years, multidetector CT pulmonary angiography (MCTPA) has become the standard of care for the detection of PE, and its use has shown a slight increase in the diagnosis of PE, but the number of patients tested without a PE has increased even more.[6,7] Wide use of MCTPA has several disadvantages, such as radiation exposure and contrast medium side effects.

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Moreover, MCTPA has high costs, is not feasible in unstable patients, is not available 24 h a day in all institutions, and should be used with caution in some patient groups, such as patients with renal failure and pregnant women.

Point-of-care ultrasonography can be rapidly performed at the bedside and is complementary to the physical examination; it should be considered as a focused diagnostic test that adds anatomic, functional, and physiologic information to the care of the emergent patient.[8] Many authors evaluated the diagnostic role of ultrasonography in patients with suspected PE, focusing on subpleural infarcts investigated by lung ultrasonography,[9,10] right ventricular dilatation by heart ultrasonography,[11-16] and DVT by leg vein ultrasonography.[17,18] However, due to the relatively low sensitivity, not one of these ultrasonographic methods can be safely used to rule out PE as a standalone test, while no previous studies have investigated the diagnostic accuracy of a combination of lung, heart, and leg vein ultrasonography for detecting PE. The aims of this study were to investigate the accuracy of multiorgan ultrasonography (lung, heart, and veins) in the diagnostic process of symptomatic patients with suspected PE and to evaluate whether a diagnostic model that integrates multiorgan ultrasonography to clinical assessment and to D-dimer level may be useful in reducing the number of patients who undergo MTCPA, while maintaining acceptable safety standards.

Materials and Methods

Design, Setting, Protocol, and Population

This was a multicenter prospective accuracy study, and the local ethic committees approved the study (No. 2012/20938 and 2012/5069). Written informed consent was obtained for inclusion in the study. The patients were recruited from June 2012 to November 2012 in the ED of three Italian hospitals: two university hospitals with an annual census of 120,000 and 50,000 visits, respectively, and one community hospital with an annual census of 50,000 visits.

Consecutive patients aged > 18 years, presenting to the EDs, and suspected of having a PE were considered for the study. The initial assessment included Wells score calculated by the attending physician and blood samplings for high sensitive D-dimer levels, in addition to all of the routine tests. D-dimer levels were assayed with automated latex agglutination tests (Hemosil D-Dimer HS; Instrumentation Laboratories spa, and Siemens AG). Patients with a Wells score ≤ 4 and a D-dimer value < 500 ng/mL, fibrinogen equivalent unit (negative D-dimer) were not considered for the study as no further tests are required to exclude PE according to international guidelines.[19] Patients with a Wells score > 4 or D-dimer value ≥ 500 ng/mL (positive D-dimer) who underwent MCTPA during ED evaluation were included.

Multiorgan ultrasonography was performed before and within 3 h from MCTPA by one of 13 sonographer investigators, including one emergency physician expert in lung ultrasound and chair of the scientific committee of the first international consensus conference on lung ultrasound, eight emergency medicine staff physicians with at least 5 years practicing point-of-care ultrasonography in emergency, and four resident physicians (two emergency medicine and two internal medicine) performing their training in emergency ultrasound with focus in cardiac, vein, and lung point-of-care examination. The following multiprobe machines were used: three MyLab30 Gold and one MyLab40 (Esaote S.p.A.), one Logiq3 (General Electric), and one HD7 (Koninklijke Philips N.V.). The investigators were blinded to clinical information other than the visible physical signs and symptoms of the patient's presentation.

Multiorgan Ultrasonography

Each ultrasonographic examination was performed by following a systematic and standardized sequence: lung, heart, and leg veins. Lung ultrasonography was performed by a 4- to 8-MHz linear probe or a 3.5- to 5-MHz curved array probe. The lung was examined by longitudinal and oblique scans both on anterior and posterior chest. The examination was performed with the patient in the supine position. The dorsal areas were scanned by turning the patient in the lateral decubitus on both sides or, when possible, in the sitting position. The examination was targeted to the detection of pulmonary subpleural infarcts, which consist of pleural-based, well-demarcated echo-poor triangular or rounded consolidations of at least 0.5 cm in size (e-Fig 1, Video 1).[10] The number and location of pulmonary subpleural infarcts were reported. Consolidations suggestive of pneumonia, pleural effusion, and diffuse interstitial syndrome were also noted according to international recommendations on point-of-care lung ultrasonography.[20]

Heart ultrasonography was performed with a 2- to 5-MHz phased-array probe. Right ventricular dilatation was diagnosed in the presence of at least one of the following criteria: right/left ventricular end-diastolic diameter ratio > 0.9 in the apical four chamber or in the subcostal view or right ventricular end-diastolic diameter > 30 mm in the parasternal view (e-Fig 2, Video 2).[15,21] Moreover, thrombi in the right cavities and signs of pericardial effusion and aortic dissection were recorded when detected.

Leg vein ultrasonography was performed by a 4- to 8-MHz linear probe and consisted of short-axis visualization and compression of the common and superficial femoral veins and of the popliteal veins. DVT was defined as absence of vein total collapse during compression (e-Fig 3, Video 3).[22,23]

Multiorgan ultrasonography was considered diagnostic of PE when lung ultrasonography visualized at least one pulmonary subpleural infarct, or heart ultrasonography detected right ventricular dilatation or thrombi in the right cavities, or leg vein ultrasonography detected DVT. In cases where multiorgan ultrasonography was negative for PE, the investigator was asked to specify whether an alternative ultrasonography diagnosis among pneumonia, pleural effusion, diffuse interstitial syndrome, pericardial effusion, or aortic dissection could justify the symptoms of presentation. Immediately after the completion of the exam, the investigators filled in a standardized form (e-Fig 4).

Manuscript received May 6, 2013; revision accepted September 2, 2013; originally published Online First October 3, 2013.
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Funding/Support: The authors have reported to *CHEST* that no funding was received for this study.
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DOI: 10.1378/chest.13-1087

Final Diagnosis and Sample Size

The final diagnosis of acute PE was established by MCTPA. All MTCPAs were performed by one Lightspeed VCT64 (General Electric) and two Somatom Definition AS128 (Siemens AG). Two radiologists, expert in PE diagnosis, blinded to clinical data and to multiorgan ultrasonography results, independently reviewed the studies. In case of discordance, a third senior radiologist (M. B.) adjudicated the diagnosis. In patients without PE, the other final diagnoses were established by S. G. after reviewing all available clinical data including MCTPA data and medical records for hospitalized patients. S. G. was blinded to multiorgan ultrasonography.

The sample was calculated on the basis of previous studies, which reported a maximal sensitivity of each single ultrasonography at around 80%.[9] When we set the type 1 error level at 5%, a sample size of 330 subjects led to 90% of power to detect an absolute difference of 10% in sensitivity between each single-organ ultrasonography test and multiorgan ultrasonography protocol.

Statistical Analysis

Data points are expressed as mean ± SD. The unpaired Student *t* test was used to compare normally distributed data. The Fisher exact test was used for the comparison of noncontinuous variables expressed as proportions. $P < .05$ indicates statistical significance. All *P* values are two-sided. To assess the agreement between the two radiologists evaluating MCTPA for PE diagnosis, we used the κ statistic.[24] The diagnostic performance of lung, heart, and leg vein ultrasonography alone and of multiorgan ultrasonography was assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios. To evaluate the performance of ultrasonography to rule out PE, in patients with a multiorgan ultrasonography examination negative for PE we also calculated the accuracy of detecting an alternative ultrasonography diagnosis that could justify the symptoms of presentation. The McNemar test was used to compare the sensitivities of each single-organ ultrasonography with multiorgan ultrasonography sensitivity. Calculations were performed with the use of SPSS statistical package, version 17.0 (IBM).

Results

A total of 510 patients with clinically suspected PE presented to the EDs. Ninety-seven patients (19%) had a Wells score ≤ 4 and a negative D-dimer and were not considered for the study. Among the 413 patients with a Wells score > 4 or a positive D-dimer, 56 (13.6%) were excluded because they met exclusion criteria (Fig 1); thus, 357 patients were included. Included patients had a mean age of 71 ± 14 years (range, 19-100 years), and 188 (52.7%) were women. PE was diagnosed by MCTPA in 110 patients (30.8%) with an optimal agreement between radiologists (κ = 0.95) (Table 1). The main characteristics of enrolled patients according to presence or absence of PE are shown in Table 2. Among the 175 patients with Wells score > 4, PE was present in 72 (41.1%); D-dimer results were negative in three of 72 patients (4.2%) with PE. In the 182 patients with Wells score ≤ 4 and a positive D-dimer, PE was diagnosed in 38 (21%).

Lung and leg vein ultrasonography were feasible in all patients, but in 25 (7%), pulmonary examination was performed only by anterior scans. Heart ultrasonography was not conclusive in five patients (1.4%) because of poor acoustic windows.

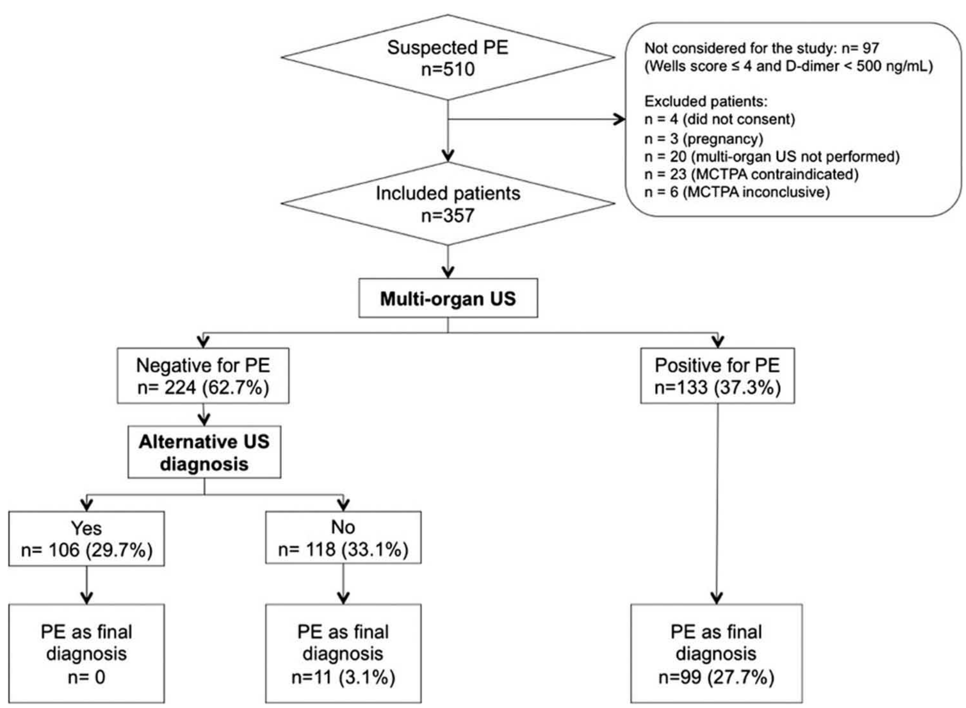

Figure 1. Flow diagram of the study and main results. Percentage (%) refers to the 357 included patients. MCTPA = multidetector CT pulmonary angiography; PE = pulmonary embolism; US = ultrasonography.

Table 1—*Final Diagnosis in the Study Patients*

Diagnosis	No. (%)
Pulmonary embolism	110 (30.8)
Pneumonia	84 (23.5)
Heart failure	27 (7.6)
COPD	22 (6.2)
Pleural effusion	17 (4.8)
Syncope	16 (4.5)
Musculoskeletal chest pain	13 (3.6)
Sepsis	13 (3.6)
Acute coronary syndrome	12 (3.4)
Tachyarrhythmia	12 (3.4)
Psychogenic dyspnea	6 (1.7)
Aortic dissection	5 (1.4)
Pulmonary fibrosis	4 (1.1)
Pericardial effusion	3 (0.8)
Miscellaneous	13 (3.6)

Seventy-seven patients (21.6%) showed at least one subpleural infarct at lung ultrasonography with a mean of 2.1 lesions; in 67 of these patients (87%), PE was diagnosed by MCTPA. Figure 2 shows the distribution of the subpleural infarcts in the chest areas. Fifty-seven patients (16%) showed signs of right ventricular dilatation at heart ultrasonography, and in three patients a thrombus was visualized in the right cavities. PE was diagnosed by MCTPA in 36 of 58 patients (62.1%) with positive heart ultrasonography. Of 64 patients with a positive leg vein ultrasonography, PE was present in 58 (90.6%).

Table 2—*Characteristics of the Study Population According to Final Diagnosis*

Characteristic	PE Negative (n = 247)	PE Positive (n = 110)	*P* Value
Age, mean ± SD, y	70.7 ± 14.4	72.7 ± 12.3	.214
Women	123 (49.8)	65 (59.1)	.11
Signs and symptoms of presentation			
Syncope	50 (20.2)	14 (12.7)	.101
Cardiac arrest	2 (0.8)	1 (0.9)	1
Palpitations	25 (10.1)	13 (11.8)	.71
Chest pain			
Total	72 (29.1)	26 (23.6)	.306
Pleuritic	43 (17.4)	18 (16.4)	.88
Dyspnea	152 (61.5)	82 (74.5)	.022
Shock/hypotension	44 (17.8)	11 (10)	.08
Wells score and single items			
Signs and symptoms of DVT	30 (12.1)	54 (49.1)	< .001
PE most likely diagnosis	112 (45.3)	72 (65.5)	.001
HR > 100 bpm	122 (49.4)	46 (41.8)	.207
Immobilization or surgery	65 (26.3)	28 (25.5)	.897
Previous DVT or PE	31 (12.6)	14 (12.7)	1
Hemoptysis	9 (3.6)	1 (0.9)	.185
Malignancy	53 (21.5)	30 (27.3)	.278
Wells score > 4	103 (41.7)	72 (65.4)	< .001
D-dimer			
Positive level, ≥500 ng/mL	187 (75.7)	107 (97.3)	< .001

Data are given as No. (%) unless otherwise indicated. bpm = beats/min; HR = heart rate; PE = pulmonary embolism.

Ninety-nine of 133 patients (74.4%) with positive multiorgan ultrasonography had a diagnosis of PE confirmed by MCTPA, whereas PE was still diagnosed in 11 of 224 patients (4.9%) with negative ultrasonography results (Fig 1). Fifty-five of 224 patients (24.5%) with negative multiorgan ultrasonography for PE had negative D-dimer results. None of these 55 patients, representing 15.4% of the overall population, had a diagnosis of PE by MCTPA. Among the 224 patients with multiorgan ultrasonography results negative for PE, alternative ultrasonography diagnoses were detected in 106 patients (47.3%): pneumonia (n = 62), diffuse interstitial syndrome (n = 23), pleural effusion (n = 15), pericardial effusion (n = 3), aortic dissection (n = 3). None of these 106 patients, representing 29.7% of the overall population, had PE diagnosed by MCTPA (Fig 1). Test characteristics of single-organ, and of multiorgan, ultrasonography are reported in Table 3.

Discussion

This study indicates that multiorgan ultrasonography is feasible in almost all patients presenting to the ED with suspected PE. Multiorgan ultrasonography sensitivity is significantly superior to that of lung, heart, and leg vein ultrasonography alone; our multiorgan protocol may be useful as a routine pretest evaluation to improve the potential of Wells scoring and D-dimer assay in the selection of patients who should undergo MCTPA.

Today, MCTPA has become the standard of care in patients with clinically suspected PE. However, as the use of MCTPA has exponentially increased over recent years, there is a growing concern about irradiation of the general population and contrast medium adverse effects.[25,26] Prevalence of PE among patients with suspected PE who underwent an MCTPA is as low as 5% to 10% in the United States and 20% to 30% in Europe.[27-30] Accordingly, in our ED, among the population submitted to MCTPA, we had 30.8% of positive diagnoses.

Previous studies evaluated the accuracy of lung, heart, and vein ultrasonography for the diagnosis of PE. Pulmonary subpleural infarcts detected by lung ultrasonography showed a sensitivity of 70% to 98% and a specificity of 50% to 99%.[9,10,31] Right ventricular dilatation detected by heart ultrasonography showed a sensitivity of 31% to 72% and a specificity of 87% to 98%.[11-16] Heart ultrasonography also has the potential to visualize thrombi in the right-side heart cavities.[32] DVT detected by leg vein ultrasonography showed a sensitivity of 39% to 55% and a specificity of 96% to 99%.[17,18] In our study, the sensitivities of the single

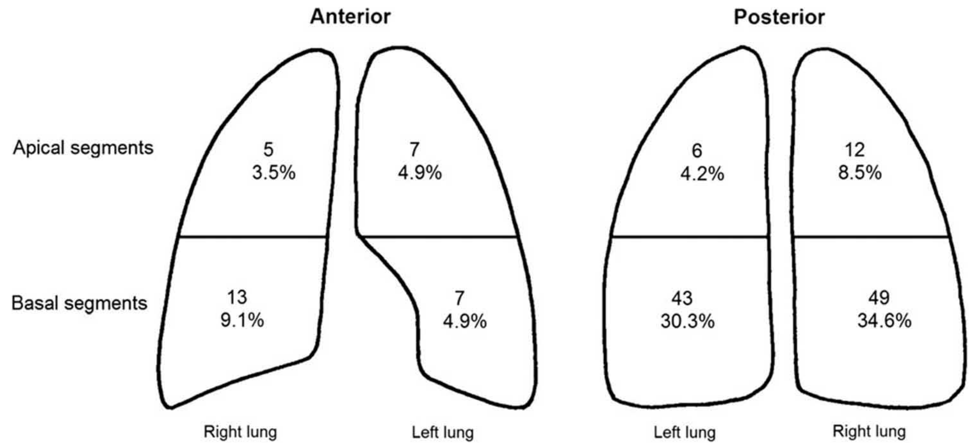

Figure 2. Number and percentage of subpleural infarcts detected in different chest areas.

ultrasonographic tests were low, with the higher sensitivity obtained by lung ultrasonography (61%), thus confirming the limitation of a single-organ ultrasonography to rule out PE. Sensitivity of lung ultrasonography was lower compared with previous studies. The reason for this discrepancy could be explained by the fact that the examinations performed in emergency situations and unstable patients are sometimes limited by the difficulty in scanning the whole chest and restriction of time.

Multiorgan ultrasonography sensitivity (90%) was significantly superior to that of lung, heart, and leg vein ultrasonography alone. Only two previous studies investigated the diagnostic accuracy of a combination of vein and heart ultrasonography.[15,33] The first study included 117 patients and showed a sensitivity of 89% and a specificity of 74% of venous and cardiac ultrasonography in combination with a specifically designed but not validated clinical score. In the second study, which included 76 patients, the combination of vein and heart ultrasonography showed a sensitivity of 87% and a specificity of 69%. Both studies were based on the measurement of specific echocardiographic parameters to evaluate right ventricular dysfunction, a complex methodology that cannot be widely used in the daily routine of an ED.

Lichtenstein and Mezière[34] introduced a different ultrasonography bedside method to be applied in critically ill patients with severe acute respiratory failure, the Bedside Lung Ultrasound in Emergency (BLUE) protocol. This protocol allows diagnosis of PE based on a positive vein ultrasonography in combination with the exclusion by lung ultrasonography of other causes of respiratory failure, like interstitial syndrome, pneumothorax, or pneumonia. The BLUE protocol showed a sensitivity of 81% for PE. Similarly, Volpicelli et al[35,36] showed the usefulness of lung ultrasonography in the diagnosis of any pulmonary condition in patients with acute pleuritic pain. The two methodologies have been validated on specific populations that represent only a small part of the total population tested for PE in emergency. However, these studies on patients with severe respiratory failure and pleuritic pain show that lung ultrasonography may allow diagnoses alternative to PE. Interestingly, in our study, an alternative ultrasonography diagnosis to PE was detected in almost one-third of patients. None of these patients with an alternative ultrasonographic finding had PE, thus showing an added value of lung and heart ultrasonography in emergency (Fig 1). Similarly, none of the patients with negative multiorgan ultrasonography for PE combined with negative D-dimer results had PE as final

Table 3—*Accuracy of Lung, Heart, Veins, and Multiorgan Ultrasonography for the Diagnosis of PE*

Ultrasonography	Sens % (95% CI)	Spec % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	−LR (95% CI)
Lung	60.9 (51.1-70.1)	95.9 (92.7-98)	87 (77.4-93.6)	84.6 (79.9-88.7)	15 (8-28.1)	0.4 (0.3-0.5)
Heart[a]	32.7 (24.1-42.3)	90.9 (86.6-94.2)	62.1 (48.4-74.5)	74.8 (69.5-79.7)	3.6 (2.2-5.8)	0.7 (0.6-0.8)
Vein	52.7 (43-62.3)	97.6 (94.8-99.1)	90.6 (80.7-96.5)	82.2 (77.4-86.4)	21.7 (9.7-48.8)	0.5 (0.4-0.6)
Multiorgan	90 (82.8-94.9)	86.2 (81.3-90.3)	74.4 (66.1-81.6)	95.1 (91.4-97.5)	6.5 (4.8-8.9)	0.12 (0.07-0.2)
Negative multiorgan, plus alternative diagnosis	100 (96.7-100)	42.9 (36.7-49.3)	43.8 (37.6-50.2)	100 (96.5-100)	1.75 (1.6-1.9)	0

−LR = negative likelihood ratio; NPV = negative predictive value; +LR = positive likelihood ratio; PPV = positive predictive value; Sens = sensibility; Spec = specificity. See Table 2 legend for expansion of other abbreviation.
[a]Calculated in 352 patients with available heart ultrasonography.

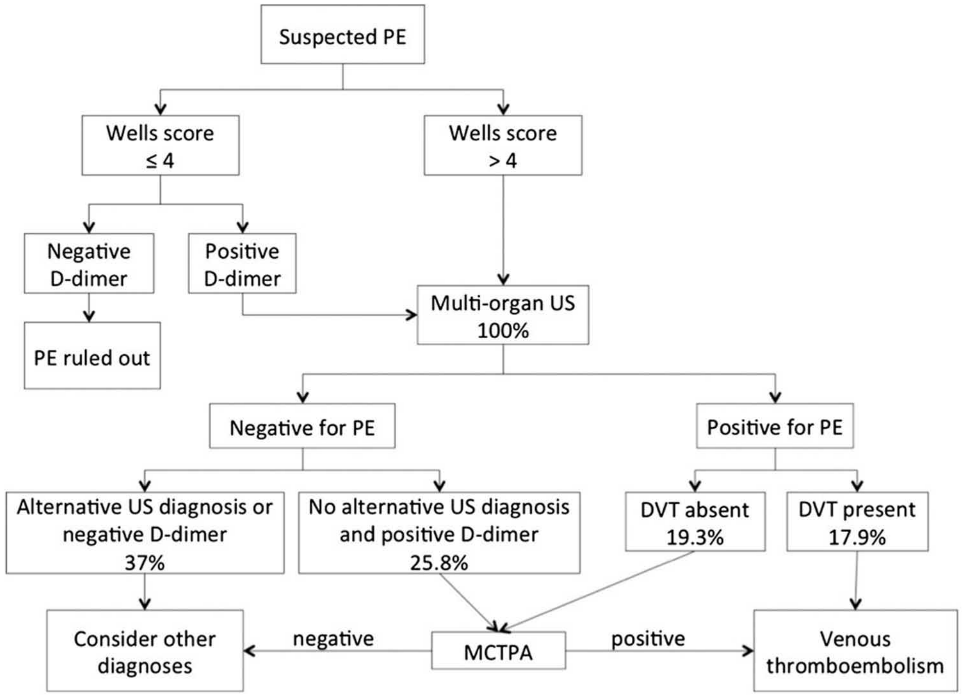

Figure 3. Proposed diagnostic algorithm for suspected PE based on Wells score, D-dimer, multiorgan US, and MCTPA. Percentage (%) refers to the 357 included patients. See Figure 1 legend for expansion of abbreviations.

diagnosis, thus indicating the possibility of a novel pretest strategy for PE in patients with positive Wells scoring.

According to international guidelines, a second-level diagnostic test in emergency is not necessary in symptomatic patients with suspected PE and DVT detected at vein ultrasonography.[19] Adding patients with a diagnosis of DVT to those with multiorgan ultrasonography negative for PE and an alternative ultrasonography diagnosis or a negative D-dimer result, we identify about 50% of our population suspected of PE who might safely avoid submission to MCTPA. Guidelines suggest the use of compression vein ultrasonography in suspected DVT[37]; similarly, we propose a diagnostic algorithm based on multiorgan ultrasonography for patients with suspected pulmonary embolism that could be tested in further studies (Fig 3).

Limitations and Conclusions

Multiorgan ultrasonography tests were performed in the ED by emergency physicians with at least 2 years' experience in ultrasonography. Application of the same methodology by physicians with less experience may lower accuracy and safety. Moreover, the accuracy of multiorgan ultrasonography performed in different settings, such as inpatient or outpatient clinics, may be different. Another note is that patients with contraindications to MCTPA were excluded from our study.

Multiorgan ultrasonography is a bedside method, feasible in almost all patients presenting to the ED with suspected PE and it may be a valuable tool to better select patients who should undergo MCTPA. Moreover, the multiorgan ultrasonography approach represents a more effective and reliable alternative than single-organ ultrasonography, when MCTPA is not available or not feasible.

Acknowledgments

Author contributions: Dr Nazerian is the guarantor of the manuscript.

Dr Nazerian: contributed to study conception and design and data acquisition, analysis, and interpretation; drafted the manuscript; edited the manuscript for important intellectual and scientific content; served as the principal author; edited the revision; and approved the final draft.

Dr Vanni: contributed to study conception and design, conducted statistical analysis, drafted the manuscript, edited the revision, and approved the final draft.

Dr Volpicelli: contributed to study design and data acquisition, drafted and edited the manuscript for important intellectual and scientific content, edited the revision, and approved the final draft.

Dr Gigli: contributed to data acquisition, conducted statistical analysis, edited the revision, and approved the final draft.

Dr Zanobetti: contributed to data acquisition, analysis, and interpretation and approved the final draft.

Dr Bartolucci: contributed to data acquisition and approved the final draft.

Dr Ciavattone: contributed to data acquisition and approved the final draft.

Dr Lamorte: contributed to data acquisition and approved the final draft.

Dr Veltri: contributed to data acquisition and approved the final draft.
Dr Fabbri: contributed to data acquisition and approved the final draft.
Dr Grifoni: contributed to data analysis and interpretation and approved the final draft.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Other contributions: We thank all of the patients who participated in the study and other staff physicians and nurse staff who assisted with the study. The work was performed at the following institutions: Careggi University Hospital, Firenze; San Luigi Gonzaga University Hospital, Torino; and Pierantoni Morgagni Hospital, Forlì, Italy.
Additional information: The e-Figures and Videos can be found in the "Supplemental Materials" area of the online article.

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