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Diagnostic performance of Wells score combined with point-of-care lung and venous ultrasound in suspected pulmonary embolism

Author list

Peiman Nazerian, MD, Giovanni Volpicelli, FCCP, Chiara Gigli, MD, Cecilia Becattini, PhD, Giuseppe Francesco Sferrazza Papa, MD, Stefano Grifoni, MD**,** Simone Vanni, PhD, on behalf of the Ultrasound Wells study group

Authors' affiliations

Department of Emergency Medicine (Dr. Nazerian, Dr. Gigli, Dr. Vanni, Dr. Grifoni), Careggi University Hospital, Firenze, Italy;

Department of Emergency Medicine (Dr. Volpicelli), San Luigi Gonzaga University Hospital, Torino, Italy;

Department of Internal Medicine (Dr. Becattini), University Hospital of Perugia, Perugia, Italy;

Respiratory Unit, Dipartimento Scienze della Salute (Dr. Sferrazza Papa), San Paolo Hospital, Università degli Studi di Milano, Milano, Italy;

Casa di Cura del Policlinico, Dipartimento di Scienze Neuroriabilitative (Dr. Sferrazza Papa), Milano, Italy;

Ultrasound Wells study group and affiliations

Department of Emergency Medicine (Marco Vittorini, MD, Michele Baioni, MD, Mirco Donati, MD), Careggi University Hospital, Firenze, Italy;

Department of Emergency Medicine (Emanuela Gambetta, MD, Mattia Tullio, MD, Alessandro Lamorte, MD), San Luigi Gonzaga University Hospital, Torino, Italy;

Department of Internal Medicine (Valentina Salvatori, MD), University Hospital of Perugia, Perugia, Italy;

Respiratory Unit, Dipartimento Scienze della Salute (Stefano Centanni, MD, PhD, Fabrizio Nava, MD), San Paolo Hospital, Università degli Studi di Milano, Milano, Italy;

Department of Respiratory Medicine (Dr Chatziantoniou, MD), University Hospital of Heraklion, Heraklion, Greece.

Institutions at which the work was performed

- Careggi University Hospital, Firenze, Italy

- San Luigi Gonzaga University Hospital, Torino, Italy

- San Paolo University Hospital, Milano, Italy

- University Hospital of Perugia, Perugia, Italy

Corresponding author:

Peiman Nazerian, M.D.

Department of Emergency Medicine, Careggi University Hospital, largo Brambilla 3

50134 Firenze, Italy

Email: pnazerian@hotmail.com

Running title

Ultrasound enhanced Wells score in pulmonary embolism

Keywords

Pulmonary embolism; Wells score; ultrasound; prediction rule; diagnosis

Conflict of interest disclosure

P. N., G. V., C. G., C. B., G. S., S. G., S. V. report no conflict of interest.

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ABSTRACT

Objective: Lung and venous ultrasound are bedside diagnostic tools increasingly used in the early diagnostic approach of suspected pulmonary embolism (PE). However, the possibility of improving the conventional prediction rule for PE by integrating ultrasound has never been investigated.

Methods: We performed lung and venous ultrasound in consecutive patients suspected of PE in four emergency departments. Conventional Wells score (Ws) was adjudicated by the attending physician, and ultrasound was performed by one of 20 investigators. Signs of deep venous thrombosis (DVT) at venous ultrasound and signs of pulmonary infarcts or alternative diagnoses at lung ultrasound were considered to re-calculate two items of the Wells score: signs and symptoms of DVT and alternative diagnosis less likely than PE. The diagnostic performances of the ultrasound-enhanced Ws (USWs) and Ws were then compared after confirmation of the final diagnosis.

Results: 446 patients were studied. PE was confirmed in 125 patients (28%). USWs performed significantly better than Ws, with a sensitivity of 69.6% vs 57.6% and a specificity of 88.2% vs 68.2%. In combination with d-dimer, USWs showed an optimal failure rate (0.8%) and a significantly superior efficiency than Ws (32.3% vs 27.2%). A strategy based on lung and venous ultrasound combined with d-dimer would allow to avoid

CT pulmonary angiography in 50.5% of patients with suspected PE, compared to 27.2% when the rule without ultrasound is applied.

Conclusions: A pre-test risk stratification enhanced by ultrasound of lung and venous performs better than Ws in the early diagnostic process of PE.

TEXT

Introduction

Clinical prediction rules are recommended to orientate the diagnostic process of many acute diseases, such as coronary syndromes, heart failure, aortic syndromes and also venous thromboembolic disease. For suspected pulmonary embolism (PE), the international guidelines recommend the use of a combination of d-dimer with clinical scores, such as the Wells score (Ws), to optimize the diagnostic process and the use of computed tomography pulmonary angiography (CTPA) for final confirmation [1–5].

Ultrasound is a safe, rapid and powerful diagnostic tool and the integration of the clinical assessment with point-of-care ultrasound is growingly considered *in the assessment* of acute patients [6]. Moreover, with the advent of portable machines, ultrasound is exponentially used by the clinical care teams in the early evaluation of patients presenting with dyspnea, chest pain, syncope and shock, all conditions where PE is in the differential diagnosis. *The strength of ultrasound is based on its ease of use at bedside and good accuracy when performed by physician with an appropriate training*. Some authors already investigated its diagnostic performance in patients with suspected PE [7–11]. However, apart from the intrinsic diagnostic power of ultrasound in the definitive diagnosis of a complex disease, to date no one investigated the possibility of improving the prediction rules for PE by integrating clinical data with lung and venous ultrasound.

The main aim of this study was to compare the diagnostic performance of the Ws to that of the Ws combined with lung and venous ultrasound (USWs). Furthermore, as secondary outcome, we evaluated whether a diagnostic strategy based on clinical and ultrasound data could safely reduce the use of CTPA.

Methods

Study design and setting

This was an *observational* cohort multicenter *diagnostic accuracy study*. Study patients were recruited from July 2014 to April 2015 in the Emergency Departments (EDs) of four Italian university hospitals *staffed with 14, 20, 22 and 45 ED beds. The four EDs had an annual census of 50000, 50000, 80000 and 100000 visits and an admission rate of 10%, 15%, 13% and 12% respectively.* The local ethic committees approved the study. Written informed consent was obtained for inclusion in the study. The study was registered on ClinicalTrials.gov (No.: NCT02190110).

Study protocol and population

Consecutive patients, older than 18 years, *presenting with dyspnea, chest pain, syncope and palpitations* with suspected acute PE were considered eligible for the study. The suspicion of PE was subjectively established by the attending physician after the initial standard evaluation which included medical history, physical examination and electrocardiogram in all patients and arterial blood gas analysis and chest X-ray when requested for clinical reasons. The attending physician adjudicated the scores of the Ws items (e-Figure 1) and gave notification to the sonographer investigator. Patients not studied by ultrasound within three hours from enrollment were excluded. The attending physician, blinded to ultrasound results, ordered a multidetector CTPA, or scintigraphy in alternative, independently from the patient's enrollment and in accordance to the standard

of care recommended by international guidelines [1–3]. High sensitive d-dimer was part of the routine evaluation of patients suspected of PE and was considered negative based on the cut-off value (not aged adjusted) of each center.

Ultrasound examination

Lung and venous ultrasound were performed by one of 20 sonographer investigators. They were 8 senior physicians (seven internal medicine specialists and one pulmonologist) and 12 residents in internal medicine, emergency medicine or pulmonology with at least six months experience in lung and venous ultrasound *produced on their own*. *This practical personal experience was always preceded by a teaching course in emergency ultrasound, continued by a period of training assisted by an expert including a minimum of 30 lung and 30 venous ultrasound examinations*. Investigators were blinded to diagnostic tests and to all the clinical information except symptoms of presentation and visible physical signs. Ultrasound exams were performed using the following multi-probe machines: three MyLab30 Gold, one MyLab40, one Mylab50 and one Mylab alpha (Esaote SpA), one Logiq3 and one Logiq5 Pro (General Electric) and one HD7 (Koninklijke Philips N.V.). Lung and veins were studied according to predefined ultrasound protocols. *The effective time needed to perform the exam was recorded without considering machine positioning and switch on procedure.* Lung was examined by longitudinal and oblique scans on anterior-lateral and posterior thoracic areas by convex or linear probes *based on investigator convenience*. The anterior-lateral examination was performed with the patient in the supine or near-to-supine position. When feasible, dorsal areas were scanned in the sitting position or by turning the patient in the lateral decubitus on both sides in case of forced supine position. The examination was targeted to the detection of pulmonary infarcts. Pulmonary infarcts were defined as pleural-based, well-demarcated and echo-poor triangular or rounded consolidations of at least 0.5 cm in main diameter [9]. Other

pre-defined findings, consistent with alternative diagnoses that might explain the symptoms of presentation, were lung consolidations suggestive of pneumonia, pleural effusion and diffuse interstitial syndrome. All the above mentioned findings were defined and diagnosed according to international recommendations on point-of-care lung ultrasound [12]. *Pleural effusion, when not associated to a pulmonary infarct was never considered diagnostic for PE. Rather, a large isolated pleural effusion in a dyspnoic patient or an effusion combined with a consolidation and a complex ultrasound pattern typical of infection were considered alternative diagnosis.* Leg venous ultrasound was performed using a linear probe. The femoral veins and the popliteal veins were visualized in short-axis and compressed. Deep venous thrombosis (DVT) was defined by the absence of total collapse of the vein during compression. After the completion of lung and venous ultrasound examination, the investigators completed the ultrasound standardized form (e-Figure 2).

Wells and ultrasound-enhanced Wells scores

On the basis of ultrasound signs detected by the sonographer, two items of the Ws were re-calculated: the item “signs and symptoms of DVT” was replaced by “venous ultrasound positive for DVT”. The item “alternative diagnosis less likely than PE” was replaced by “alternative diagnosis less likely than PE after lung ultrasound” (Table 1). The latter item was considered positive and assigned three points if at least one pulmonary infarct was visualized at lung ultrasound, whereas it was assigned zero points in absence of infarcts and if a condition of ultrasonographic findings compatible with an alternative pulmonary diagnosis was detected. If lung ultrasound was normal, the assigned points remained those considered in the conventional Ws. The diagnosis of PE was considered “unlikely” for scores ≤4, both for Ws and USWs.

In a non-randomized subgroup of patients, we calculated the inter-observer agreement of the two items reported above for Ws and USWs. To this purpose, the subgroup was selected based on a convenience sampling *when two sonographers were available to perform the ultrasound exam in the same patient within the time limit*. Each patient of this subgroup was independently scanned by two sonographers, who filled the ultrasound form in a blinded fashion, while the items of the Ws were independently assigned by two attending physicians.

Gold standard for pulmonary embolism diagnosis

Multidetector CTPA (≥64 row-detectors) was the primary second level diagnostic imaging test used in all enrolling centers. If CTPA was contraindicated due to contrast medium allergy or severe renal failure, lung scintigraphy was scheduled. After the conclusion of this first diagnostic process, patients entered a three months follow-up. *All included patients were asked to contact the ED, in case of new, worsening or recurrent symptoms after discharge from the hospital.*

PE diagnosis was established only upon confirmation by a second level diagnostic imaging test performed in the ED or during the time course of the follow-up. This latter had three main characteristics: 1) *post-hoc* evaluation of the clinical chart in admitted patients at the end of the three months; 2) ~~fixing a control~~ visit at the end of the follow-up; 3) phone interview at the end of the follow-up and request to communicate any change during the time course. In patients who died before the diagnostic completion, PE was considered the cause of death only when confirmed by autopsy or when the cause remained unexplained and PE could not be confidently ruled out. In each center, final diagnosis was established by a physician expert in PE diagnosis who, blinded to study results, reviewed all the clinical and imaging data obtained in ED, during hospitalization and follow-up.

Data analysis

Data are expressed as mean ± standard deviation. The sample size calculation is based on a one-sided McNemar's test assuming a sensitivity of 60% of the Ws [13], a prevalence of acute PE of 25%, and an alpha error of 1%. Based on these assumptions, the minimal number of patients needed to detect a 10% increase in sensitivity of USWs with a power of 80% is 392. Unpaired Student's T-test was used to compare normally distributed data. Fisher's exact test was used for comparison of non-continuous variables expressed as proportions. P value <0.05 indicates statistical significance. All p-values are two-sided. The extended McNemar and the McNemar test were used to evaluate if there was significant difference in the sensitivities and specificities of Ws and USWs [14]. The contribution of each ultrasound item was studied by plotting the receiver operating characteristic (ROC) curves of Ws, Ws plus venous ultrasound, Ws plus lung ultrasound and USWs as a whole [15]. The k statistic was calculated to assess interobserver agreement [16].

To evaluate a diagnostic strategy to rule-out PE, the failure rate and the efficiency of d-dimer in patients with Ws or USWs unlikely were calculated. Failure rate (false negative proportion) was calculated as the number of patients with a negative d-dimer and a final diagnosis of PE divided by all patients with negative d-dimer in the unlikely groups. Efficiency was defined as the proportion of patients with negative d-dimer combined with Ws unlikely or USWs unlikely among study patients.

Calculations were performed with the use of SPSS statistical package (version 17.0, SPSS Inc., Chicago, Illinois). The study had no funding source.

Results

Study population

Out of 491 patients considered for the study, 446 patients were included in the final analysis (Figure 1). CTPA was performed in 297 (66.6%) whereas lung scintigraphy in 9 patients (2%). PE was confirmed in 125 (28%) patients (Table 2). Diagnosis of PE was established in 119 patients by CTPA, in five by lung scintigraphy and in one by autopsy. Characteristics of patients with and without PE are shown in Table 3.

Ultrasound-enhanced Wells score vs Wells score

USWs showed a 12% increase in sensitivity and 22% increase in specificity when compared to Ws ($p<0.01$ for both) (Table 4). The number of patients classified “unlikely” with the Ws was 272 (61%) vs 321 (72%) with USWs ($p<0.01$). In these “unlikely” groups, PE was then diagnosed (false negatives) in 53 (19.5%) in the Ws score group and in 38 (11.8%) when the USWs was applied ($p<0.01$). The analysis of ROC curves showed that the AUCs of Ws combined with only venous ultrasound (76.4%, 95% CI 71.1-81.7%) or Ws combined with only lung ultrasound (77.5%, 95% CI 72.5-82.5%), were significantly better in comparison to the AUC of Ws alone (65.3%, 95% CI 59.4-71.2%) ($p<0.01$ for both). The AUC of the USWs (86.2%, 95% CI 82.1-90.3%) was superior to all these three ($p<0.01$) (Figure 3). USWs overall accuracy was 85% (95% CI 80.7-89.3%) when ultrasound was performed by senior physician and 80% (95% CI 74.2-85.8%) when performed by residents. Interobserver agreement was investigated in a subgroup of 36 patients. Final diagnosis of PE was no statistically different among this group and all included patients. The k values for “signs and symptoms of DVT” and “alternative diagnosis less likely than PE” were 0.65 and 0.51 respectively, whereas the k for the respective ultrasound-enhanced items were 0.94 and 0.79 respectively.

Lung and venous ultrasound

Lung and venous ultrasound were performed in all patients. The time needed for ultrasound examination was 7 ± 3 minutes (mean ± SD). In 40 cases (9%) lung was studied only on anterior-lateral areas due to poor compliance or impossibility to move the patient. Seventy-five (16.8%) patients showed at least one pulmonary infarct at ultrasound, with a mean of 1.6 lesions per patient, and in 57 (76%) of these, PE was confirmed. *Figure 2 shows a pulmonary infarct surrounded by pleural effusion*. *In the 18 (24% of 75) patients with pulmonary infarct detected by lung ultrasound without PE, the final diagnosis were pneumonia in 7 cases, heart failure and tachyarrhythmia in 4, COPD/fibrosis in 2, lung cancer in 2, previous thromboembolic disease in 2 and muscolo-skeletal chest pain in 1.* Sensitivity, specificity, positive and negative predictive value of pulmonary infarct for PE diagnosis were 45.6%, 94.4%, 76% and 81.7%. In the 371 patients without pulmonary infarcts (83.2%), at least one alternative lung ultrasound diagnosis was detected in 176 cases (47.4%). Alternative diagnoses were pleural effusion in 105 cases, pneumonia in 87 and diffuse interstitial syndrome in 66. Out of 85 (19.1%) patients with DVT at venous ultrasound, PE was confirmed in 74 (87.1%), corresponding to 59.2% of all PE patients. Diagnostic performance of venous ultrasound is reported in Table 3.

Diagnostic strategies to rule out PE based on ultrasound, clinical scores and D-dimer

The diagnostic variables of different strategies to rule out PE, including clinical and ultrasound data without d-dimer and Ws or USWs with d-dimer, are reported in Table 5. Out of 167 patients with lung ultrasound signs of a possible alternative diagnosis, without infarcts and no evidence of DVT at venous ultrasound, PE was still diagnosed in 12 (7.2%). PE was also diagnosed in seven (5.9%) of 119 patients with a USWs=0.

In 396 (88%) patients, d-dimer was available for statistical analysis, of whom 248 with Ws unlikely and 288 with USWs unlikely. The failure rate (0.8%) of USWs ≤ 4 and negative d-dimer was half the failure rate of Ws ≤ 4 and negative d-dimer (1.9%) (p=0.33). Efficiency of USWs plus d-dimer (32.3%) was significantly superior (+5.1%) to Ws plus d-dimer (27.2%) (p<0.01).

Discussion

This multicenter study demonstrated that integration of an ultrasound study of lung and leg veins improves the accuracy of a pre-test probability score in the diagnostic process of PE at bedside. The accuracy of Ws was significantly increased when the item "signs and symptoms of DVT" was replaced by "venous ultrasound positive for DVT" and the item "alternative diagnosis less likely than PE" was replaced by "alternative diagnosis less likely than PE after lung ultrasound". The best accuracy was obtained when results from both lung and venous ultrasound were considered. In our study, we used a point-of-care ultrasound technique that was easy to learn by the operators, low cost, and non-invasive. All these characteristics potentially make this technique suitable for a wide use as an extension of the physical examination in the acute care setting. Notably, lung and venous ultrasound were rapidly feasible in all patients by a large number of physicians with different skills, expertise and professional background.

Two items of the Ws, the probability of PE and clinical signs of DVT, are based on considerations that are strictly subjective and the risk of high variability when physicians with different experience and skills adjudicate these two items is concrete [17–20]. In the proposed USWs, the two substitute items supported by an early ultrasound study of lung and veins represent the objective transposition of the probability of PE (direct visualization of pulmonary infarction or signs of alternative diagnoses) and DVT (definitive confirmation of the diagnosis). Indeed, the interobserver

agreement of the ultrasound signs was significantly superior to the clinical judgment in the present experience and in comparison to a previous study [20].

Accordingly to previous studies, to validate the safety of a diagnostic strategy to rule out PE, the upper limit of the 95% CI around the failure rate should not be higher than 3% [21–25]. Guided by this limit, *we also investigated different strategies to rule out PE and whether these strategies may allow reducing safely the number of CTPA performed in emergency (Table 5).* The strategies based on ultrasound without d-dimer (USWs=0 or lung ultrasound signs of alternative diagnosis, without infarcts and no evidence of DVT at venous ultrasound) showed to be not sufficiently safe. However, our study showed that in the group of patients with USWs unlikely, a negative d-dimer could safely rule out PE with the upper limit of the 95% CI fairly below the limit of 3% (2.3%). These results show that d-dimer is still needed even when ultrasound is used to enhance the clinical prediction rule. *In patients with Wells score unlikely, a negative d-dimer showed a 95% CI upper limit around the failure rate of 4.5%. We have to report that a diagnostic strategy based on US Wells score and d-dimer obtained a non-statistically significant decrease in the failure rate when compared with Wells score plus d-dimer (0.8% vs 1.9%).*

In the diagnostic process, we also analyzed the potential of lung and venous ultrasound to rule in PE. Our study, confirmed the high specificity of the ultrasound lung examination for infarcts reported in a recent metanalysis [26]. However, the positive predictive value was still inadequate to rule in PE without the need for a confirmative second level diagnostic test, as we had 18 false positive patients on lung ultrasound who would have been improperly treated with anticoagulants. Thus, combination with other data and imaging tools should be considered before final confirmation. Regarding venous ultrasound, a positive proximal compression technique showed a high positive predictive value for PE. Indeed, the ultrasound diagnosis of proximal DVT in patients suspected of

PE is already considered sufficient for final confirmation in emergency by the societal guidelines, and warrants anticoagulant treatment without further testing [1–3,7]. Salaun et al. investigated the application of leg venous ultrasound in suspected PE, but only when performed by specialists in vascular ultrasound [27]. In their study, 13% of patients with positive DVT, corresponding to 44% of all PE, concluded the diagnostic process for PE without CTPA. The novelty of our approach is that venous ultrasound is applied as part of a rapid point-of-care ultrasound technique in the hands of physicians with different background and not depending on external consultations of vascular specialists or radiologists. *Even if ultrasound confirmation of DVT in our USWs is not sufficient alone to give high probability (score 3), it remains a criterion to conclude the process and start treatment according to societal guidelines. Indeed, diagnosis of DVT not necessarily coincide with PE but demands starting anticoagulation.*

In Figure 4 we propose a new diagnostic strategy that integrates USWs and d-dimer that has to be validated in further studies specifically designed. The proposed integration with ultrasound allows to avoid a number of CTPA that is superior to the conventional approach (50.5% vs 27.2%). This difference is based on a better performance of USWs to rule out PE (USWs “unlikely" combined with negative d-dimer) and on the possibility to avoid CTPA when DVT is diagnosed by venous ultrasound.

Limitations

Our study did not consider other validated prediction rules. However, a recent metanalysis comparing the Ws to the revised Geneva score demonstrated a superior accuracy of the former [28]. In a metanalysis by Lucassen et al. [13], the sensitivity of the dichotomized Ws was close to that obtained in our study, whereas the specificity was superior. The high interoperator variability of two items of the Ws, confirmed in our study,

may have an influence on the discrepancy found in different studies. The aim of our study was to validate a basic ultrasound technique for the first examination of patients suspected of PE. It was necessary to assure the possibility of a wide diffusion based on ease and efficiency of implementation among physicians with different levels of skills and experience, still maintaining enough reliability and safety. For this reason, we chose to exclude cardiac ultrasound and to involve a high number of ultrasound operators. Such choices have some limitations. Firstly, including a cardiac examination might further increase the accuracy of our ultrasound approach. Indeed, a multiorgan ultrasound approach that includes the cardiac evaluation showed to be useful in the diagnosis of PE in previous studies [10,11]. However, cardiac ultrasound is not feasible in all patients due to the concrete possibility of poor ultrasound windows, in addition to being far more time-consuming and needing a longer educational training than lung and venous ultrasound. An ultrasound approach limited to lung and veins is more practical as a first level strategy. Secondly, we cannot exclude that the accuracy of lung and venous ultrasound obtained in our study may had been improved by involving only few operators with very high ultrasound skills and experience. However, involving a large number of physicians with different background and experience better represents the daily practice of the ED. *Moreover, although the technique used has proved to be of simple acquisition and application, there are still challenges and uncertainty associated with a rapid learning process and accuracy variability in different institutions and staffs. A correct and effective skill acquisition and sufficient practice should always precede the application of lung and venous ultrasound in the diagnostic process of PE. The rate of PE in this study was high (28%) and it is not know how would be the performance of Ws enhanced by lung and venous ultrasound in a population with lower PE incidence. Chest x-ray is an inexpensive and rapid diagnostic imaging test routinely used in the ED, in fact about two third of enrolled patients underwent chest x-ray. The treating physician when assigning the Ws*

item "alternative diagnosis less likely than PE" was influenced by chest x-ray results, however a specific evaluation of the diagnostic accuracy of "chest x-ray enhanced" Ws was not performed. Lastly, we have to highlight that the main aim of the study was to compare the diagnostic performance of USWs with Ws and that the study was not powered to evaluate the performance of a diagnostic strategy based on USWs plus d-dimer, therefore for this purpose the study can be considered only hypothesis generating.

Conclusions

In patients with suspected PE, point-of-care lung and venous ultrasound is feasible, rapid, and increases the accuracy of the conventional Wells score. However, integration with the d-dimer is still needed. A diagnostic strategy, which integrates clinical information, lung and venous ultrasound and d-dimer, may increase the performance of risk stratification and may reduce the use of CTPA in the diagnostic approach to PE, still maintaining an acceptable safety profile.

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Tables

Table 1. Items of the Wells score and ultrasound-enhanced Wells score

Wells score	**US Wells score**	**Points**
Signs and symptoms of DVT	Venous ultrasound positive for DVT	+ 3
Alternative diagnosis less likely than PE	Alternative diagnosis less likely than PE after lung ultrasound	+ 3
Heart rate >100 bpm		+ 1.5
Immobilization > 3 days, or surgery in the previous 4 weeks		+ 1.5
Previous, objectively diagnosed PE or DVT		+ 1.5
Haemoptysis		+ 1
Malignancy on treatment, treated within 6 months, or in palliative therapy		+ 1

DVT= deep venous thrombosis, PE= Pulmonary Embolism

Table 2. Final diagnosis in the study patients

Pulmonary embolism	125 (28%)
Pneumonia	73 (16.4%)
Heart failure	52 (11.7%)
Muscolo-skeletal chest pain	47 (10.5%)
COPD / pulmonary fibrosis	46 (10.3%)
Pleural effusion	20 (4.5%)
Syncope	16 (3.6%)
Tachyarrhythmia	15 (3.4%)
Acute coronary syndrome	13 (2.9%)
Lung cancer	11 (2.5%)
Psychogenic dyspnea	10 (2.2%)
Miscellaneous	18 (4%)

COPD= Chronic Obstructive Pulmonary Disease

Table 3. Characteristics of the study population according to final diagnosis

		PE negative (n=321)	**PE positive (n=125)**	**p value**
Mean age ± SD		69.5 ± 16.7	68.9 ± 18.5	0.778
Women		167 (52%)	70 (56%)	0.462
Symptoms of presentation				
Dyspnea		187 (58.3%)	91 (72.8%)	0.005
Chest pain	total	137 (42.7%)	38 (30.4%)	0.018

	pleuritic	105 (32.7%)	29 (23.2%)	1
Syncope		33 (10.3%)	15 (12%)	0.612
Palpitations		28 (8.7%)	11 (8.8%)	1
Wells score items				
Signs and symptoms of DVT		53 (16.5%)	44 (35.2%)	<0.001
Alternative diagnosis less likely than PE		127 (39.6%)	68 (54.4%)	0.006
HR >100 bpm		84 (26.2%)	38 (30.4%)	0.408
Immobilization or surgery		65 (20.2%)	29 (23.2%)	0.519
Previous DVT or PE		32 (10%)	33 (26.4%)	<0.001
Hemoptysis		12 (3.8%)	4 (3.2%)	1
Malignancy		45 (14%)	30 (24%)	0.016
Positive d-dimer *		148 (46.1%)	105 (84%)	<0.001

Data are presented as No. (%) or mean ± Standard Deviation (SD); DVT= deep venous thrombosis, PE= Pulmonary Embolism, HR= Heart Rate
*Calculated in 396 patients with available d-dimer level, of whom 111 patients with PE and 285 without PE.

Table 4. Accuracy of the Wells score, US Wells score and of the first two items of the Wells score and of the US Wells score for the diagnosis of PE

	Sens % (95% CI)	**Spec % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**
Wells score > 4	57.6% (48.4-66.4)	68.2% (62.8-73.3)	41.4% (34-49.1)	80.5% (75.3-85.1)	1.81 (1.46-2.26)	0.62 (0.50-0.77)
Signs and symptoms of DVT	35.2% (26.9-44.3)	83.5% (79-87.4)	45.4% (35.2-55.8)	76.8% (72-81.1)	2.13 (1.51-3)	0.78 (0.68-0.89)

Alternative diagnosis less likely than PE	54.4% (45.3-63.3)	60.4% (54.9-65.8)	34.9% (28.2-42)	77.3% (71.6-82.3)	1.37 (1.11-1.7)	0.75 (0.61-0.93)
US Wells score >4	69.6% (60.7-77.5)	88.2% (84.1-91.5)	69.6% (60.7-77.5)	88.2% (84.1-91.5)	5.88 (4.27-8.1)	0.34 (0.26-0.45)
Venous US positive for DVT	59.2% (50.1-67.9)	96.6% (94-98.3)	87.1% (78-93.4)	85.9% (81.9-89.3)	17.3 (9.49-31.44)	0.42 (0.34-0.52)
Alternative diagnosis less likely than PE after lung US	62.4% (53.3-70.9)	86.6% (82.4-90.1)	64.5% (55.3-73)	85.6% (81.2-89.2)	4.66 (3.42-6.35)	0.43 (0.34-0.55)

US Wells score= Based on lung and veins ultrasound; PE= Pulmonary embolism. DVT= Deep vein thrombosis. Sens= Sensitivity; Spec= Specificity; PPV= Positive predictive value; NPV= Negative predictive value; +LR= Positive likelihood ratio; -LR= Negative likelihood ratio; 95% CI= 95% confidence interval

Table 5. Diagnostic variables of four strategies to rule out pulmonary embolism: US Wells score=0, lung and venous US and Wells score and US Wells score unlikely combined with negative d-dimer

	US Wells score = 0	**Lung and venous US***	**Wells score ≤ 4 and negative d-dimer†**	**US Wells score ≤ 4 and negative d-dimer†**
Failure rate^ % (95% CI)	5.9 (1.7-10.1)	7.2 (3.3-11.1)	1.9 (0.4-5)	0.8 (0.7-2.3)
Efficiency+ % (95% CI)	26.7 (22.6-30.8)	37.4 (32.9-41.9)	27.2 (22.8-31.6)	32.3 (27.7-37)
Sensitivity % (95% CI)	94.4 (88.8-97.7)	90.4 (83.8-94.9)	98.2 (93.2-99.8)	99.1 (95.1-100)
Specificity % (95% CI)	34.9 (29.7-40.4)	48.3 (42.7-53.9)	36.8 (31.2-42.7)	44.6 (38.7-50.5)
PPV % (95% CI)	36.1 (30.9-41.6)	40.5 (34.7-46.5)	37.7 (32.1-43.6)	41 (35.1-47.2)
NPV % (95% CI)	94.1 (88.3-97.6)	92.8 (87.8-96.2)	98.1 (93.4-99.8)	99.2 (95.7-100)

US Wells score= Based on lung and venous ultrasound; PPV= Positive predictive value; NPV= Negative predictive value; 95% CI= 95% confidence interval.
***** No pulmonary infarcts plus an alternative diagnosis at lung US and no deep venous thrombosis at venous US
† Calculated in 396 patients with available d-dimer
^ Calculated as the number of patients within the group with a final diagnosis of PE divided by all patients in the same group
+ Calculated as the number of patients within the group divided by all included patients

Figure legend

Figure 1. Flow diagram of the study and main results

PE = Pulmonary embolism; US = Ultrasound; % refers to the box above

Figure 2. Pulmonary infarct surrounded by a small pleural effusion detected by lung ultrasound in the right posterior thoracic area of a 60 years old patient presenting with dyspnea and right pleuritic chest pain.

Figure 3. ROC curve for Wells score, Wells score plus lung or venous US and US Wells score

US = Ultrasound

Figure 4. Proposed diagnostic algorithm for suspected PE based on venous US, US Wells score and d-dimer

PE = Pulmonary embolism; US =Ultrasound; DVT = Deep venous thrombosis; CTPA = computed tomography pulmonary angiography. *Patients with available d-dimer level;

† Of whom 1 patient had a final diagnosis of PE; ^ Of whom 45 patients had a final diagnosis of PE. % refer to 396 patients

Additional figure legend for web-only publication

E-figure 1. Wells score standardized form fulfilled by the attending physician

E-figure 2. Lung and venous ultrasound standardized form fulfilled by the sonographer investigator

Figure 1

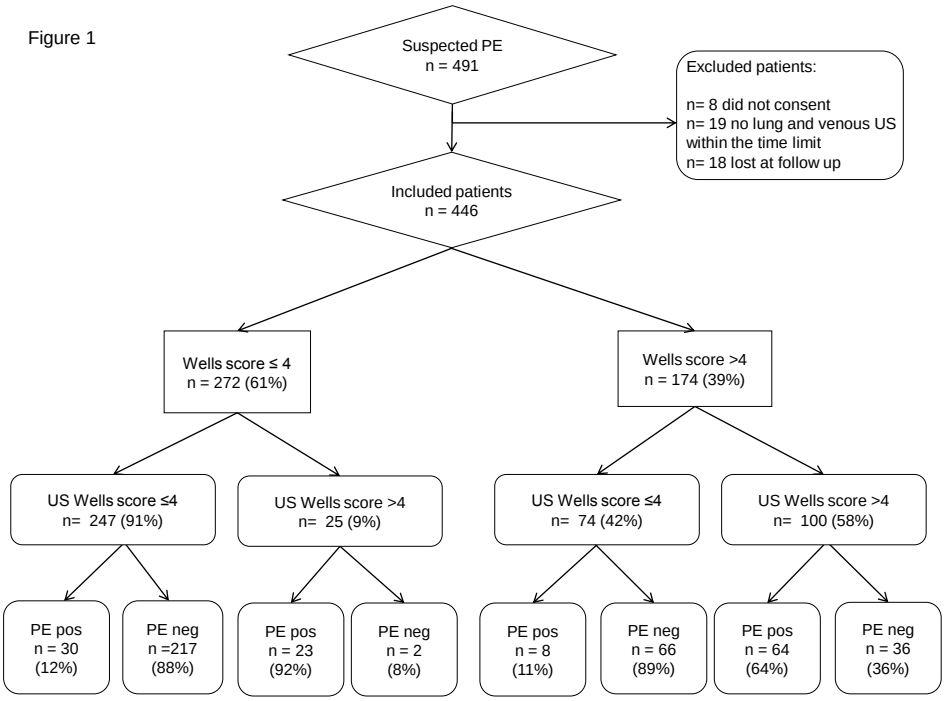

Figure 2

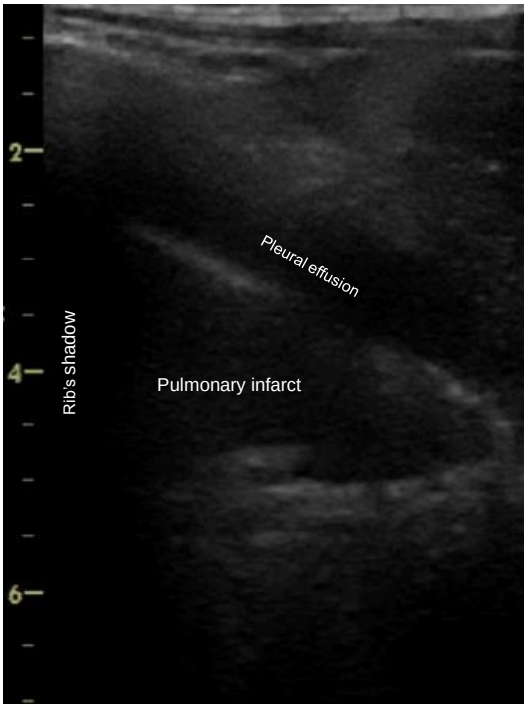

Figure 3

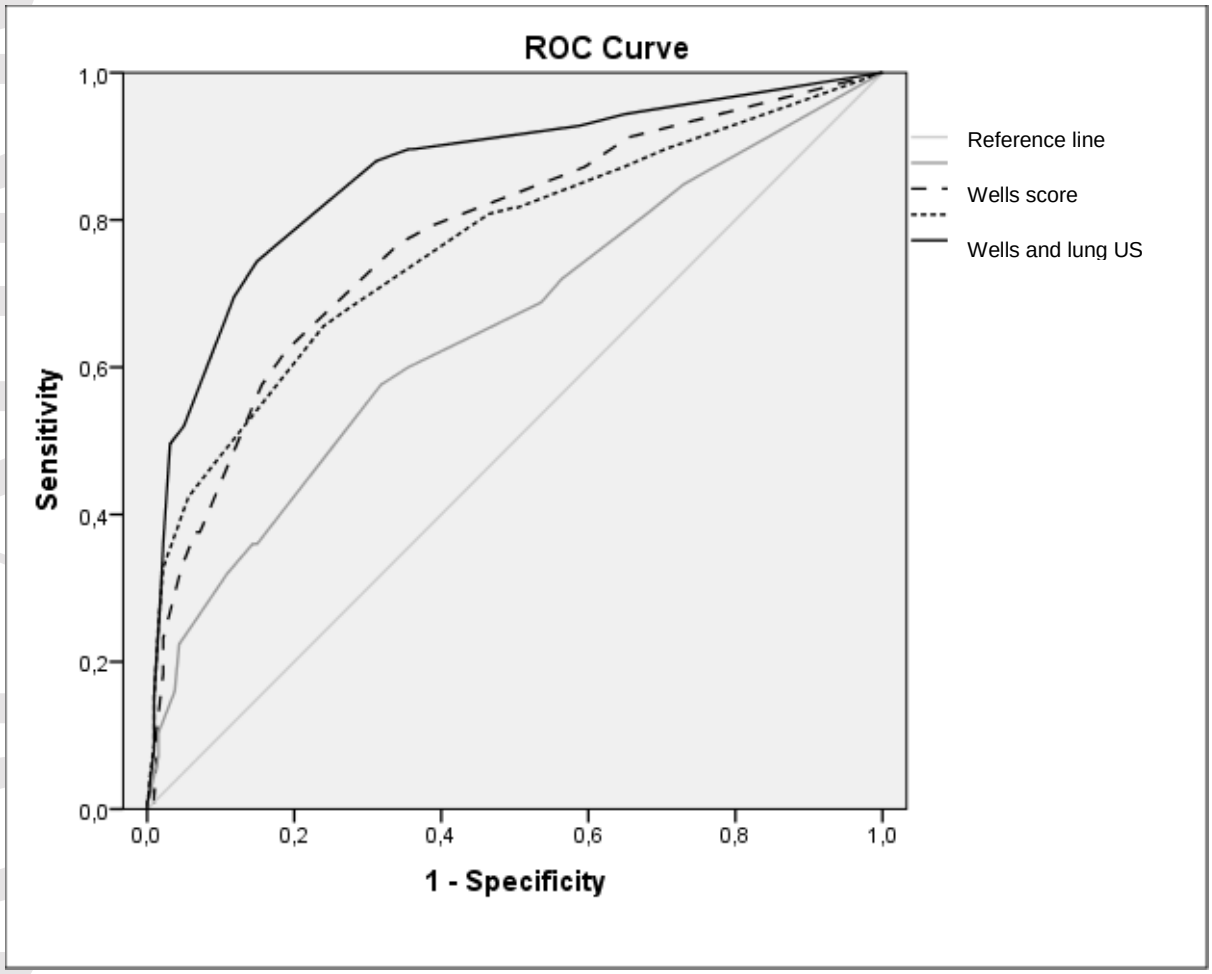

Figure 4