Clinical value of thoracic ultrasonography in the diagnosis of pulmonary embolism: a systematic review and meta-analysis

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Introduction

Pulmonary embolism (PE) is a common and often deadly disease that is often misdiagnosed [1]. Although the awareness regarding PE has been increased and the diagnostics have been improved, a considerable number of fatal PEs have not been diagnosed until autopsy [1-3]. It is estimated that 1.35 million Americans suffer from PE every year [4]. Short-term mortality is widely varied, ranging from 2.5% to as high as 33% [5-7]. Pulmonary embolism causes 25,000 people in the U.S. to be admitted to hospitals and about 60,000 die from it annually [8].

For a long time, there has been no epidemiological data of PE in Chinese communities. A previous study comprehensively evaluated the incidence of PE in Chinese hospitals from 1997 to 2008. Of the total 16,972,182 hospital admissions, 18,206 patients were diagnosed with PE and the annual incidence was 0.1% (95% CI 0.1–0.2%) [9].

Computed tomography pulmonary angiography (CTPA) is the international and widely accepted gold standard to investigate patients with suspected pulmonary embolism [10]. CTPA is readily available in most of the hospitals and has been proved to be highly sensitive and specific to PE when compared with the traditional invasive pulmonary angiography (PA). However, several problems were raised for lowering the threshold and increasing the frequency of CTPA use. Firstly, the overuse of CTPA as the one and only diagnostic test for patients with suspected PE resulted in a very low prevalence of PE diagnosis (<10%) [11]. This low diagnostic rate seems to be consistent with the trend of overdiagnosis, because an increase in the incidence of PE was observed after the introduction of CTPA, with little changes in the mortality rate [12]. Secondly, there is a growing concern about
the long-term radiation complications, allergic reactions to iodine contrast agents and kidney diseases caused by contrast agents [13-15].

Thoracic ultrasonography (TUS) was first described 50 years ago to detect pulmonary thromboembolic lesions [16,17]. In recent years, TUS has been used as a diagnostic tool to complement traditional radiographic methods in the diagnosis of a variety of mediastinal and pleural conditions, as well as for detecting pleural effusions and as a guide in pulmonary thoracentesis [18,19]. It is not only non-invasive, but it is also fast, cheap and radiation-free. Moreover, it has already been proposed as an alternative to CT, for example, in patients too unstable to be moved to the CT room to monitor the evolution of acute respiratory distress syndrome (ARDS) [20]. The relative ease of TUS and the availability of inexpensive, user-friendly, portable equipment have made TUS an interesting and alternative method in many clinical settings, including the intensive care units because it offers accurate information that is of therapeutic and diagnostic relevance [21]. Furthermore, it is the only imaging technique able to provide an immediate diagnosis of the underlying aetiology of acute respiratory failure in the prehospital diagnosis, even in extreme settings [22]. However, the diagnostic value of TUS in PE is still unclear. For example, Comert et al reported that the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and the accuracy of TUS in clinically suspicious PE cases were found to be 90%, 60%, 80%, 77.1%, and 78%, respectively [23]. However, according to a recent study by Abotalebi et al, the sensitivity, specificity, NPV, PPV, and accuracy of TUS for diagnosing PE were 84%, 94%, 87%, 92%, and 91%, respectively [24] Therefore, the present systematic review and meta-analysis was conducted to assess the diagnostic accuracy of TUS in PE.

Material and methods

The present meta-analysis was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). [25]

Search strategy

A systematic search in PubMed, EMBASE and Cochrane Library was performed from their inception till March 2019. Our search included the following terms and combinations: “thoracic ultrasound or ultrasonography or sonography”, “transthoracic ultrasound or ultrasonography or sonography” OR “chest ultrasound or ultrasonography or sonography”, AND “pulmonary embolism”. There is no language restriction when performing the literature search. Moreover, the references of the retrieved manuscripts were also manually cross-searched for the eligibility of any further relevant publications.

Study selection

Studies were included if they met the following criteria: (1) patients with suspected PE; (2) all patients underwent TUS; (3) data on true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) could be extracted; and (4) studies with a reference gold standard for diagnosing PE. We excluded case reports, letters, reviews and meta-analysis.

Data extraction and quality assessment

Two reviewers independently screened the titles and abstracts of the search results to determine the studies that met the inclusion criteria. Disagreements were resolved through discussion and if no agreement was reached, then a third researcher was consulted. The following information was extracted from each study: first author, year of publication and journal, study design, inclusion and exclusion criteria, demographics (age, gender, country), reference criteria and accuracy data defining PE diagnosis (TP, FP, FN and TN). A systematic quality assessment of the study was conducted by using the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, which assesses the risk of bias and clinical applicability of the study in four key areas of patient selection, index text, reference standard, and flow and timing.

Statistical analysis

All analyses were conducted by using Stata 14.0 software (StataCorp, College Station, TX, USA). The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds’ ratio (DOR) were summarized by using a bivariate meta-analysis model. The summary ROC (SROC) curves were plotted by using the sensitivity and specificity of each included study and the area under the SROC curve (AUC) was also calculated. The between-study heterogeneity was evaluated by using Q test and I² statistics. If a P value of less than 0.10 for the Q test or I² value ≥50% indicated substantial heterogeneity, then a random-effects model was applied. Clinical utility of TUS for PE was evaluated by the Fagan nomogram. As publication bias is a concern for meta-analyses, the Deeks’ funnel plot asymmetry test was used, with p<0.10 indicating statistical significance.

Results

Characteristics of the studies

The initial search yielded 444 studies (441 from database searches and 3 from manual search). Of these, 118 were excluded due to duplications between databases. Subsequently, 285 unrelated studies were excluded by
screening the abstracts, and 13 studies were excluded due to letters, reviews, or meta-analysis. After reading the full-texts of the remaining articles, 12 were considered inappropriate and therefore excluded. Finally, 16 studies [23,24,26-39] including 1,916 patients were included in the quantitative analysis. The flowchart of the study selection process and the reasons for exclusion are presented in figure 1. The main characteristics of the eligible studies are shown in Table I. The 16 included studies were published between 1990 and 2019 and 6 were conducted in Austria, 4 in Germany, 3 in Turkey and 1 in Italy, Iran and France. Fourteen studies were published in English, and 2 studies were published in German. The median sample size was 120, ranging from 33 to 383. The quality of the included studies was assessed by using QUADAS-2 (fig 2).

In terms of risk of bias, 16 studies were included in our meta-analysis. Patient selection showed a high risk of bias in 5 studies and an unclear bias in 6 studies. There were 9 studies that were judged as having a low risk of bias in the index tests, 8 studies were allocated as having low risk of bias in terms of reference standards and 7 studies were judged as having low risk of bias in terms of flow and timing. In terms of applicability concerns, 11 studies demonstrated a high risk of bias in patient selection. All 16 studies had a low risk of bias in relation to index tests and 2 studies caused a high concern about the reference standards.

Quantitative synthesis

Study data and individual diagnostic estimates are summarized in Table II. Overall, 1,916 patients were included in this review, and 762 (39.8%) of whom were confirmed with PE. The overall sensitivity and specificity of TUS for PE were 82% (95%CI, 72%–88%) and 89% (95%CI, 79%–95%), (fig 3). Other parameters that were used to assess the efficacy included PLR (7.6; 95% CI, 4.0–14.5), NLR (0.21; 95% CI, 0.14–0.30) and DOR (36.86; 95% CI, 21.41–63.48). Overall, the pooled AUC was 0.91(95% CI, 0.88–0.93) (fig 4).

Subgroup analysis

As significant evidence of heterogeneity was found in the overall comparison, a subgroup analysis was conducted based on publication years (pre-2000 vs post-2000), different country (Asian vs European country), consecutive (yes vs no) and sample size (≥100 vs <100). Table III summarized all the results of subgroup analyses for the diagnosis of PE. Subgroup analysis based on sample size implied that the heterogeneities were almost eliminated in pooled estimates. TUS demonstrated significantly higher sensitivity in the sample size of <100 (0.85; 95% CI, 0.80–0.88) than in the sample size of ≥100 studies (0.70; 95% CI, 0.66–0.75), while its speci-
From Fagan's Nomogram (Figure 5), we found that 50% was selected as the pretest probability; in other words, the probability that a man suffers from PE was 50% via evaluation. After the calculation was done, the post-test probability was raised to 88% with a PLR of 8, and the probability decreased to 17%, and the NLR was 0.21. Furthermore, the Fagan plot demonstrated that when the pretest probabilities were 25% and 75%, the positive post-test probabilities were 72% and 96%, and the negative post-test probabilities were 6% and 38%, respectively (fig 5).

**Publication bias**

The publication bias of the studies was assessed using the Deeks' funnel plot asymmetry test. The slope coefficient of the 6 studies was associated with a p value of 0.57 (fig 6). These results indicated symmetrical data and no significant publication bias.
Discussion

Our meta-analysis revealed an overall sensitivity of 82%, specificity of 89% and AUC of 0.91 for TUS. These results suggested that a negative ultrasonography test could not definitively rule out PE. However, TUS has an acceptable diagnostic value for patients with suspected PE.

Although there are new improvements in technology, such as multislice CTPA, these techniques cannot be used in every medical centre due to its high cost, potential harmful radiation and the use of contrast agents. So, PE remain undiagnosed especially at the emergency units in the majority of patients. On the contrary, accurate diagnosis and early treatment of PE are very important and play an important role in life-saving [18]. The decision about the suspected cases of PE should be judged in real-time and the judgment time should be short. Thromboembolic occlusion of pulmonary artery leads to intra-alveolar haemorrhage, necrosis, and atelectasis due to loss of surfactant, increasing the permeability because of mediator secretion and alveolar oedema. These changes mainly occur in the subpleural area around the lungs. These pathological conditions, whether or not there is pleural effusion, provide an ultrasound window. These lesions are formed early within a few minutes and are possible to be identified with ultrasound in the early period [18,40].

| Table II. Summary of results of the studies included in this meta-analysis |
| Authors | Sample size (PE+/PE-) | TP | FP | FN | TN | Se (%) | Sp (%) |
| Mathis [33] | 33(28/5) | 27 | 2 | 1 | 3 | 96 | 60 |
| Kroschel [28] | 33(31/2) | 28 | 1 | 3 | 1 | 90 | 50 |
| Mathis [34] | 54(42/12) | 41 | 4 | 1 | 8 | 98 | 67 |
| Lechleitner [29] | 67(21/46) | 18 | 15 | 3 | 31 | 86 | 67 |
| Mathis [31] | 117(70/47) | 66 | 6 | 4 | 41 | 94 | 87 |
| Reissig [38] | 69(44/25) | 35 | 2 | 9 | 23 | 80 | 92 |
| Lechleitner [30] | 55(36/19) | 29 | 1 | 7 | 18 | 81 | 95 |
| Mohn [35] | 74(31/43) | 22 | 10 | 9 | 33 | 71 | 77 |
| Reissig [39] | 62(39/23) | 30 | 2 | 9 | 21 | 77 | 91 |
| Mathis [32] | 352(194/158) | 144 | 8 | 50 | 150 | 74 | 95 |
| Pfeil [37] | 33(10/23) | 7 | 7 | 3 | 16 | 70 | 70 |
| Comert [23] | 50(30/20) | 27 | 8 | 3 | 12 | 90 | 60 |
| Nazerian [36] | 357(110/247) | 67 | 10 | 43 | 237 | 61 | 96 |
| Abootalebi [24] | 77(25/52) | 21 | 3 | 4 | 49 | 84 | 94 |
| Acar [26] | 100(38/62) | 16 | 1 | 22 | 61 | 42 | 98 |
| Bekgoz [27] | 383(13/370) | 6 | 0 | 7 | 370 | 46 | 100 |

PE: pulmonary embolism; FN: False-negative; FP: False-positive; TN: True-negative; TP: True-positive; Se: Sensitivity; Sp: Specificity

| Table III. Subgroup analysis of the meta-analysis |
| Subgroup | Number of trials | Sensitivity (95% CI) | Specificity (95% CI) | DOR | Heterogeneity | AUC |
| Years | Pre-2000 | 5 | 0.94 (0.89, 0.97) | 0.75 (0.66, 0.83) | 37.28 (12.39, 112.17) | I²=37.8%, p=0.169 | 0.92 |
| Post-2000 | 11 | 0.71 (0.67, 0.75) | 0.95 (0.94, 0.96) | 31.74 (17.29, 58.26) | I²=51.9%, p=0.023 | 0.87 |
| Country | Asian | 4 | 0.66 (0.56, 0.75) | 0.98 (0.96, 0.99) | 55.81 (13.93, 223.6) | I²=52.2%, p=0.099 | 0.91 |
| European | 12 | 0.78 (0.75, 0.81) | 0.90 (0.87, 0.92) | 29.54 (16.8, 51.95) | I²=46.5%, p=0.038 | 0.91 |
| Consecutive | Yes | 10 | 0.76 (0.72, 0.80) | 0.93 (0.91, 0.95) | 26.78 (14.19, 50.55) | I²=39.3%, p=0.096 | 0.89 |
| No | 6 | 0.77 (0.72, 0.81) | 0.92 (0.89, 0.95) | 44.57 (19.24, 103.26) | I²=46.3%, p=0.097 | 0.93 |
| Sample size | ≥100 | 5 | 0.70 (0.66, 0.75) | 0.97 (0.96, 0.98) | 56.63 (31.94, 100.41) | I²=18.7%, p=0.295 | 0.95 |
| <100 | 11 | 0.85 (0.80, 0.88) | 0.80 (0.74, 0.84) | 21.41 (11.61, 39.49) | I²=29.5%, p=0.165 | 0.89 |

DOR: diagnostic odds ratio; AUC: the area under the curve.
TUS has already been compared with CT for the diagnosis of other lung conditions. The advantages of TUS are that it can be done at the bedside easily without need of patient mobilization, it is noninvasive, does not utilize ionizing radiation and is easily reproducible. Shrestha et al reported [41] that the diagnostic accuracy of TUS for common conditions such as pleural effusion, pneumothorax, pulmonary oedema and pneumonia is superior to a chest radiograph and is comparable to a chest CT scan. Furthermore, Chiumello et al [42] found that global agreement between TUS and CT ranged from 0.640 (0.391–0.889) to 0.934 (0.605–1.000) and was on average 0.775 (0.577–0.973) in ARDS. The overall sensitiv-
ity and specificity of TUS ranged from 82.7% to 92.3% and from 90.2% to 98.6%, respectively.

There are several categories that can be applied to the diagnosis of PE. The most characteristic manifestations of PE include hypoechoic and pleural-based parenchymal alterations. More than 85 lesions were wedge-shaped [18,38] and they may also have rounded or polygonal configurations. There is a single hypoechoic structure in the centre of the lesion, suggesting that 20% of patients may have an air-filled bronchiole [18,34,38]. Pleural involvement in PE initially led to local effusion near the affected lung region and may eventually develop into basal pleural effusion [18,38]. Colour Doppler ultrasound examination of lesions provide additional diagnostic information. During pulmonary infarction, colour Doppler ultrasound is unable to detect the pulmonary artery blood flow, which is known as the “consolidation with little perfusion” [18,43]. A congested thromboembolic vessel can be referred to as a “vascular sign” [18,34]. However, the above-described TUS findings supported the diagnosis of PE but PE cannot be excluded without them.

In this meta-analysis, two included studies found that the sensitivity of TUS for diagnosing PE remained low. Acar et al reported that TUS demonstrated 42% sensitivity and 98% specificity for diagnosing PE [26]. In this study, the patients were evaluated within a few hours of the onset of the symptoms and so oedema, alveolar haemorrhage and tissue necrosis have not yet occurred by the time they performed TUS. In another recent study, Bekgoz et al showed that TUS demonstrated 46% sensitivity and 100% specificity for diagnosing PE [27]. However, these results were probably due to the inclusion of a small number of PE patients in this study. These results may explain why the 2 included studies were different from the other studies. Heterogeneity is a potential problem when interpreting the results of meta-analyses. Heterogeneity was observed in the overall analyses, and thus a subgroup analysis was performed. Based on the data collected, the sample size demonstrated partial contribution to the between-study heterogeneity.

The use of Fagan plot analysis to explore the clinical application of TUS for diagnosing PE was the strength of our study. When the pre-test probability was 25% (low clinical suspicion), the post-test probability of PE with a negative result was 6%. When the pre-test probability of PE reaction was 75% (high clinical suspicion), the post-test probability of PE with a positive result was 96%. However, TUS is generally not suitable for diagnosing PE due to lack of appropriate tools to calculate the pre-test probability of PE.

Due to several limitations, our results should be evaluated with caution. Firstly, the average prevalence of PE in the included studies was 40%. This high ratio indicated a possibility of selection bias and the likelihood of including the patient may not be representative of the general population. Secondly, the included studies have different diagnostic criteria for PE, reducing the diagnostic efficiency of TUS. Thirdly, significant heterogeneity limited the robustness of the conclusions obtained. Finally, the availability of the limited number of studies for the synthesis is also a major restraint of our research. However, we conducted a comprehensive search that included all the studies that could be combined.

In conclusion, although TUS cannot safely rule out PE, it can be used as an aid or guidance to establish the procedures and help to improve the diagnostic deficits in patients with PE.

Conflict of interest: None

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