Review

Med Ultrason 2022, Vol. 24, no. 2, 226-234
DOI: 10.11152/mu-3049

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

Wu Chen, Kun Xu, Yiying Li, Meifang Hao, Yongsheng Yang, Xiaofang Liu, Xiaochun Huang, Yuqin Huang, Qianjun Ye

Department of Ultrasound, The First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

Abstract

Aims: The present study investigated and evaluated the accuracy of thoracic ultrasonography (TUS) in the diagnosis of pulmonary embolism (PE) by conducting a systematic review and meta-analysis. **Material and methods:** The PubMed, Embase and the Cochrane library databases were searched till March 2019 to retrieve relevant articles and the overall diagnostic accuracy of TUS in PE diagnosis was evaluated by meta-analysis. **Results:** Overall, 16 studies including 1,916 patients were enrolled in this meta-analysis. Of these, 762 (39.8%) had confirmed PE. The overall sensitivity, specificity, and area under the ROC curve (AUC) of TUS for PE were 82% (95% confidence interval (CI), 72%–88%), 89% (95% CI, 79%–95%), and 0.91 (95% CI, 0.88–0.93), respectively. Other efficacy parameters assessed demonstrated a positive likelihood ratio (PLR) of (7.6; 95% CI, 4.0–14.5), negative likelihood ratio of (NLR) (0.21; 95% CI, 0.14–0.30), and diagnostic odds' ratio (DOR) of (36.86; 95% CI, 21.41–63.48). **Conclusions:** The current study suggested that although TUS cannot safely rule out PE, it is likely to be used as an aid or guidance to establish procedures and help to improve the diagnostic deficits in patients with PE.

Keywords: thoracic ultrasonography; diagnosis; pulmonary embolism; meta-analysis

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

Received 27.01.2020 Accepted 11.03.2021
Med Ultrason
2022, Vol. 24, No 2, 226-234
Corresponding author: Wu Chen
Department of Ultrasound, The First Hospital of Shanxi Medical University,
85 Jiefang South Road, Yingze District,
Taiyuan, Shanxi 030001, China
Phone: +86- 13633411868
Fax: +86-21-57643271
E-mail: 13633411868@163.com

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 Abootalebi 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 I^2 statistics. If a P value of less than 0.10 for the Q test or I^2 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 specificity in the sample size of ≥100 studies (0.97; 95% CI, 0.96–0.98) was significantly higher than that in the sample size of <100 studies (0.80; 95% CI, 0.74–0.84). This suggested that the sample size might be the decisive factor on heterogeneity.

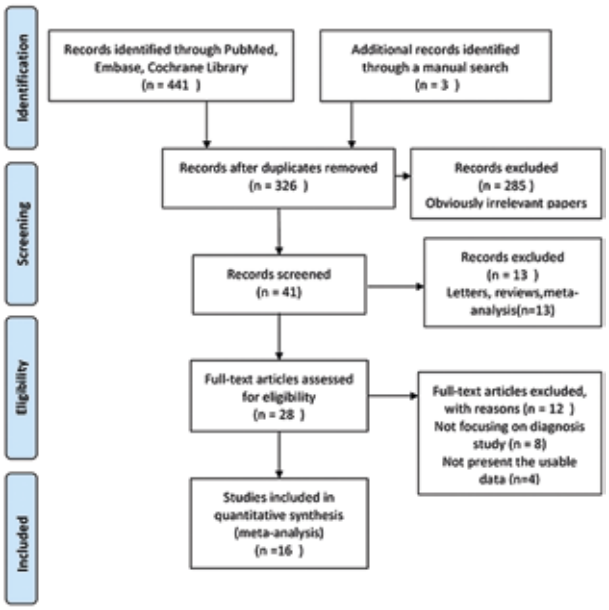

Fig 1. Flow diagram of studies identification.

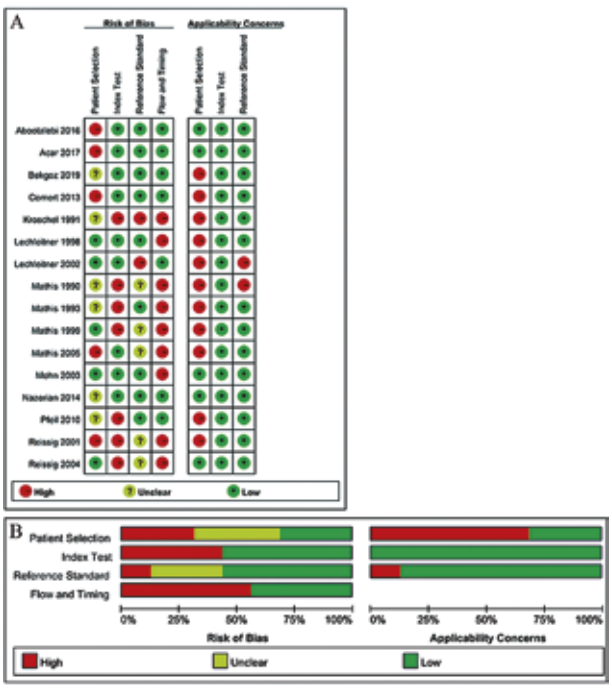

Fig 2. Risk of bias and applicability concerns summary for each domain of the QUADAS-2 for each included study. A) Risk of bias summary; B) Risk of bias graph. Symbols. (+): low risk of bias; (?): unclear risk of bias; (-): high risk of bias.

Table I. Characteristics of the studies included in this meta-analysis

Authors, year of publication, country	Male (%)	Mean age	Patients (N)	Consecutive	Machine	Probe	MHz	Reference test
Mathis, 1990 [33] Austria	NA	NA	33	No	NA	Sector	5	Chest x-ray, lung scan, pulmonary angiography
Kroschel, 1991 [28] Germany	35	59(17-88)	33	Yes	Toshiba SAL 270	Curved or liner	3.5 or 5	Perfusion lung scan
Mathis,1993 [34] Austria	54	63(21-88)	54	Yes	Ultramark 4	Sector s	3,5 or 7.5	Chest x-ray, V/Q lung scan, pulmonary angiography
Lechleitner,1998 [29] Austria	39	66(18-89)	67	Yes	Toshiba Sonolayer SSH-140 AIC	Linear or sector	3.75 or 7.5	Chest x-ray, V/Q lung scan, D-dimer
Mathis,1999 [31] Austria	58	NA	117	No	General Electric Logitech 500	Sector or convex	3.5-5	CTPA, echocardiography, D-dimer
Reissig, 2001 [38] Germany	61	62.8(24-88)	69	Yes	AU-5 Harmonic, Esaote Biomedica	Convex or linear	3.5,5 or 7.5	CTPA, V/Q scan, echocardiography, D-dimer
Lechleitner, 2002 [30] Austria	25	69(23-91)	55	Yes	Vingmed, SystemFive, Toshiba Sonolayer SSH-140 A/C	Linear	3.75,7.5 or 10	MRI-Angiography, V/Q scans, D-dimer
Mohn, 2003 [35] France	57	66±17	74	Yes	NA	Linear	5	CTPA, lung scan,
Reissig, 2004 [39] Germany	60	62.2(24-88)	62	Yes	AU-5 Harmonic, Esaote Biomedica	Convex	5 or 3.5	X-ray, echocardiography, ventilation/ perfusion scanning, legs venous duplex US, contrast venography, pulmonary angiography
Mathis, 2005 [32] Austria	47	64(18-98)	352	No	NA	Convex or sector	3.5-6	CTPA
Pfeil, 2010 [37] Germany	52	65.4(19-92)	33	No	AU5 Harmonic, Esaote Biomedica	Convex	5 or 3.5	MSCT
Comert, 2013 [23] Turkey	54	54.1±17.9	50	Yes	GE Logic 7	Convex	3.5	Multislice CTPA
Nazerian, 2014 [36] Italy	47	PE+: 72.7±12.3 PE-: 70.7±14.4	357	Yes	MyLab30,Gold, MyLab40, Logiq3	Linear or convex	4-8 or 3.5-5	MCTPA
Abootalebi, 2016 [24] Iran	40	52.8±20.24	77	No	Akola SSD-2000	NA	3.5 or 7	64 MSCT scan
Acar, 2017 [26] Turkey	56	PE+:66±17.3 PE-:64.8±14.7	100	No	Esaote MyLab Five	Linear or convex	1-8 or 4-13	Chest CT
Bekgoz, 2019 [27] Turkey	52	65.5±15.5	383	Yes	Fujifilm Fazone CB®	Micro-convex	2-6	Thorax computed tomography

V/Q scan: ventilation/perfusion scan; CTPA: computed tomography pulmonary angiography; MSCT: multislice computed tomography; MCTPA: multidetector CT pulmonary angiography; NA: not available.

Clinical utility assessment

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.

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)	I^2=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)	I^2=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)	I^2=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)	I^2=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)	I^2=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)	I^2=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)	I^2=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)	I^2=29.5%, p=0.165	0.89

DOR: diagnostic odds ratio; AUC: the area under the curve.

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 intraalveolar 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].

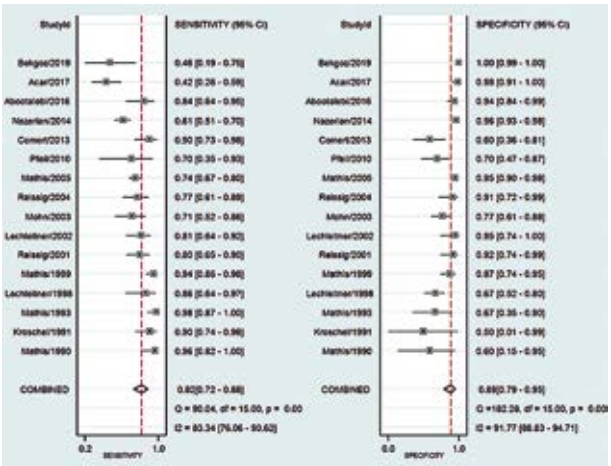

Fig 3. Forest plots of the pooled sensitivity and specificity. Each solid square represents an individual study. Error bars represent 95% CI. Diamond indicates the pooled sensitivity and specificity for all of the studies.

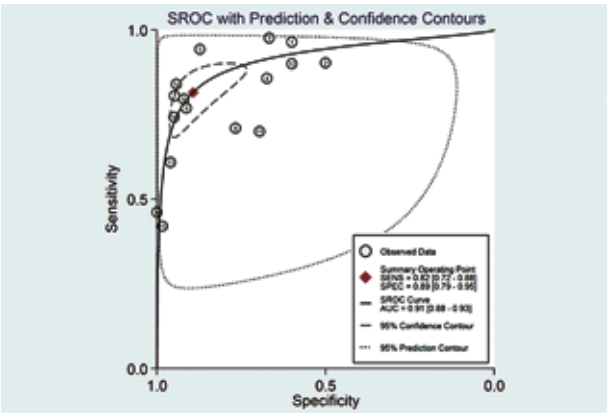

Fig 4. SROC curve of thoracic ultrasonography for diagnosis of pulmonary embolism. Each ○ represents individual study estimates. The diamond is the summary point representing the average sensitivity and specificity estimates. The ellipses around this summary point are the 95% confidence region (dashed line) and the 95% prediction region (dotted line).

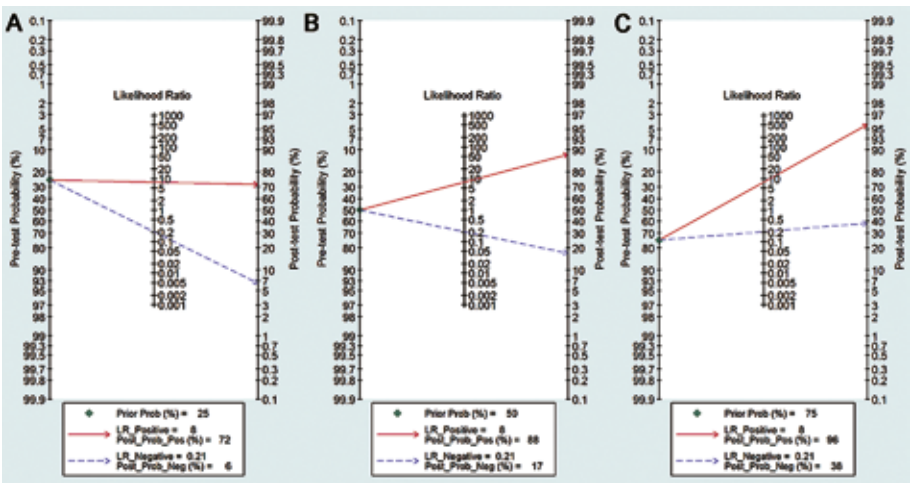

Fig 5. Analysis of the Fagan plot to evaluate the clinical efficacy utility of thoracic ultrasonography in pulmonary embolism. (A) Pre-test probability=25%; (B) pre-test probability=50%; (C) pre-test probability=75%. Each Fagan plot contains a vertical axis on the left for the pre-test probability, an axis in the middle that represents the likelihood ratio, and a vertical axis on the right that represents the post-test probability. NLR=negative likelihood ratio, PLR=positive likelihood ratio.

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-

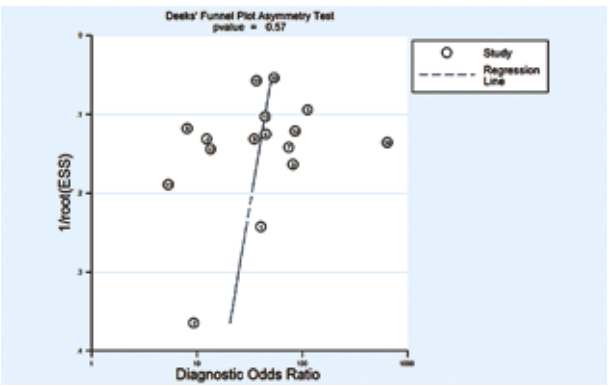

Fig 6. Deeks' funnel plot with regression line.

ity and specificity of TUS ranged from 82.7% to 92.3% and from 90.2% to 98.6%, respectively.

There are several criteria 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 hyperechoic 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

Acknowledgments: This work was supported by key R & D and social development projects in Shanxi Province [201803D31102]; the key science and technology project of Shanxi Province [20140313013-6]. The Taiyuan Science and Technology Project [12016902]; and the Science and Technology Innovation Fund of Shanxi Medical University [01201416].

References

1. Hepburn-Brown M, Darvall J, Hammerschlag G. Acute pulmonary embolism: a concise review of diagnosis and management. Intern Med J 2019;49:15-27.
2. Gupta R, Fortman DD, Morgenstern DR, Cooper CJ. Short- and Long-term Mortality Risk After Acute Pulmonary Embolism. Curr Cardiol Rep 2018;20:135.
3. Righini M, Robert-Ebadi H, Le Gal G. Diagnosis of acute pulmonary embolism. J Thromb Haemost 2017;15:1251-1261.
4. Goldhaber SZ. Pulmonary embolism. Lancet 2004;363:1295-1305.
5. Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. N Engl J Med 1992;326:1240-1245.
6. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 1999;159:445-453.
7. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-1389.
8. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Arch Intern Med 2003;163:1711-1717.
9. Yang Y, Liang L, Zhai Z, et al. Pulmonary embolism incidence and fatality trends in chinese hospitals from

1997 to 2008: a multicenter registration study. PLoS One 2011;6:e26861.
10. Estrada-Y-Martin RM, Oldham SA. CTPA as the gold standard for the diagnosis of pulmonary embolism. Int J Comput Assist Radiol Surg 2011;6:557-563.
11. Mamlouk MD, vanSonnenberg E, Gosalia R, et al. Pulmonary embolism at CT angiography: implications for appropriateness, cost, and radiation exposure in 2003 patients. Radiology 2010;256:625-632.
12. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011;171:831-837.
13. Kooiman J, Klok FA, Mos IC, et al. Incidence and predictors of contrast-induced nephropathy following CT-angiography for clinically suspected acute pulmonary embolism. J Thromb Haemost 2010;8:409-411.
14. Mortele KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. AJR Am J Roentgenol 2005;184:31-34.
15. Remy-Jardin M, Pistolesi M, Goodman LR, et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. Radiology 2007;245:315-329.
16. Joyner CR Jr, Miller LD, Dudrick SJ, Eskin DJ, Knight DH. Reflected ultrasound in the detection of pulmonary embolism. Trans Assoc Am Physicians 1966;79:262-277.
17. Miller LD, Joyner CR Jr, Dudrick SJ, Eskin DJ. Clinical use of ultrasound in the early diagnosis of pulmonary embolism. Ann Surg 1967;166:381-393.
18. Reissig A, Kroegel C. Transthoracic ultrasound of lung and pleura in the diagnosis of pulmonary embolism: a novel non-invasive bedside approach. Respiration 2003;70:441-452.
19. Mayo PH, Copetti R, Feller-Kopman D, et al. Thoracic ultrasonography: a narrative review. Intensive Care Med 2019;45:1200-1211.
20. Gardelli G, Feletti F, Gamberini E, Bonarelli S, Nanni A, Mughetti M. Using sonography to assess lung recruitment in patients with acute respiratory distress syndrome. Emerg Radiol 2009;16:219-221.
21. Gardelli G, Feletti F, Nanni A, Mughetti M, Piraccini A, Zompatori M. Chest ultrasonography in the ICU. Respir Care 2012;57:773-781.
22. Feletti F, Mucci V, Aliverti A. Chest Ultrasonography in Modern Day Extreme Settings: From Military Setting and Natural Disasters to Space Flights and Extreme Sports. Can Respir J 2018;2018:8739704.
23. Comert SS, Caglayan B, Akturk U, et al. The role of thoracic ultrasonography in the diagnosis of pulmonary embolism. Ann Thorac Med 2013;8:99-104.
24. Abootalebi A, Golshani K, Karami M, Masoumi B, Aliasgharlou M. Diagnostic validity of ultrasonography in evaluation of pulmonary thromboembolism. Adv Biomed Res 2016;5:4.
25. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-269.
26. Acar H, Yilmaz S, Yaka E, Dogan NO, Ozbek AE, Pekdemir M. Evaluation of the Diagnostic Role of Bedside Lung Ultrasonography in Patients with Suspected Pulmonary Embolism in the Emergency Department. Balkan Med J 2017;34:356-361.
27. Bekgoz B, Kilicaslan I, Bildik F, et al. BLUE protocol ultrasonography in Emergency Department patients presenting with acute dyspnea. Am J Emerg Med 2019;37:2020-2027.
28. Kroschel U, Seitz K, Reuss J, Rettenmaier G. Sonographic imaging of lung emboli. Results of a prospective study. Ultraschall Med 1991;12:263-268.
29. Lechleitner P, Raneburger W, Gamper G, Riedl B, Benedikt E, Theurl A. Lung sonographic findings in patients with suspected pulmonary embolism. Ultraschall Med 1998;19:78-82.
30. Lechleitner P, Riedl B, Raneburger W, Gamper G, Theurl A, Lederer A. Chest sonography in the diagnosis of pulmonary embolism: a comparison with MRI angiography and ventilation perfusion scintigraphy. Ultraschall Med 2002;23:373-378.
31. Mathis G, Bitschnau R, Gehmacher O, et al. Chest ultrasound in diagnosis of pulmonary embolism in comparison to helical CT. Ultraschall Med 1999;20:54-59.
32. Mathis G, Blank W, Reissig A, et al. Thoracic ultrasound for diagnosing pulmonary embolism: a prospective multicenter study of 352 patients. Chest 2005;128:1531-1538.
33. Mathis G, Metzler J, Feurstein M, Fussenegger D, Sutterlutti G. Lung infarcts detected with ultrasonography. Ultraschall Med 1990;11:281-283.
34. Mathis G, Metzler J, Fussenegger D, Sutterlutti G, Feurstein M, Fritzsche H. Sonographic observation of pulmonary infarction and early infarctions by pulmonary embolism. Eur Heart J 1993;14:804-808.
35. Mohn K, Quiot JJ, Nonent M, et al. Transthoracic sonography of the lung and pleura in view of a suspected pulmonary embolism: a pilot study. J Ultrasound Med 2003;22:673-678.
36. 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.
37. Pfeil A, Reissig A, Heyne JP, et al. Transthoracic sonography in comparison to multislice computed tomography in detection of peripheral pulmonary embolism. Lung 2010;188:43-50.
38. Reissig A, Heyne JP, Kroegel C. Sonography of lung and pleura in pulmonary embolism: sonomorphologic characterization and comparison with spiral CT scanning. Chest 2001;120:1977-1983.
39. Reissig A, Heyne JP, Kroegel C. Ancillary lung parenchymal findings at spiral CT scanning in pulmonary embolism. Relationship to chest sonography. Eur J Radiol 2004;49:250-257.
40. Reissig A, Gorg C, Mathis G. Transthoracic sonography in the diagnosis of pulmonary diseases: a systematic approach. Ultraschall Med 2009;30:438-454.

41. Shrestha GS, Weeratunga D, Baker K. Point-of-Care Lung Ultrasound in Critically ill Patients. Rev Recent Clin Trials 2018;13:15-26.
42. Chiumello D, Umbrello M, Sferrazza Papa GF, et al. Global and Regional Diagnostic Accuracy of Lung Ultrasound Compared to CT in Patients With Acute Respiratory Distress Syndrome. Crit Care Med 2019;47:1599-1606.
43. Yang P. Applications of colour Doppler ultrasound in the diagnosis of chest diseases. Respirology 1997;2:231-238.