

Original Article

A meta analysis on diagnostic effectiveness of ultrasound in diagnosis of acute pulmonary edema in ICU

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Abstract: Acute dyspnea is one of the common diseases in emergency department. This systematic review aims to evaluate the sensitiveness and specificity of acute dyspnea by ultrasonic examination. Studies were searched from database PubMed, EMBASE, Ovid MEDLINE and Cochrane Library. This study includes randomized controlled trial, perspective study or prospective case control study. Patients represented the symptoms of acute dyspnea, suspicious congestive heart failure or sensitiveness/specificity of ACPE. The patients who represent no typical symptom and patients not with ACPE were excluded. Database retrieval and literature review were independently processed by two authors. The acceptable research methodology quality was evaluated by QUADAS-2, and related sensitiveness and specificity were analyzed by situation analysis tables. Results indicated that there were total 7 studies met inclusion criteria (1075 patients), related methodologies were in range of medium to excellent. B lung ultrasound examination showed that the sensitiveness of ACPE was 94.1% (95% CI: 81.3%-98.3%), and the specificity was 92.4% (95% CI: 84.2%-96.4%). The related subgroup analysis results showed no obvious significant difference among research types, patient population distribution and methods for lung ultrasound examination. In conclusion, B lung ultrasound has relatively higher sensitiveness and specificity for diagnosis of expiratory dyspnea, which is caused by acute cardiac pulmonary edema. For moderate and severe pulmonary edema, B lung ultrasound can help emergency physicians make diagnosis effectively and accurately. If result of ultrasound examination is negative, then pulmonary edema or mild pulmonary edema can be excluded, but it still need a lot of specimens for further confirmation.

Keywords: Acute pulmonary edema, ultrasonic examination, meta analysis

Introduction

Expiratory dyspnea always caused by the acute cardiac pulmonary edema (ACPE), and which is also one of the common diseases in the emergency department. It will be dangerous for patients when the disease attacking the individuals. And it is difficult to diagnose for the patients who are old, fat and with chronic obstructive pulmonary disease (COPD). Therefore, the related death incident rate is relatively higher. The key method for treatment is to diagnose this disease quickly and accurately [1-5]. Ultrasonic examination can be applied to diagnose many kinds of emergency diseases quickly and effectively. Then, many researches suggested that the pulmonary B line ultrasonic examination can be used for the auxiliary diag-

nosis to expiratory dyspnea [6, 7]. Based on the above backgrounds, this review aims to evaluate the accuracy of B pulmonary ultrasonography in testing the expiratory dyspnea caused by ACPE, by comparing and referring the related literatures. At the same time, we made a subgroup analysis for the types of research (alignment or case-control study), patient population distribution and concrete operation of ultrasonic to explore whether the threshold effect exists or not.

Materials and methods

Literature retrieval and data statistics

The retrieval databases, including the PubMed, EMBASE, Ovid MEDLINE and Cochrane Library,

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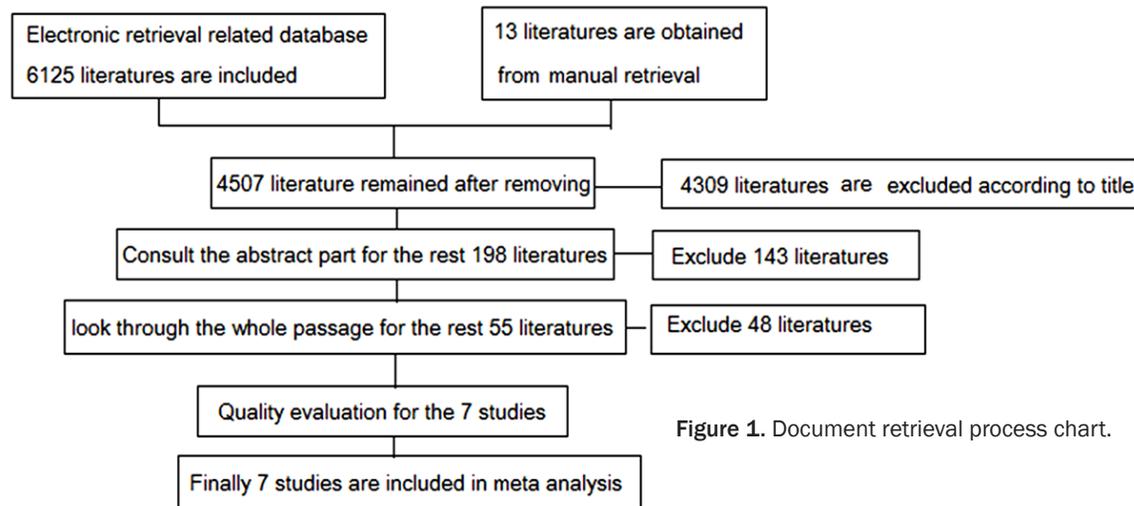


Figure 1. Document retrieval process chart.

were used in this study. And the key words, including “lung ultrasound”, “emergency treatment”, “acute pulmonary edema”, “sensitivity” and “specificity” were researched in the above databases. At the same time, EndNote software was applied to organize related references and reference documentations. The relevant conference abstracts were retrieved by manual searching.

Inclusion criteria: ① Types of the research were prospective cohort and prospective case control study, which contain the sensitivity and specificity of using B lung ultrasound to diagnose ACPE. ② The patients who were included in the research expressed expiratory dyspnea, and they were suspected to be infected by ACPE. ③ Parameters were tested by using the B line ultrasonic examination. There was no limitation on the specific operational methods which were applied for using lung ultrasound to diagnose ACPE. But the research indicated to use B line ultrasound for auxiliary diagnosis, which should be the premise. There also was no specific limitation on Specific ultrasonic testing machine model, operator title and so on. Volpicelli method (anocelia was divided into 8 sections) was applied to diagnoses of ACPE or diffuse interstitial syndrome. If there were at least positive 2 sections in each side of the chest wall, then the diagnosis was established. The section was positive if there were at least 3 groups of B line in intercostal space. In Vitturi and other researches, 8 groups of B line existed in the whole anocelia, then it was defined as positive. While Gargani and etc defined that if comet score was more than 5 scores, then it

meant the acute dyspnea was caused by acute cardiac pulmonary edema. At present, there was no unified diagnostic criteria of ACPE, but the linear relationship truly existed in the number of B line and the water level outside the pulmonary vessels. It was always difficult to distinguish congestive heart failure and ACPE, lung ultrasound was usually regarded as one of the effective methods for auxiliary diagnosis. ④ Data extraction and processing: 2 researchers preliminary selected title and summary of the electronic and manual searches according to objective and inclusion criteria of the study. Then compared and discussed the literature which were consistent with the requirement with each other, obtained and screened the whole passage, extracted relevant variable data. If these two researchers had disagreement, then the result would be judged by the third party.

Exclusive criteria: ① Pure case reports, retrospective studies and other kinds of case-control studies; ② The symptoms were not typical or non ACPE patients.

Quality and risk evaluation

Two researchers independently analyzed and evaluated the quality of the studies, which were included in this study by using QUADAS-2. There were 4 main aspects, including ① cases selection; ② parameters examination; ③ reference standards; ④ flow and time.

There is a high risk of bias in the following situations: ① the case studies were not in the con-

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Table 1. Basic characteristics of the studies

Characteristics	Lichtenstein [19]	Lichtenstein [6]	Gargani [12]	Liteplo [7]	Vitturi [11]	Prosen [22]	Cibinel [23]
Published tme	1998	2008	2008	2009	2011	2011	2012
Magazine	Intensive Care Medicine	Chest	European Journal of Heart Failure	Academic Emergency Medicine	Journal of Ultrasound	Critical Care	International Emergency Medicine
Country	France	France	Italy	America	Italy	Slovenia	Italy
Case number	146	260	149	94	152	218	56
Ultrasonic instrument	Hitachi 405	Hitachi 405	Philips Sono	Sonosite	Toshiba Aplio XV	Sonosite	GE Electric LOGIQ 3
Type of probe	3.5-MHz cardiac	5-MHz microconvex	2.5- to 3.5-MHz cardiac	2.5-MHz curved array	3.5-MHz convex	/	3.5-MHz convex
Ultrasound operator	Lichtenstein	Lichtenstein	Comet score	Volpicelli	Comet score	Volpicelli	Volpicelli
Reference standards	Blind trial case	Blind trial case	Blind trial case	Blind trial case	Blind trial case	Final diagnosis	Final diagnosis
Ultrasonic testing time	<1 min	<3 min	<5 min	<5 min	<3 min	<1 min	<5 min
Type of reseach	Casecontrol	Alignment	Alignment	Alignment	Alignment	Alignment	Alignment
Sensitivity, % (95% CI)	100	97	76.2	58 (33-77)	97	100 (98-100)	93.6
Specificity, % (95% CI)	97	95	88	85 (69-95)	79	95 (91-100)	84

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Table 2. QUADAS-2 methodological quality assessment

Study	Bias risk			Possible error of practical application			
	Case selection	Test parameters	Reference standards	Flow and time	Patient selection	Inspection of parameters	Reference standard
Lichtenstein [19]	High	Unknown	Unknown	High	Low	Low	Low
Lichtenstein [6]	Unknown	Low	Low	Unknown	Low	Low	Low
Gargani [12]	Low	Unknown	Low	Low	Low	Low	Low
Liteplo [7]	Unknown	Low	Low	Low	Low	Low	Low
Vitturi [11]	Low	Low	Low	Unknown	High	High	Low
Prosen [22]	Unknown	Low	Low	Low	Low	Low	Low
Cibinel [23]	Low	Low	Low	Low	Low	Low	Low

Table 3. Features of ultrasonic operator

Study	Number of operator	Training level	Inherent reliability
Lichtenstein [19]	May be 2	ICU physician	Unreported
Lichtenstein [6]	2	ICU physician	Unreported
Gargani [12]	Unclear	Unclear	Unreported
Liteplo [7]	7	2 Electro physiological physicians, 5 trained medical students	0.82
Vitturi [11]	Unclear	Unclear	0.98
Prosen [22]	10	Electro physiological physician	Unreported
Cibinel [23]	Unclear	Electro physiological physician	0.92

trol study; ② non-continuity or non-randomness selection of patient samples in this study; ③ not properly adopted. If the patients did not receive ultrasonic examination during the emergency treatment or detected after knowing the result of the chest X-ray or BNP level, it was regarded that the level of applicability was higher.

Reference standards: If the reference standards were not able to accurately define the target, then the related bias risk would be higher. If in-appropriate intervals existed in test parameters and reference standards, not all the patients accepted the reference standards, all patients received different reference standards or the research analysis did not include all the patients, then the related bias risk would be higher.

Data analysis

By intuitive evaluation of sensitivity and specific heterogeneity in the study through forest map, the initial aim was to make meta analysis by curve model for hierarchical summary receiver operating characteristics (HSR-OC). This model assumed that the ROC curves

lied in each study, which is similar to the random effect model of the traditional meta analysis in a certain degree, the related variables existed in or between the studies. In addition, the advantage of this model also included the control of reference standards, which was the general limitation of DTA research. At the same time, we made subgroup heterogeneity analysis of 3 aspects, including disease category, basic feature design and operation method for ultrasonic examination. All the related data were analyzed by using the STATA 11.2 statistical analysis software.

Results

By the method of electronic access database, there were total 6125 literatures, and 13 literatures were retrieved by other manual ways (**Figure 1**). Through retrieving 198 abstracts and 55 articles for the second time, there were finally 7 passages met the inclusion criteria (1075 cases, **Table 1**). **Table 2** showed that QUADAS-2 quality assessment levels of all the studies were from the moderate to excellent range. All the ultrasono-grapher knew nothing about the result of reference standards in all the researches. Only 1 case was the control

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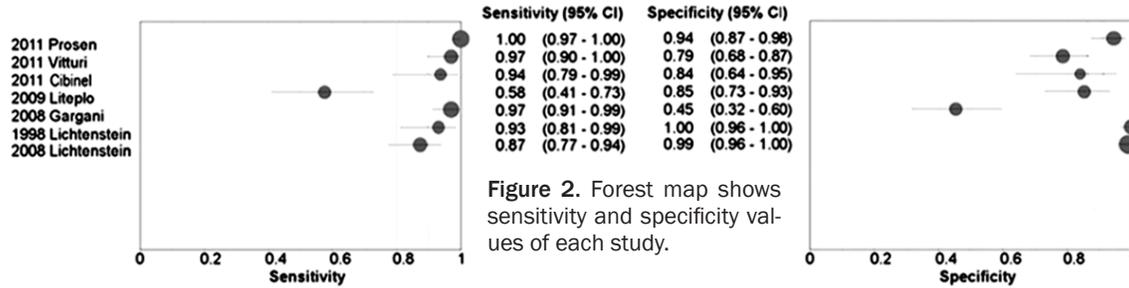


Table 4. Analysis of 2 meta study results

Variable	Meta analysis of 7 studies	Meta analysis of 4 studies
Sensitivity	94.1% (81.3-98.3)	93.4% (81.8-97.8)
Specificity	92.4% (84.2-96.4)	88.8% (78.6-94.5)
HSROC λ	5.4 (3.7-7.1)	4.7 (3.2-6.1)
HSROC θ	-0.53 (-1.9-0.8)	-0.22 (-1.7-1.3)
HSROC β	-0.51 (-1.5-0.5)	-0.43 (-1.7-0.8)

Exclude Liteplo and Lichtenstein, there were total 3 researches. Because Cook's distance >1.0 , which indicated that large residual error or impact on the higher overall results.

study, and pulmonary ultrasonic examination method for 5 researches were basically the same. By scanning the anterior or lateral chest to test B line, if there were more than 3 groups exist in each side of the chest, then the result was positive. In the 2 studies, comet score was applied to the diagnosis of ACPE (Figure 1).

The ultrasonic inspection operators were the physician-in-charge who were trained before. Medical students finished the operation part in one research. Table 3 showed quantitative information of the related operators. However, in this study, there was no way to specifically analyze and compare reliability quality of each operator. Figure 2 showed sensitivity and specificity values of each research. The sensitiveness of ACPE which was diagnosed by B pulmonary ultrasonography was 94.1% (95% CI: 81.3%-98.3%), and the specificity was 92.4% (95% CI: 84.2%-96.4%). In the further subgroup analysis, there were no obvious effects of research type, patient population distribution and concrete operation of ultrasonic inspection on the sensitiveness and specificity analysis in this study. At the same time, a further diagnostic threshold effects showed no significant relevance (relevant parameter of Spearman were 0.393, $P=0.383$).

Cook's distance measurement showed that there were 3 studies might change the whole sensitivity and specificity analysis results. Liteplo and other studies (Cook's distance were 2.03, 3.84) were excluded from the initial meta analysis to evaluate the effect of it on the whole evaluation results. The obtained sensitiveness was 93.4% (95% CI=81.8%-97.8%) and the specificity was 88.8% (95% CI=78.6%-94.5%) (Table 4).

Discussion

The main objective of this study is to evaluate the sensitiveness and specificity of acute dyspnea by using the ultrasonic examination. In clinical, the acute dyspnea is caused by the acute cardiac pulmonary edema (ACPE). Two studies were chosen from emergency study (156 cases), which reported different degrees of sensitiveness and specificity. Volpicelli pulmonary ultrasonic examination method was applied in both of these two studies, but the methodological differences between studies were one of the reasons that causes the different results. The ultrasonic inspection operators in Liteplo's studies were mainly medical students, while the operators in Cibinel et al.'s study were physicians. Patients with no definite diagnosis were probably included in Liteplo, and all the patients were detected by NT-BNP. So that it probably caused further decrease of lung ultrasound examination. And the patients were inspected by ultrasound after entering the hospital for a period of time. The patients maybe received diuretic or nitrate treatment, therefore, the degree of pulmonary edema might decrease significantly. Therefore, the sensitivity of detection was decreased. These differences led to the different accuracy among studies. Therefore, from this point of view, an accurate research of the patients with dyspnea in the emergency department is really necessary in clinical [8-10].

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The other test methods for cardiac pulmonary edema, such as chest X-ray examination, BNP examination, were also very important. It was reported that the sensitivity and specificity of ACPE, which was diagnosed by chest X-ray examination, were 14% to 68% and 53% to 96%, respectively. The latest 2 meta analysis results on BNP showed that the BNP was suggested to exclude the ACPE. However, both of these two inspection methods presents the characterize of deficiency in chronergy and convenience. And compared with them, lung ultrasound examination processes the advantages of high efficiency, convenience, good repeatability and so on, which could significantly assistant the clinical decision [11-13, 19, 20]. The result of this study showed that B linear lung ultrasound could be applied near the bed, which not only could assist to diagnose ACPE, but also could distinguish ACPE and the diseases which were caused by acute respiratory problems. This was very important for the patients with acute dyspnea who were in the emergency department [14, 15]. In the study, we applied strict search strategy to retrieve the related literature and made systematic review. At the same time, standardized and validated data were used in this study, which improved the validity of the results.

Although we have received some of the interest results, there are also a few limitations. First of all, the cases amounts finally included in the research were limited, and there was no evaluation of the publication bias. The patients who were included came from different population, the operation methods for ultrasonic examination were different. Meanwhile, the other related reasons all included different checking machines, different training degree for operators, *and ect* [16-18]. We made subgroup and sensitivity analysis, a further limitation could also be found in the subjectivity of each variable in the study.

At present, it is widely accepted to apply Volpicelli method of B line positioning to detect ACPE, but the specific positioning in operation also depends on patient's position and maintenance time of a certain posture [19-25]. In 5 researches, patients were in dorsal decubitus or semireclining position. In 1 research, the patients were in their comfortable position. While there was no description in another study. It is still not clear that whether it will cause any

bias to the results of the research, a further confirmation is needed. At the same time, the evaluation of research quality, which includes in the research was poor ($\kappa=0.44$), and the instrument was Cochrane Collaboration. In the latest report, the value of kappas was between 0.53 and 0.82 by using this instrument. Quantitative quality assessment results were not shown in this meta analysis.

In conclusion, this study confirmed that B linear lung ultrasound could help emergency physicians to diagnose expiratory dyspnea, which was caused by acute cardiac pulmonary edema. B linear lung ultrasound processes good sensitivity and specificity, which could help emergency physicians diagnose moderate and severe pulmonary edema efficiently and accurately. If the ultrasound result was negative, then pulmonary edema could be excluded or only mild pulmonary edema exists, so a large number of specimens will be needed to confirm.

Disclosure of conflict of interest

None.

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