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Original Article

Effectiveness of ultrasound in acute pulmonary edema diagnosis in ICU: a meta-analysis

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Abstract: Acute dyspnea, mostly due to potentially life-threatening cardiac or respiratory conditions, is one of the common diseases in emergency. Ultrasound examination of the lungs has a valuable role in the exact diagnosis of pneumonia in ICU. This study aimed to evaluate the sensitivity and specificity of ultrasound in the diagnosis of acute dyspnea caused by acute cardiac pulmonary edema (ACPE) through systemic review and meta-analysis. PubMed, EMBASE, Ovid MEDLINE and the Cochrane Library databases were involved for scientific literature searching. The published date of the studies we searched was till January 2014, without the limitation of start time. Inclusion criteria were as follows: included studies were randomized controlled trials, prospective studies or prospective case-control studies; patients with acute dyspnea or suspected congestive heart failure; lung ultrasound was used for ACPE diagnosis with sensitivity and/or specificity. Patients with atypical symptoms or without ACPE were ruled out. Two reviewers independently searched the databases, screened the articles, and evaluated the quality of research method by QUADAS-2. Case analysis table was applied to analyze specificity and sensitivity. A total of seven studies (1075 patients) were conformed to the inclusion criteria with methodology evaluation as moderate to excellent. The sensitivity of ultrasound on ACPE diagnosis was 94.1% (95% CI: 81.3%-98.3%); and the specificity was 92.4% (95% CI: 84.2%-96.4%). Further subgroup analysis about research types, population distribution and ultrasound examine method showed no significant difference. Lung ultrasound presented high sensitivity and specificity to dyspnea caused by ACPE, which may assist emergency physicians to take accurate diagnosis, especially towards moderate pulmonary edema. Negative ultrasound result was characterized as excluding pulmonary or slight edema.

Keywords: Pulmonary edema, acute, ultrasound, meta-analysis

Introduction

Dyspnea caused by cardiac pulmonary edema is a common medical emergency. Aging patients or patients with obesity and chronic obstructive pulmonary disease (COPD) lay overwhelming burden for diagnosis and lead to a high death rate. Quick and accurate diagnosis is the key to the treatment [1-5]. Ultrasound examination offers favorable support on the fast and efficient diagnosis of a variety of emergency diseases. Plenty of researches suggested the application of ultrasound examination in acute dyspnea caused by cardiac pulmonary edema for auxiliary diagnosis [6, 7]. This system review intended to evaluate the accuracy of lung ultrasound on acute dyspnea caused by cardiac pulmonary edema, and further explore whether there is a threshold effect based on subgroup analysis of study type (cohort or case-control studies), patients' distribution, and specific ultrasound manipulation.

Methods

Literature research

We searched the PubMed, EMBASE, Ovid MEDLINE and the Cochrane Library databases with the following terms and all possible combinations: "lung ultrasound", "emergency", "acute pulmonary edema", "sensitivity", and "specificity". The published date of the studies we searched was till January 2014, without the limitation of start time. Endnote software (Thomson Reuters, US) was used for treating literatures. Related eligible summary was searched and the full text was obtained.

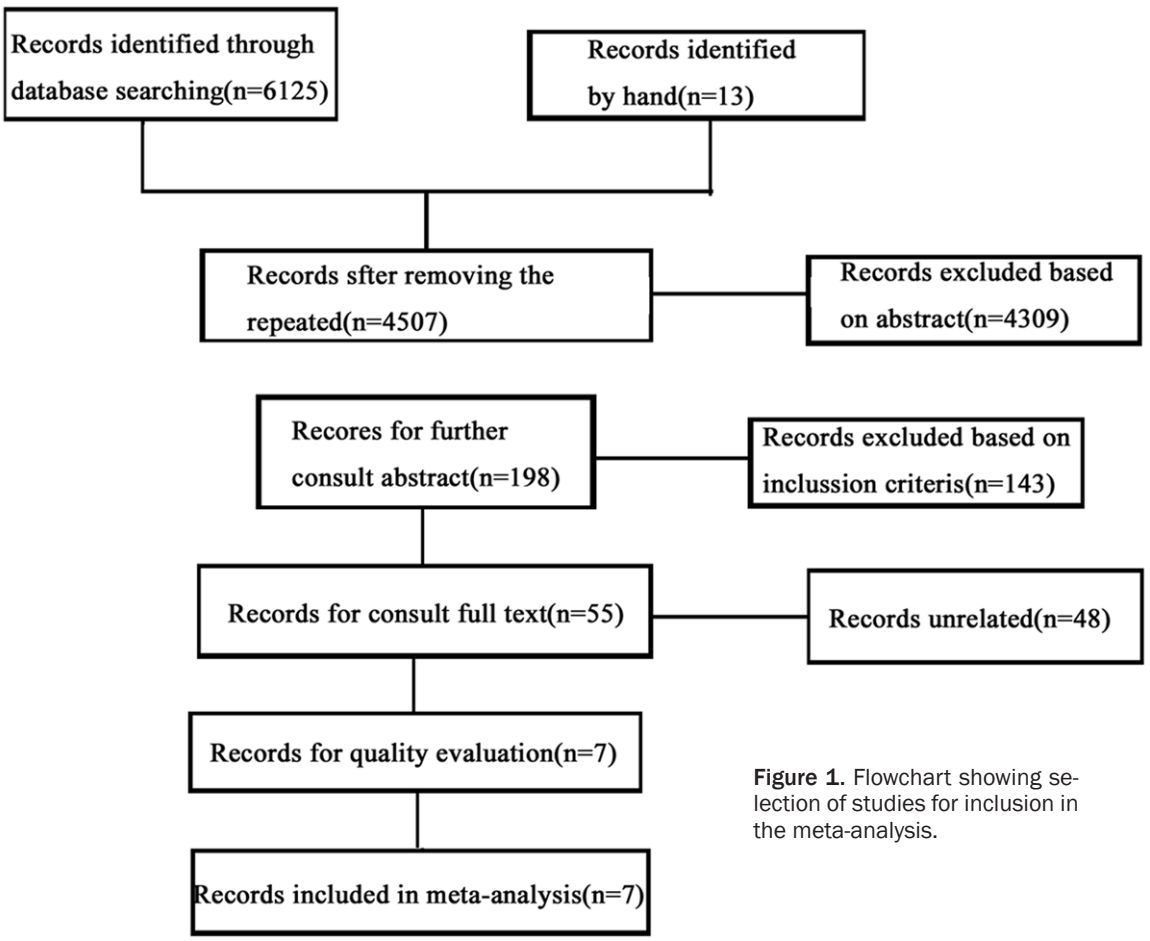

Figure 1. Flowchart showing selection of studies for inclusion in the meta-analysis.

Studies included in our review were required to meet the following criteria: (1) study type was prospective cohort study or prospective case-control study included the sensitivity and specificity of using ultrasound to diagnose ACPE. Case report, retrospective study, and other types of case-control study were excluded; (2) Patient featured as dyspnea in emergency and suspected for ACPE was included. Patient with atypical symptom or without ACPE was excluded; (3) Ultrasound parameter, machine, or operator was not limited. ACPE or diffused interstitial syndrome should be diagnosed using Volpicelli method (chest is divided into eight sections) [8]. Diagnosis was established when at least two sections appeared positive in each side of the chest wall or three groups appeared positive in rib gap [9, 10]. Specially, Vitturi et al. defined positive as eight groups of B line in the whole chest [11]. Gargani et al. defined cardiac dyspnea as the comet score over 5 [12]. Though there are no uniform diagnostic criteria for ACPE currently, the number of B line and the level of extra vascular pulmonary edema had clear linear relationship. As decompensated congestive heart failure was often difficult to distinguish from ACPE, lung ultrasound is one of the effective ways for auxiliary diagnosis. (4) Two investigators reviewed each eligible study and extracted data. Divergence would be solved via discussion with the third author.

Quality evaluation and risk assessment

Two investigators evaluated the quality of enrolled study independently using QUADAS-2, which mainly included the following aspects: (1) case selection; (2) detected parameter; (3) reference standard; (4) flow and time.

Higher bias risk may exist under following conditions: 1) case-control study; 2) patient selection was discontinuous or not random; 3) inappropriate adoption. Patient did not perform ultrasound in emergency or performed after knowing the chest X-ray result or BNP levels was considered with poor applicability.

Table 1. Basic characteristics of the enrolled studies

Name	Published time	Journal	Country	Case number	Ultrasound instrument	Probe type	Ultrasound manipulation	Reference standard	Examine time	Study type	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Lichtenstein 19	1998	Intensive Care Medicine	France	146	Hitachi 405	3.5-MHz cardiac	Lichtenstein	Blind case	< 1 min	Case-control	100	97
Lichtenstein 6	2008	Chest	France	260	Hitachi 405	5-MHz microconvex	Lichtenstein	Blind case	< 3 min	Cohort	97	95
Gargani12	2008	European Journal of Heart Failure	Italy	149	Philips Sono	2.5-to 3.5-MHz cardiac	Comet score	Blind case	< 5 min	Cohort	76.2	88
Liteplo7	2009	Academic Emergency Medicine	USA	94	Sonosite	2.5-MHz curved array	Volpicelli	Blind case	< 5 min	Cohort	58 (33-77)	85 (69-95)
Vitturi11	2011	Journal of Ultrasound	Italy	152	Toshiba Aplio XV	3.5-MHz convex	Comet score	Blind case	< 3 min	Cohort	97	79
Prosen22	2011	Critical Care	Slovenia	218	Sonosite	/	Volpicelli	Hospital diagnosis	< 1 min	Cohort	100 (98-100)	95 (91-100)
Cibinel23	2012	International Emergency Medicine	Italy	56	GE Electric LOGIQ 3	3.5-MHz convex	Volpicelli	Hospital diagnosis	< 5 min	Cohort	93.6	84

Table 2. QUADAS-2 methodology quality evaluation of enrolled studies

Study	Risk of bias				Possible error in actual application		
	Case selection	Detected parameter	Reference standard	Flow and time	Case selection	Detected parameter	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. Characteristics of ultrasound manipulator

Study	Manipulator number	Training level	Inherent reliability
Lichtenstein 19	Probably two	ICU physician	Unreported
Lichtenstein 6	2	ICU physician	Unreported
Gargani 12	Unknown	Unknown	Unreported
Liteplo 7	7	2 electrophysiological physicians and 5 trained medical students	0.82
Vitturi 11	Unknown	Unknown	0.98
Prosen 22	10	Electrophysiological physicians	Unreported
Cibinel 23	Unknown	Electrophysiological physicians	0.92

If a reference standard is not available for the exact determination of the target, the bias risk might be high. If the testing parameter has improper interval with reference standard, not all the patients receive the same reference standard, or not all patients are incorporated in the study, the bias risk might be high.

Data analysis

Forest plot was applied to assess the heterogeneity of sensitivity and specificity. The original purpose was to collect hierarchical summary receiver operating characteristic (HSROC) for meta-analysis. This model assumed that the ROC curve potentially existed in each study, which was similar to random effects model in traditional meta-analysis to some extent. Relevant variables existed within or between researches. The other advantage of this model was also characterized by controlling the reference standard, which was the common limitation for DTA research. Meanwhile, we performed subgroup analysis about disease category, basic characteristics and the operation approach. All data analysis was performed on STATA11.2 software (Stata, US).

Results

A total of 6125 articles were identified after searching the databases, another 13 articles were found manully (**Figure 1**). After screening 198 abstracts and 55 full-texts of these articles, 7 articles were finally included (1075 cases, **Table 1**). As shown in **Table 2**, QUADAS-2 quality evaluation revealed that all studies were between moderate and excellent. Ultrasound operators in all studies did not know the result of the reference standard. Only one research type belonged to case-control study. Five researches mentioned similar ultrasound examination method by detecting B line in anterior or lateral chest, and three groups or more B lines in at least two sections in each side of the chest were considered positive. Two studies used comet score for ACPE diagnosis (**Table 1**).

Ultrasound examination was conducted by trained doctors. In one study, however, some manipulation was performed by medical students. **Table 3** presented the related manipulator number. Three studies reported the internal reliability of the operator, but our study cannot compare the operator reliability in different studies. **Figure 2** revealed the sensitivity and

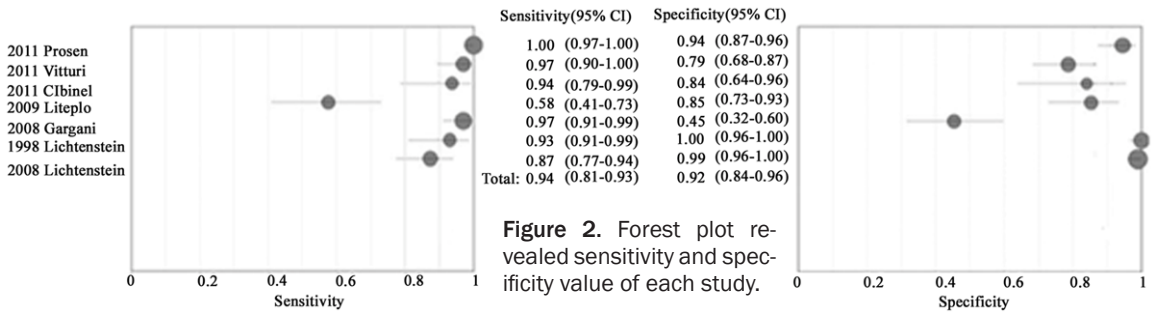

Figure 2. Forest plot revealed sensitivity and specificity value of each study.

Table 4. Two meta-analysis results

Variable	7 studies for meta-analysis	4 studies for meta-analysis
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)

Three studies including Liteplo and Lichtenstein were ruled out since their Cook's distance > 1.0. It suggested that they had large residual error and/or high impact to the overall result.

specificity value of different studies. The sensitivity of B line pulmonary ultrasound examination in diagnosing ACPE was 94.1% (95% CI: 81.3%-98.3%), and the specificity was 92.4% (95% CI: 84.2%-96.4%). Subgroup analysis demonstrated that research types, population distribution and ultrasound examine method had no significant impact. Further diagnosis threshold effect analysis did not show obvious correlation (Spearman correlation parameter was 0.393, P = 0.383).

Cook's distance measurement indicated that three studies might significantly affect the overall sensitivity and specificity analysis results. The research conducted by Liteplo et al. was excluded from the original meta-analysis to assess its impact on the overall results (Cook's distance was 2.03, 2.03) [14]. The sensitivity and specificity was 93.4% (95% CI: 81.8%-97.8%) and 88.8% (95% CI: 78.6%-94.5%), respectively (**Table 4**).

Discussion

The main purpose of this study was to evaluate the effectiveness and specificity of pulmonary ultrasound in emergency for the diagnosis of acute dyspnea caused by ACPE. Two studies from emergency (156 cases) exhibited different levels of sensitivity and specificity. The two studies both utilized Volpicellipulmonary ultrasonic method, but the methodological differences caused inconsistent results. The operators in Liteplo study mainly consisted of medical students, while operators in Cibinel were doctor-in-charge. Liteplo study may enroll patients with undefined diagnosis. All patients received NT-BNP testing, which may reduce further pulmonary ultrasound examination. Furthermore, all patients received pulmonary ultrasound examination after admission for a period of time when patients may have received diuretic or nitrate treatment. Their pulmonary edema level may significantly decrease resulting in the reduction of susceptibility. Thus, accurate investigation about dyspnea patient in emergency is inevitable [8-10].

Other test methods for cardiac pulmonary edema, such as chest X-ray and BNP, are also of great importance. It was reported that the sensitivity and specificity of chest X-ray in diagnosing ACPE were 14%-68% and 53%-96%, respectively. The latest two meta-analysis studies on BNP recommended BNP test to exclude ACPE. However, the two methods presented poor timeliness and convenience in emergency cases. By contrast, pulmonary ultrasound had the advantages of high efficiency, convenient, and good repeatability to help clinical decision-making and treatment [11-15]. Our results showed the performance of pulmonary ultrasound being conducted on the bed, which not only assisted ACPE diagnosis, but quickly distinguished ACPE from other causes for acute dyspnea disease (for example, COPD acute exacerbation). It is vital for patients in emergency [16, 17]. In the study, we used strictly searching strategy and performed systematical review. Moreover, we utilized standardized and validated data to limit bias and improve the reliability.

There are still somehow limitations in the study. The number of enrolled cases was not sufficient enough. We also did not assess the publication bias. Enrolled patients were from different populations, and the ultrasonic inspection method was not consistent. Other relevant factors included different inspection machine and operators' different training levels [18-20]. We performed subgroup analysis and sensitivity analysis. It was found that the limitation includes subjectivity in each variables and a lack of definite diagnosis for ACPE.

The Volpicelli method for the detection of ACPE in B line positioning has been widely accepted, but the specific positioning depends on patient's posture and posture maintaining time [21-25]. Whether it may affect bias is still unclear and needs further investigation. Meanwhile, quality evaluation of the enrolled studies was poor (kappa = 0.44). We used Cochrane Collaboration for assessment, while it was reported that the kappa value was between 0.53 and 0.82 in using this tool. The quantitative result of the quality assessment was not involved in this meta-analysis.

To sum up, this study confirmed that B line pulmonary ultrasound could assist diagnosing acute dyspnea caused by cardiac pulmonary edema. It presented good sensitivity and specificity. Specially, ultrasound may help emergency physicians make accurate diagnosis for moderate and severe pulmonary edema. Negative ultrasound result was characterized as excluding pulmonary or slight edema. Further large-scale investigation still needs to be further conducted to conclusively define such a role.

Disclosure of conflict of interest

None.

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