Accuracy of Bedside Lung Ultrasound in Emergency (BLUE) Protocol to Diagnose the Cause of Acute Respiratory Distress Syndrome (ARDS): A Meta-Analysis

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ABSTRACT

Background**:** *There is a stigma that ultrasound cannot be used to see abnormalities in the air-filled organs makes ultrasound rarely used to identify lung abnormalities. This study purpose comparing diagnostic accuracy of BLUE protocol with gold standard for each diagnosis causing acute respiratory failure.* ***Methods*****:** *Systematic search was done in 6 databases (Pubmed/MEDLINE, Embase, Cochrane Central, Scopus, Ebscohost/CINAHL dan Proquest) and multiple grey-literature sources for cross-sectional studies. We manually extracted the data from eligible studies and calculated pooled sensitivity, pooled specificity, likelihood ratio (LR) and diagnostic odds ratio (DOR). We follow PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline throughout these processes.* ***Results*****:** *Four studies has been picked from total 509 studies involved. The results yield parameters indicating BLUE protocol as a reliable modality to diagnose pneumonia with pooled sensitivity 84% (95% CI, 76-89%), pooled specificity 98% (95% CI, 93-99%), LR+ 42 (95% CI, 12-147), LR- 0.12 (95% CI, 0.07-0.2) and DOR 252 (95% CI, 81-788), respectively. It also considerably applicable to diagnose pulmonary oedema with pooled sensitivity 89% (95% CI, 81-93%), pooled specificity 94% (95% CI, 89-96%), LR+ 14 (95% CI, 8-25), LR- 0.165 (95% CI, 0.11-0.24), and DOR 116 (95% CI, 42-320), respectively.* ***Conclusion*****:** *BLUE protocol has good diagnostic accuracy to diagnose pneumonia and pulmonary oedema. We recommend implementing BLUE protocol as a tool in evaluating cause of ARF.*

Keywords**:** *Ultrasonography, BLUE protocol, Accuracy, Respiratory Failure, Meta-analysis*

INTRODUCTION

Dyspnea is a common symptom and is an important sign of acute respiratory failure (ARF). This condition is a life-threatening situation and it is not uncommon for patients with ARF to require intensive oxygen therapy such as a mechanical ventilator. The case of ARF continues to increase every year with a mortality rate reaching 37%. Determining the cause of respiratory failure is an important step in the management of ARF.[1-3]

The BLUE (Bedside Lung Ultrasound in Emergency) protocol is an ultrasound examination algorithm of the lung to assist in searching for the diagnosis of various lung disorders by combining various artefacts.[4-9] The accuracy of the BLUE protocol reaches 90.5% with a duration of approximately 3 minutes, so this Protocol very suitable for use in patients with ARF. However, the stigma that ultrasound cannot be used to see abnormalities in the air-filled organs makes ultrasound rarely used to identify lung abnormalities.[9-10]

Through this meta-analysis, the authors are going to assess several previous studies regarding the accuracy of the BLUE Protocol in diagnosing pulmonary disorders. With prompt and precise diagnosis, appropriate management for the patient can also be achieved. This study aims to determine the accuracy of the BLUE protocol in diagnosing the causes of ARF.

METHODS

Search Strategy

A comprehensive search was carried out from six online databases namely Pubmed/ MEDLINE, Embase, Cochrane Central, Scopus, Ebscohost/CINAHL, and Proquest on 6-13 September 2020 . The search is performed with a combination of keywords based on MESH and text word combined with the Boolean operator. The keywords used come from the Population and Index Test components of the research questions that have been formulated. The keyword used from the Population component is Acute Respiratory Failure with its synonym and examples of the diagnosis of the cause of respiratory failure. The keyword used in the Index Test component is the BLUE protocol or Bedside Lung Ultrasound in Emergency. A manual search for grey-literature was carried out at various sources on September 7, 2020. The search was carried out on several portals, namely the GARUDA portal (Indonesia Ministry of Research and Technology Portal), Proquest (focus on thesis results, dissertations, scientific posters, or proceeding books), abstracts from the scientific book Jakarta International Chest and Critical Care Internal Medicine (JICCIM) in the last 5 years, snowballing method, the repository of the Library of the University of Indonesia and the National Library as well as the Global Index Medicus (GIM).

Study Selection

Inclusion criteria are diagnostic studies with a cross-sectional design, study subject age > 18 years, and comparing the diagnostic ability of the BLUE protocol with the gold standard. No language or year limits were applied. Exclusion criteria were studies that didn't include data to calculate overall accuracy. The assessment of risk of bias and study quality was carried out by APA dan CWP. If there are differences of opinion regarding the selection criteria of an article, it will be resolved through consensus and reviewed by KH. The authors use the Covidence® software to assist in the selection stages of articles in this meta-analysis.

Ethics Approval and Consent to Participate

PROSPERO Systematic Review Registry number: CRD42020203208.

BLUE Protocol Method

Bedside lung ultrasound examination was introduced by Dr. Lichtenstein in 1989 to monitor critically ill patients in ICU setting. It has been widely used for detecting many lung disorders such as pleural effusion, pulmonary oedema, pneumothorax, pneumonia, and pulmonary embolism. He formulized the lung ultrasound findings into one framework called BLUE Protocol and become one of the most important parts of Point of Care Ultrasound (POCUS). In BLUE Protocol, patients were positioned in semi recumbent or supine position. Scans were done longitudinally and evaluated based on artefacts finding on some certain anatomical landmarks. The normal

lung is characterized by normal A or B Line with lung sliding. BLUE Protocol also evaluate the presence of alveolar consolidation and/or pleural effusion.[10] Details of the BLUE protocol's component is shown in **Figure 1**.

Data Extraction and Quality Assessment

Data extraction was carried out independently by two researchers. Basic characteristics data such as name of the principal investigator, type of study, place/country, year of publication, basic demographic characteristics of study subjects, population eligibility, eligibility of the gold standard used, sample size, characteristics of the ultrasound device, The characteristics of the ultrasound operator, duration of lung ultrasound, blinding, and comparison of outcomes from selected studies will be displayed in the form of a descriptive table. The output is written in a 2x2 table form and is displayed in terms of sensitivity and specificity. The performance of the BLUE protocol is displayed in the form of a receiver operating characteristic (ROC) curve. Assessment of the quality and risk of bias of selected studies was carried out using the Quality Assessment of Diagnostic Accuracy Study - 2 (QUADAS - 2).

Data Synthesis and Statistical Analysis

Statistical analysis on this meta-analysis was performed using RevMan software version 5.4 (Cochrane Collaboration, the Nordic Cochrane Center, Copenhagen) and STATA 14. The results of data analysis are presented in the form of a forrest plot if meta-analysis can be done. Heterogeneity assessed using I^2 or X^2 test with result of I^2 <25%, 26-50%, and >50% reflecting low or insignificant, moderate, and significant heterogeneity, respectively. Fixed-effect model was chosen for insignificant heterogeneity, otherwise random-effect model was used. The expected results are in the form of accuracy, sensitivity, and specificity along with the confidence interval, likelihood ratio, diagnostic odds ratio, and the area under the ROC curve. The analysis was carried out in the form of an accumulation of all diagnoses and then continued with the analysis of each diagnosis.

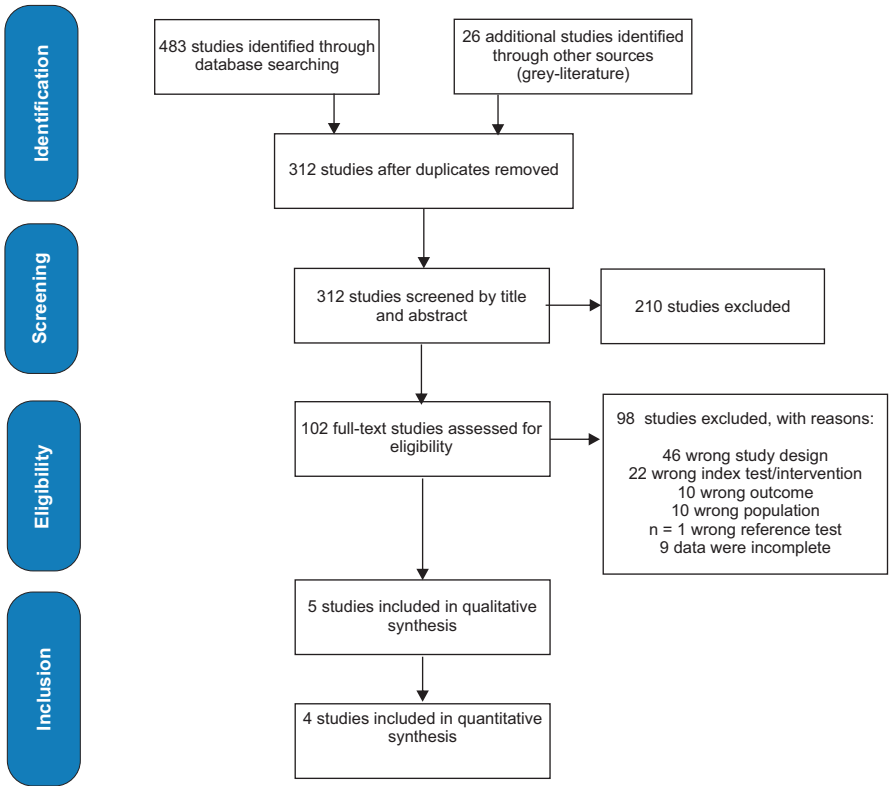


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram for Study Selection

RESULTS

Literature search

Based on the systematic search carried out, a total of 509 articles were obtained and after adjusting for the eligibility criteria only 4 studies could be continued for the meta-analysis process (**Figure 1**).

Study Characteristics

In general, these studies classified as homogenous because most of the important characteristics were almost the same such as population eligibility, the unit site of the study, BLUE protocol implementation, ultrasound device/specification, gold standard used, and the presented output (**Table 1** and **2**). The unit/site used for Lichtenstein, Neto, and Danish study is the ICU whereas Patel and Bekgoz study takes place at the ER. The ICU and ER has almost the same characteristics, both taking care patient with breathing problem which life-threatening cases and require immediate care. From the origin of the country of the study, the findings from this meta-analysis could represent various types of major populations in the world.[11-14]

The population eligibility used by the five studies is almost the same which is patients with breathing problem and admitted into the criteria of breathing failure with indication intensive care. Patel's research used population age above 12 years which is different from the other four studies which used adult population. The author had sent email correspondence on requisition for research data by Patel et al. however, to the date of this report is finished, the author had not received any reply therefore the author excluded Patel et al. research in both qualitative and quantitative synthesis. However, the author tried to include Patel et al research in sensitivity analysis to see if its exclusion from this research would produce significant output relative to the findings of this meta-analysis. The total samples used in the 4 studies is 770 patients.

There is a difference in the ultrasound operator which performs the BLUE protocol. In the Lichtenstein, Bekgoz, and Danish studies, they used certified ultrasound operators with 2 years minimum experience on lung ultrasound. Neto et al used ultrasound operators who had received 5 hours theoretical training and performed 10 times lung ultrasound under supervision. The probes used in the five studies have similar characteristics, they are the probes with low frequency (curvilinear and microconvex) which frequency range 2-6 MHz. Low-frequency probes is the best option for lung ultrasound because it has broader and deeper exploration area than high-frequency probes.[11-14].

Assessment of Risk of Bias

Two reviewers (O.D.A and A.P.A) evaluate the methodological quality of included studies according to Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria. The assessment shown in **Figure 2**. Any discrepancies found would be resolved by consultation with the third expert reviewer (K.H).

Data synthesis and analysis

The results of t he included studies can be seen in **Table 3**. From all of the studies, it was found that the sensitivity of the BLUE protocol in diagnosing pneumonia was in the range of 83% to 97% with the combined sensitivity calculation being 84% (95% CI 76-89%). Whereas the specificity of the BLUE protocol in diagnosing pneumonia was in the range of 86% to 100% with the combined specificity calculation was 98% (95% CI 93-99%). Forest plot for pneumonia can be seen in **Figure 3** and summary receiving operating characteristic (SROC) curve can be seen in **Figure 4**. The combined result of LR + is 42 (95% CI 12-147) and and LR- 0.12 (95% CI 0.07–0.2) respectively with DOR of 252 (95% CI 81–788).

In diagnosing pulmonary edema, the sensitivity of the BLUE protocol was found to be in the range of 76% to 94% with a combined sensitivity calculation of 89% (95% CI, 81-93%). Meanwhile, the specificity of the BLUE protocol in diagnosing pneumonia is in the range of 90% to 100% with the calculation of the combined sensitivity is 94% (95% CI, 89-96%). The combined results for LR+ were 14 (95% CI, 8-25) and LR- 0.165 (95% CI, 0.11-0.24), respectively, with a DOR number of 116 (95% CI, 42-320). Forest plot for pulmonary edema can be seen in **Figure 5** and summary receiving operating characteristic (SROC) curve can be seen in **Figure 6**.

Table 1. Study Characteristics.

Study	Year	Country	Unit	Study Design	Number of Patients	Inclusion Criteria	Mean Age	Ultrasound Operator	Ultrasound Device	Number of Area	Blinded
Lichtenstein et al[11]	2008	France	ICU	Cross sectional	260	adult patients with acute respiratory failure	68	Investigators (several years of experience)	Microconvex probe 5-MHz (Hitachi-405; Hitachi Medical; Tokyo, Japan)	6 points	No, investigators were not blinded to the patient's clinical presentation
Neto et al[12]	2015	Brazil	ICU	Cross sectional	37	age ≥ 18 years and admission to the ICU for ARF, defined by one of the following: a respiratory rate ≥ 30 breaths/ min; a PaO2 ≤ 60 mmHg; an oxygen saturation on room air ≤ 90%, as measured by pulse oximetry; or a carbon dioxide tension (PCO2) ≥ 45 mmHg with an arterial pH ≤ 7.35	73.2	Newly trained operators (attending 5 hours of theoretical training and performing 10 supervised LUS examinations)	Curvilinier Probe 3-5 MHz (Toshiba Tosbee; Toshiba, Tokyo, Japan)	6 points	Yes
Patel et al[15]	2018	India	ER	Cross sectional	50	Patients having age >12 years, Patients and/or relatives giving informed consent, Patients of acute respiratory distress requiring ICU admission were included.	59.64	Ultrasound was performed in emergency department by same emergency physician	Curvilinier (2-5 MHz) and Linear probe (5-10 MHz), Micromax ultrasound system, Sonosite	6 points	No
Bekgoz et al[13]	2019	Turkey	ER	Cross sectional	383	All consecutive patients aged >18 years admitted to the ED with a primary complaint of acute dyspnea and who consented to paricipate	65.5	LUS was conducted by 5 ED physicians who had been previously certified by basic and advanced US education and had at least 2 years of ED and US experience. These ED physicians were also informed by 2 h of theoretical lectures regarding LUS and the BLUE protocol. They also performed 10 supervised LUS examinations according to the BLUE protocol	Microconvex probe 2-6 MHz (Fujifilm Fazone CB, Japan)	4 points	Yes
Danish et al[14]	2019	India	ICU	Cross sectional	90	Adult patients admitted to medical-surgi- cal ICU who had evidence of lung pathology as demonstrated by an acute lung injury (ALI) score of ≥1	47.66	The intensivist performing LUS had >2 years of experience in performing LUS	Curvilinier Probe (2-5 MHz) SonoSite M-turbo (Fujifilm SonoSite Inc., Bothell, WA, USA)	3 points	Yes

Table 2. Gold Standards Used in Included Studies.

	Lichtenstein et al[11]	Neto et al[12]	Patel et al[15]	Bekgoz et al[13]	Danish et al[14]
Pneumonia	Infectious profile, radiologic asymmetry, microorganism isolated (blood, invasive tests), recovery with antibiotics. Included were infectious, aspiration, community, or hospital-acquired pneumonia. Pneumonia complicating chronic respiratory disease was classified as pneumonia	Not stated	Infectious profile, radiologic asymmetry, microorganism isolated (blood), recovery with antibiotics	infection findings, chest X-rays, microorganism isolation (if possible), CT (if necessary)	Not stated
Pulmonary Edema	Evaluation of cardiac function using echocardiography, functional tests, and American Heart Association recommendations	Not stated	Chest radiography, evaluation of cardiac function using echocardiography, responding to diuretics	electrocardiography, cardiac biomarkers echocardiography (by a cardiologist)	Not stated
Pneumothorax	Radiography (CT if necessary)	-	Chest radiography (CT if necessary)	Chest X-rays and CT (if necessary)	Not stated
Pulmonary Embolism	Helical CT	-	Helical CT	Thorax CT angiography	-
Asthma/COPD	Asthma (History, responds to bronchodilator treatment) COPD (Condition defined as exacerbation of chronic respiratory disease without pneumonia, pneumothorax, pulmonary edema, pleurisy, or pulmonary embolism. COPD was confirmed by functional tests.)	Not stated	History, responds to bronchodilator treatment, chest radiography, and COPD was confirmed by functional tests	History, respiratory functional tests, and responses to bronchodilator treatment	-
For all patients	History, clinical examination, radiography read by radiologists, CT when available, favorable clinical progression under treatment	The final diagnosis of the episode of ARF made by the ICU team before patients were discharged from the ICU was considered the gold standard	For all patients: History, clinical examination, basic blood tests and specific blood investigations (arterial blood gas analysis, D-dimer), electrocardiography, radiography reporting by radiologists, CT as needed, favorable clinical progression under treatment was followed along with	The final clinical diagnosis was made by attending emergency physicians (for 215 ED patients before discharge from the ED), attending consultant physicians (for 126 hospitalized patients before discharge from the hospital), and an ICU team (for 46 ICU patients before discharge from the ICU)	Thorax CT scan

Table 3. Results of Included Studies

	Lichtenstein et.al[11]		Neto et.al[12]		Patel et.al[15]		Bekgoz et.al[13]		Danish et.al[14]	
	Sn (%)	Sp (%)	Sn (%)	Sp (%)	Sn (%)	Sp (%)	Sn (%)	**Sp (%)**	**Sn (%)**	**Sp (%)**
Pneumonia	89	94	88	90	94.11	93.93	82	98	75.9	100
Pulmonary Edema	97	95	85	87	92.3	100	87	97	83.3	88.5
Pneumothorax	88	100	-	-	80	100	85	100	88.9	100
Pulmonary Embolism	81	100	-	-	100	100	46.2	100	-	-
Asthma/ COPD	89	97	67	100	85.17	88.88	96	75	-	-

Table 4. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) of Each Outcome[16]

GRADE Recommendations for BLUE Protocol Accuracy by Each Outcomes					
GRADE Domain	**Pneumonia (4 cross-sectional studies)**	**Pulmonary Edema (4 cross-sectional studies)**	**Pneumothorax (3 cross-sectional studies)**	**Pulmonary Emboly (2 cross-sectional studies)**	**Asthma/COPD (3 cross-sectional studies)**
Risk of Bias	None	None	None	None	None
Inconsistency	None	None	None	Serious (-1)	Serious (-1)
Indirectness	None	None	None	None	None
Imprecision	None	None	Serious (-1)	Serious (-1)	Serious (-1)
Publication Bias	None	None	Serious (-1)	Serious (-1)	Serious (-1)
Certainty of Evidence	⊕⊕⊕⊕	⊕⊕⊕⊕	⊕⊕◯◯	⊕◯◯◯	⊕◯◯◯
Results					
Sensitivity	84%	89%	71-89%	46-81%	50-98%
Specificity	98%	94%	100%	99-100%	69-100%

⊕⊕⊕⊕	High certainty (we are very confident that the true effect lies close to that of the estimate of the effect)
⊕⊕⊕◯	Moderate certainty (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)
⊕⊕◯◯	Low certainty (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect)
⊕◯◯◯	Very low certainty (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

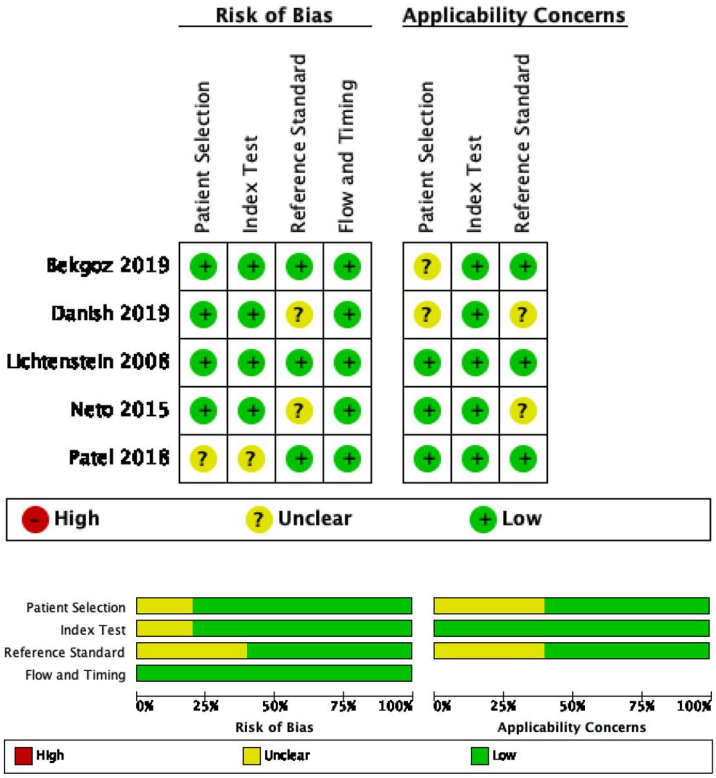
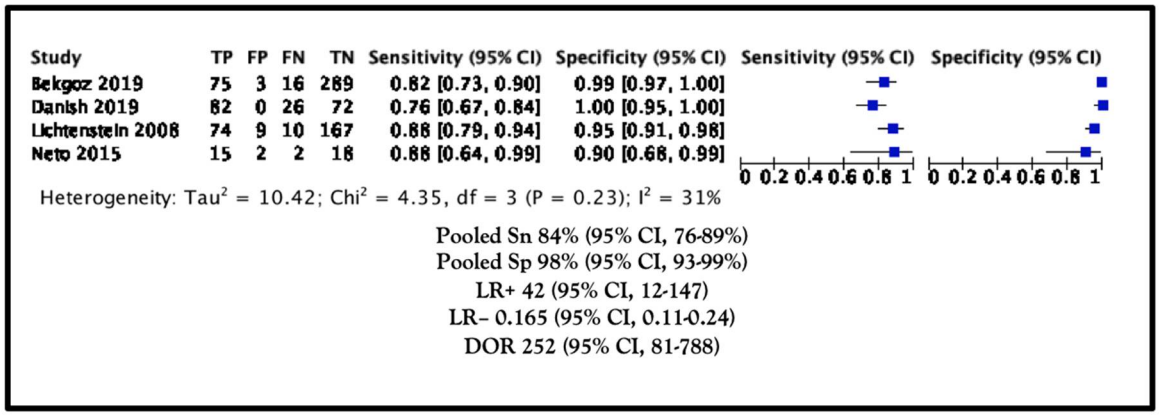


Figure 2. Quality of Assessment of Included Studies by QUADAS-2 Tool.



CI = *confidence interval*; DOR = *diagnostic odds ratio;* FN = *false negative*; FP = *false positive*; LR+ = *Positive likelihood ratio*; LR- = *Negative likelihood ratio*; Sn = *Sensitivity*; Sp = *Specificity*; TN = *true negative*; TP = *true positive*

Figure 3. Forest Plot and Diagnostic Accuracy of BLUE Protocol for Pneumonia.

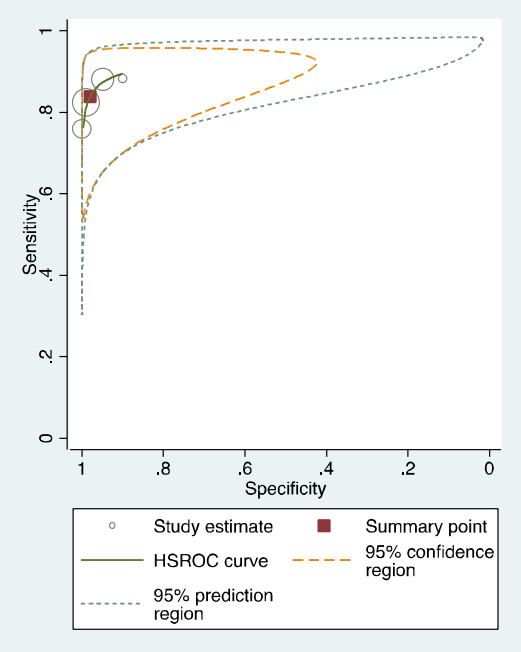
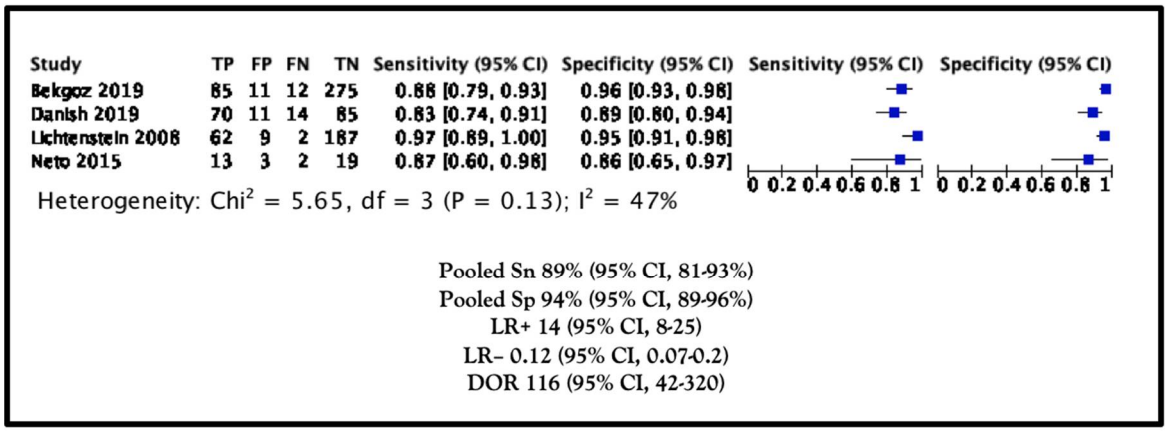


Figure 4. Summary Receiving Operating Characteristic Curve of BLUE Protocol for Pneumonia



CI = *confidence interval*; DOR = *diagnostic odds ratio;* FN = *false negative*; FP = *false positive*; LR+ = *Positive likelihood ratio*; LR- = *Negative likelihood ratio*; Sn = *Sensitivity*; Sp = *Specificity*; TN = *true negative*; TP = *true positive*

Figure 5. Forest Plot and Diagnostic Accuracy of BLUE Protocol for Pulmonary Edema

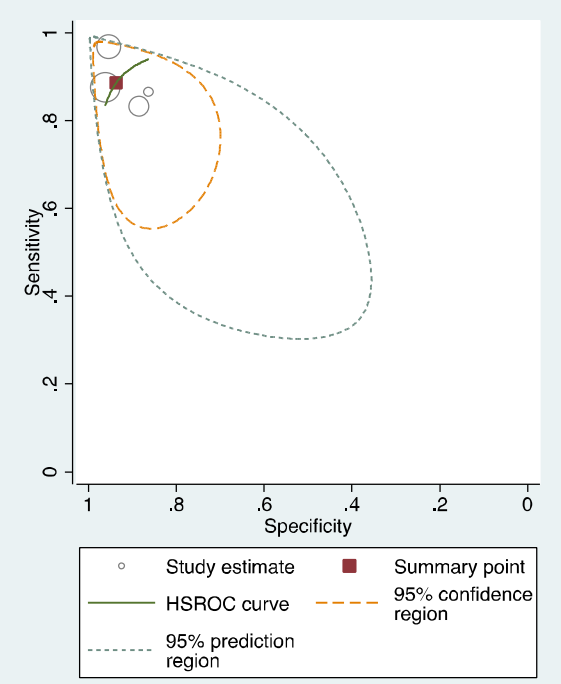
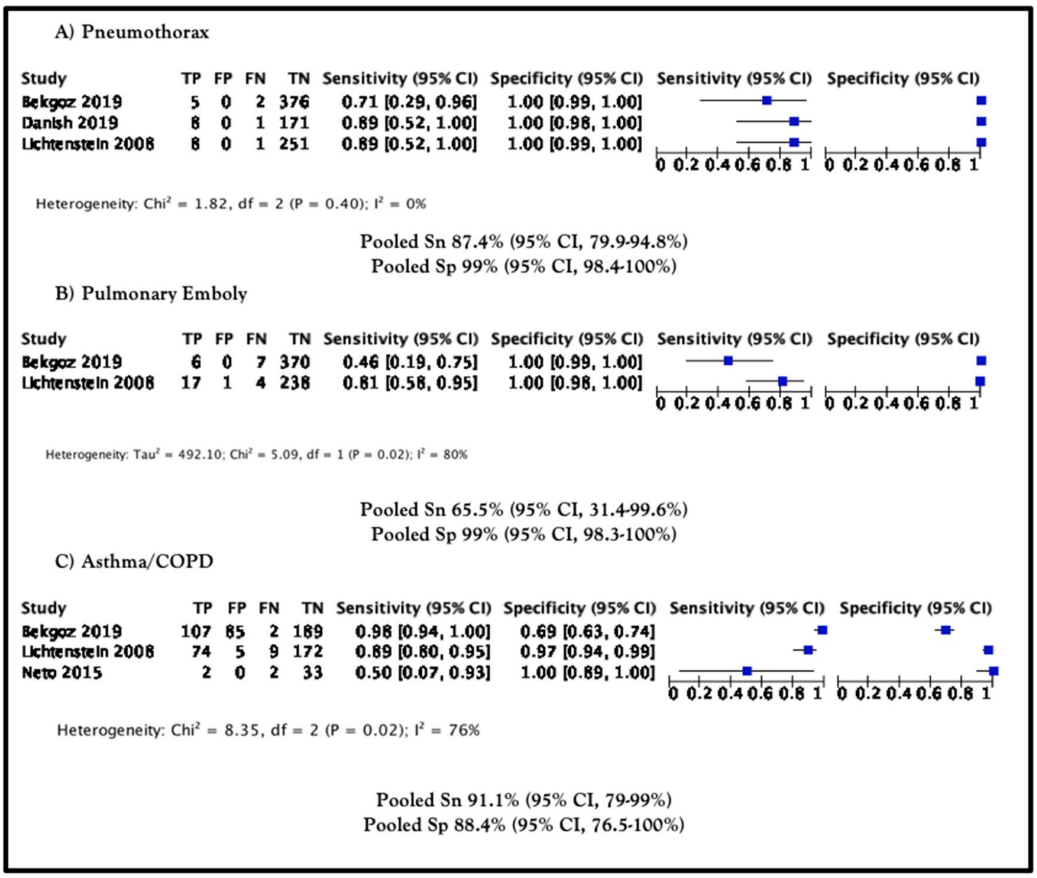


Figure 6. Summary Receiving Operating Characteristic Curve of BLUE Protocol for Pulmonary Edema



CI = *confidence interval*; FN = *false negative*; FP = *false positive*; Sn = *Sensitivity*; Sp = *Specificity*; TN = *true negative*; TP = *true positive*

Figure 7. Forest Plot and Diagnostic Accuracy of BLUE Protocol for Pneumothorax, Pulmonary Emboly, Asthma/COPD

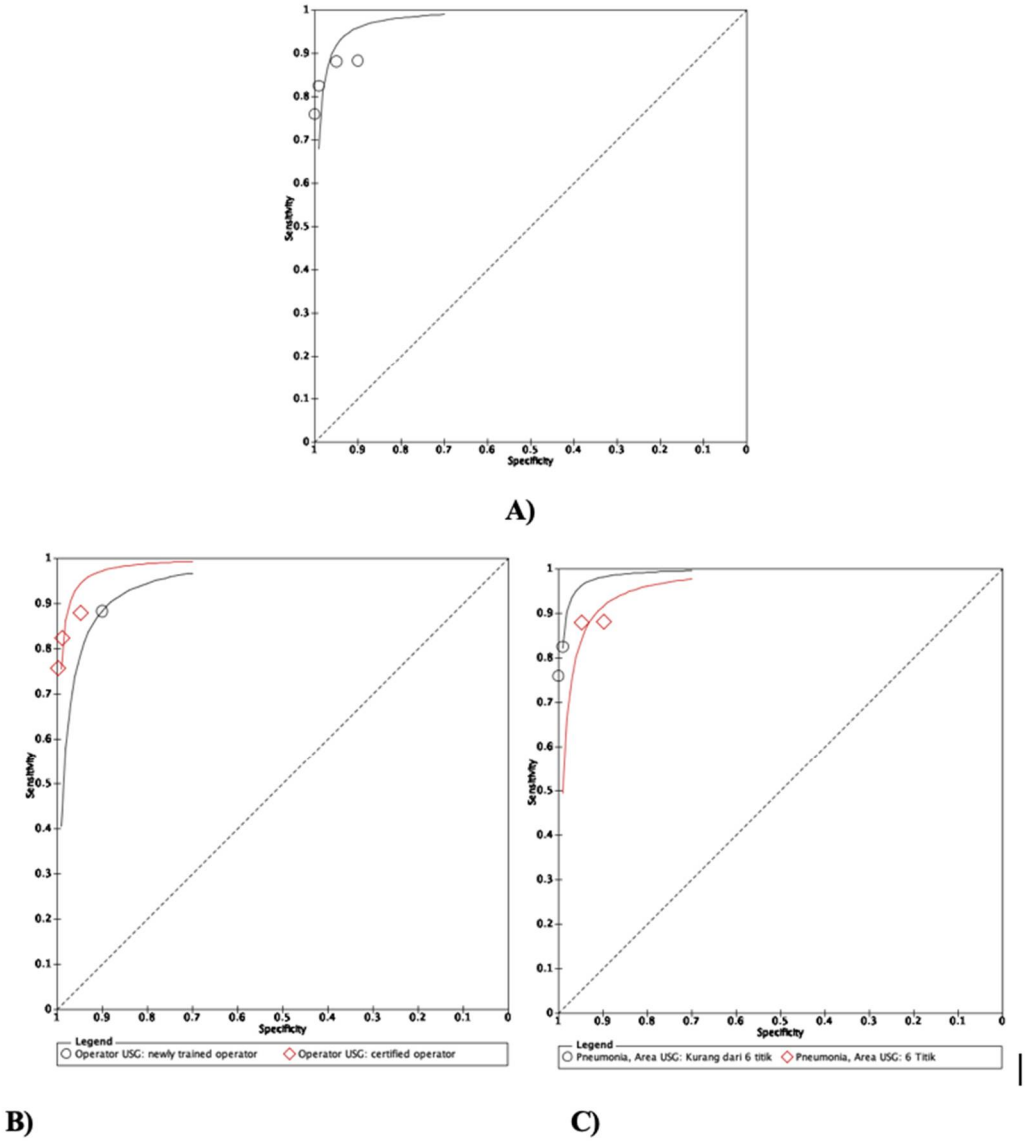


Figure 8. Area Under Curve (AUC) BLUE Protocol for A) Pneumonia B). Subgroup Analysis: Ultrasound Operator C) Subgroup Analysis: Number of Ultrasound Zone.

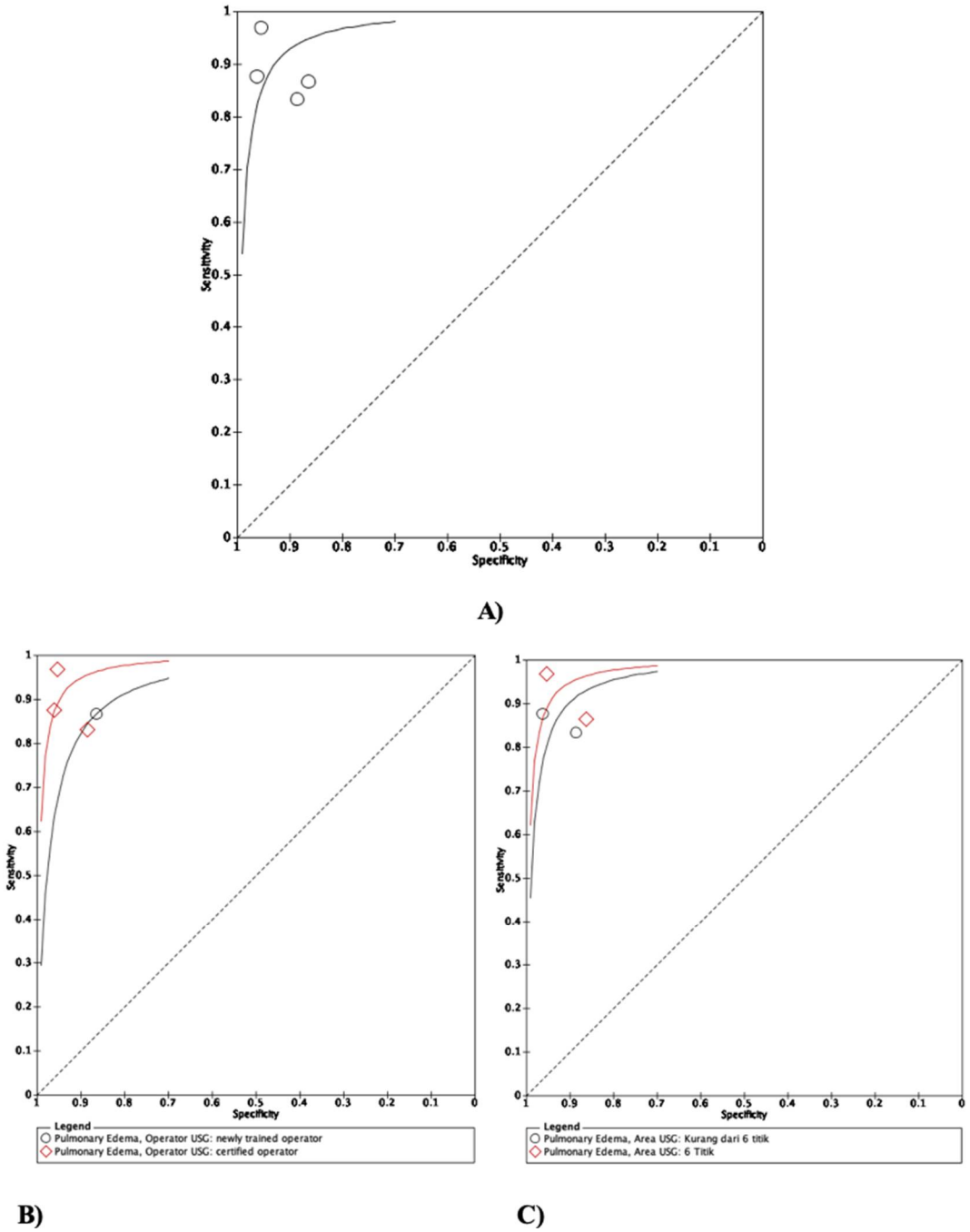


Figure 9. Area Under Curve (AUC) BLUE Protocol for A) Pulmonary Edema B) Subgrup Analysis: Ultrasound Operator C) Subgroup Analysis: Number of Ultrasound Zone.

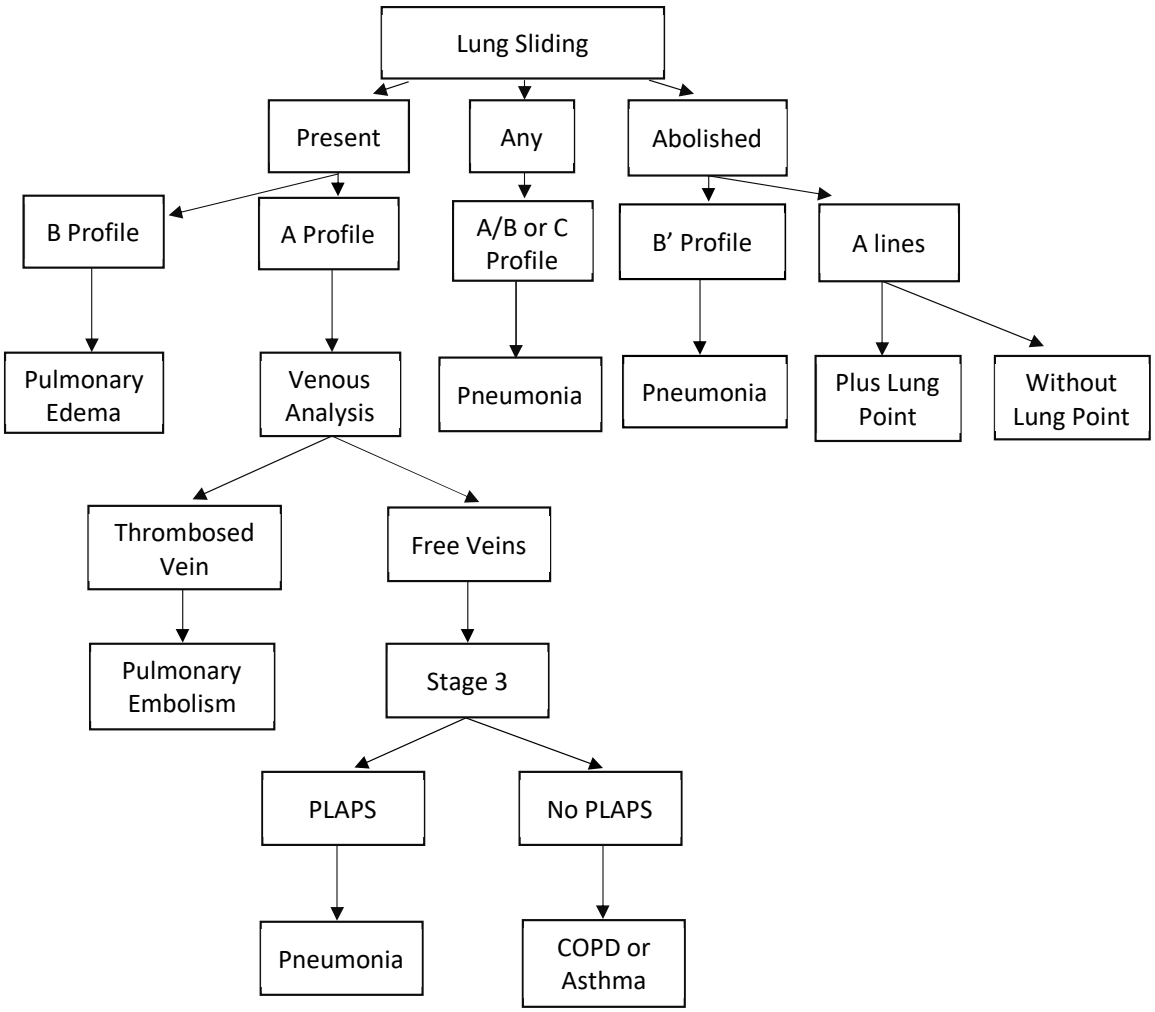


Figure 10. BLUE Protocol Alghoritm

Not all studies have examined every diagnosis used by Lichtenstein as the original author of the BLUE protocol. The sensitivity and specificity ranges of the BLUE protocol in pneumothorax are 71-89% and 50-98%, in pulmonary emboli it ranges from 46-81% and 100%, and in asthma/COPD ranges from 50-98% and 69-100%, respectively. Forest plot for pneumothorax, pulmonary emboli, and asthma/COPD can be seen in **Figure 7**.

DISCUSSION

Several meta-analyses on the roles of lung ultrasound for diagnosing lung abnormalities had been conducted by previous researchers. The author recorded that there are at least 4 meta-analysis with lung ultrasound topics in diagnosing pneumonia. The main difference of this meta-analysis with previous study is in the population. This study enrolled all patients with breathing problems whereas the previous 4 meta-analysis studies specifically enrolled population suspected with pneumonia. During the search process, the authors found 14 original studies that discussed the accuracy of BLUE protocol but among them, there were 9 studies in the form of gray-literature that could not be included in the analysis because there was no complete text. Another limitation is that there are studies that did not include findings of pleural effusions. The discovery of a pleural effusion may guide the diagnosis of pulmonary disorders.[32-35] In addition, the intervention/index test used by those meta-analysis studies were not standardized, whereas this study specified the assessment on the accuracy of the BLUE Protocol. However, the

accuracy of this 4 meta-analyses are nearly even with current study. The range of sensitivity and specificity of the lung ultrasound in pneumonia diagnosis by meta-analysis conducted by Chavez et al. is 80-95%, Ye et al., Long et.al, Llamas-Alvarez et al. is 70-96%, consecutively.[7, 15-17]

Three of five studies analyzed by this study included the operator who didn't know the patient's clinical and still produce good accuracy because the ultrasound output is objective. Ultrasound accuracy might be better if it is adjusted with patient's clinical examination data. History taking and physical examination is mandatory and irreplaceable. Lung ultrasound is complimentary of history taking and physical examination to enhance the physician's diagnosis probability. A study in Italy by Peris et al. shows that lung ultrasound could reduce the need for thorax X-Ray imaging by 26% and thorax CT scan by 47%.[1, 28-31]. We use GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to summarize our recommendations. Summary of this approach for this meta-analysis is shown in **Table 4**.[36]

In sensitivity analysis calculation, the author included Patel et al. study and compared it to the analysis results without Patel et al. The author analyzed the accuracy of pneumonia diagnosis using the 5 studies in total and obtained the aggregate sensitivity 85% (95%CI 78-90%), specificity 97% (95%CI 93-99%), LR positive 34 (95%CI 12-94%), LR negative 0.15 (95%CI 0.1-0.23%) and the DOR 222 (95%CI 89-554%). These findings is not much different with the findings of the 4 studies which qualified the inclusion criteria presented in this paper.[14]

The sensitivity of the BLUE Protocol for pulmonary emboli and asthma/COPD has varied range from 46% to 98%. This inconsistent result might be caused by the BLUE Protocol algorithm to diagnose lung emboli and asthma/COPD which is based on exclusion criteria and it needs to be confirmed with emboli findings in extremity's vein. Performing ultrasound on the extremity's vein requires a skilled operator and longer ultrasound procedure. From the date, the author did not recommend lung ultrasound to screen asthma/COPD or lung emboli, but if emboli was found in the vein extremities and no lung image abnormality in any case this might lead to emboli diagnosis. This is also found in pneumothorax cases which image shows the loss of lung sliding and the presence of lung point and barcode sign which is specifically found in pneumothorax.[18-20] The ultrasound area used in the five studies is almost the same except in the study by Danish et al. and Bekgoz et al. Lichtenstein et al., Neto et al., and Patel et al., in performing lung ultrasound at 6 points of each hemithorax, therefore, resulted 12 examined points in total. Danish et al. performed lung ultrasound at 3 points of each hemithorax and the total is 6 points and Bekgoz et al. performed it at 4 points and the total is 8 points of all lung areas. This variability might explain the lower sensitivity value of pneumonia and lung edema in the research by Danish et al. and Bekgoz et al. when compared to other researches. Lung edema yield better AUC value in 6 points examination of each hemithorax (**Figure 8** and **9**). This is slightly different on pneumonia which shows that the lung ultrasound at 6 locations did not any better than 3 or 4 locations.[11-15]

The four studies also show that the lung ultrasound can be performed within the first 20 minutes when the patient is admitted to the intensive unit or emergency unit without any necessary interruption to the standard procedure because the duration of the examination is brief and performed beside the patient's bed. Lichtenstein et al. and Bekgoz et al. only need less than 3-5 minutes, sequentially to complete the BLUE protocol. The lung ultrasound can be performed while other medic or paramedic doing other procedures. For any patient who needs advanced breathing support, lung ultrasound can also be performed right after the procedure without having to remove the patient to radiology unit.[21-23]

Operator bias tends to be found in ultrasound examination. Subgroup analysis with operator competence as a variable showed an experienced and certified operator yield better accuracy than newly trained operators, in both groups. However, the accuracy level of newly trained operators is considerably good in both groups. The operator in Neto et al. research is a rookie doctor in lung ultrasound who received 5 hours BLUE

protocol theoretical training and performed 10 lung ultrasounds under supervision. The research shows sensitivity 85-88% and specificity 87-90% to detect lung edema and pneumonia. Certain shows that the BLUE protocol can be learned in relatively short time by any doctor who possesses basic knowledge of ultrasound. It is feasible for any on-duty doctor in intensive or emergency unit to be trained with BLUE protocol to help them manage patients with acute breathing problem (**Figure 8** and **9**). The study to assess the time needed training duration could be the subject for future research.[24-27]

CONCLUSION

In conclusion, the BLUE protocol has high sensitivity and specificity in diagnosing pneumonia and pulmonary edema. These high diagnostic accuracy values came from a good quality study based on the GRADE approach. The BLUE protocol has high specificity in diagnose pneumothorax and pulmonary embolism but with varying sensitivity. This accuracy assessment comes from a poor-quality study based on the GRADE approach.

ABBREVIATION

BLUE	Bedside Lung Ultrasound in Emergency
ARF	Acute Respiratory Failure
LR	Likelihood Ratio
DOR	Diagnostic Odds Ratio
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
JICCIM	Jakarta International Chest and Critical Care Internal Medicine
GIM	Global Index Medicus
ROC	Receiver Operating Characteristic
QUADAS - 2	Quality Assessment of Diagnostic Accuracy Study - 2
ICU	Intensive Care Unit
ER	Emergency Room
SROC	Summary Receiving Operating Characteristic
COPD	Chronic Obstructive Pulmonary Disease
AUC	Area Under Curve
GRADE	Grading of Recommendations, Assessment, Development and Evaluations

COMPETING INTERESTS

The authors declare that there is no competing interest.

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AUTHORS' CONTRIBUTIONS

ODA is the chief principle of the study and also the coordinator of the Study. ODA, CWP, VW conceived the Idea and developed the theory and design of the study. KH help to finalize the study conception and design, verified the analytical method and supervised the analytical calculation ODA and APA carried out the data collection and analyze the result. CWP and VW review the data collection and gave revision regarding interpretation of the data. ODA, APA and KH made draft manuscript preparation.All authors reviewed the results and approved the final version of the manuscript.

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