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Lung and cardiac ultrasound (LuCUS) protocol in diagnosing acute heart failure in patients with acute dyspnea

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ABSTRACT

Objective: To investigate the accuracy of lung and cardiac ultrasound (LuCUS) protocol in diagnosing Acute Heart Failure (AHF) in patients who refer to Emergency Department (ED) with acute dyspnea.
Methods: This was an interventional study on adult patients, who were referred with chief complaint of undifferentiated acute dyspnea to the ED of Namazi hospital, the largest referral center in southern Iran. The intervention was LuCUS protocol, which was performed by Emergency Physicians (EPs) at the bedside. All patients' files were reviewed separately by two independent specialists, who were blinded to LuCUS results for final diagnosis as gold standard, then the results of LuCUS were compared with it. All data were analyzed and diagnostic tests were calculated ($\alpha = 0.05$).
Results: In 100 patients enrolled in the study, 28% had the final diagnosis as AHF. The LuCUS protocol had the sensitivity of 64% (95%CI, 44%–81%), specificity of 97% (95%CI, 90%–100%), positive predicative value of 90% (95%CI, 69%–97%), negative predicative value of 88% (95%CI, 81%–92%), positive likelihood ratio of 23.14 (95%CI, 5.74–93.3), negative likelihood ratio of 0.37 (95%CI, 0.22–0.6), and accuracy of 88% (95%CI, 80%–94%).
Conclusion: LuCUS protocol can be used by EPs as a practical tool to differentiate the cardiac and non-cardiac etiologies of acute dyspnea, specifically AHF, as it is more accurate than clinical diagnosis by itself. Hence, it is recommend that while conducting further studies in order to achieve more generalizable results, EPs can employ it alongside their clinical evaluations to have a faster and more accurate diagnosis.

1. Introduction

Dyspnea is a term used to describe an experience of impairment and difficulty in breathing with various qualities and intensities, which is used by physicians, while patients use a wide array of terms to describe their clinical conditions, including breathing difficulty, shortness of breath, feeling of suffocation and increased effort to breathe. These terms makes it difficult to present a single definition of dyspnea. If dyspnea occurs while resting or engaging in mild and moderate activity, it is pathologic and indicates the presence of disease. Multiple mechanisms are defined for it, and various physiological, psychological, environmental and social factors are effective in this experience [1,2]. Dyspnea occurrence is a predictor of mortality in the long term [2], which is one of the most common signs in pulmonary and cardiac patients [3]. It was reported that acute dyspnea is one of the main causes of ED's admission [4] and CDC estimated the rate of 3% among US adults referring to EDs in 2013 [5].

Evaluation and management of patients visiting the ED with chief complaint of acute dyspnea is a challenging matter, as this sign is non-specific, and many patients with dyspnea due to heart failure (HF) show very similar signs to patients with dyspnea due to lung disease. Thereby, Emergency Physicians (EPs) have to decide quickly as to which management strategy to use [6]. Of the differential diagnoses of acute dyspnea, HF is a common and clinically significant cause, which is known to be a spreading problem throughout the world [7]. Acute heart failure (AHF) is a life-threatening condition, which is defined as rapid onset of new typical HF's signs and symptoms for the first time. It leads to 4–7% in-hospital mortality, and 4–11 days length of stay [8]. Early diagnosis and goal-directed therapies are necessary for these patients to

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increase the efficacy and appropriateness of management, avoid unnecessary and potentially harmful interventions, and avoid delays in care [9].

Nowadays, various tools exist to differentiate the causes of dyspnea [10]. The European Society of Cardiology investigated the limitations of common methods, namely electrocardiogram, chest x-ray, N-terminal brain natriuretic peptide testing and blood samples [11]. It is recommended to take echocardiograms; however, as cardiologists are often not available in the EDs, and it is rarely possible in practice. Emphasis has also been put on the great value of lung ultrasound in diagnosis of acute respiratory failure [12,13]. Point-of-care ultrasound (POCUS) can improve the immediate diagnosis of AHF, COPD/asthma and pneumonia in these patients [14]. Moreover, it was shown the usefulness of early lung ultrasound in diagnosis of severe dyspnea cases admitted to the ICU [15] and ED [9,10,16,17], but it seems that there is no sufficient studies. Lung and Cardiac Ultrasound (LuCUS) is another protocol suggested in this regard [9,10,16,17]. Therefore, the current study aimed to examine if the LuCUS protocol is a useful tool in diagnosing AHF in patients referring to EDs with undifferentiated acute dyspnea.

2. Methods

2.1. Study design

The current interventional study was carried out from Jan 2016 to Dec 2016 on patients, who were referred with chief complaint of undifferentiated acute dyspnea to ED of Namazi hospital, the biggest referral hospital in southern Iran, with about 90,000 admissions annually.

2.2. Participants

The inclusion criteria were patients 18 years or older, with undifferentiated acute dyspnea. The exclusion criteria were patients with history of chronic dyspnea, patients showing ST-segment elevation in their electrocardiogram (ECG), patients who were confident in their diagnoses after initial assessment by clinicians, patients treated for HF with nitroglycerin and diuresis, as well as patients who refused to sign the written informed consent for ultrasound. On the data collection form demographic information, such as age, gender, as well as medical comorbidities, vital sings at presentation, and other information were collected.

2.3. Sample size

The Medcalc software for Windows was used to calculate the number of participants (α =5%, β =20%, confidence interval (CI) =95%, degree of freedom (df) = 1) [9], which was obtained at 64 participants, but 100 patients were enrolled in the study (power = 90% at the end of the study).

2.4. Study protocol and intervention

Undifferentiated dyspnea was defined as a case of dyspnea with at least two probable causes, and AHF was not required to be a potential diagnosis. Regard differentiated dyspnea, it refers to a case of a patient diagnosed with AHF who does not comply with physicians' orders, such as medication or diet.

Senior emergency medicine residents were tasked with primary evaluation of patients, which included: obtaining medical history, checking the vital signs, clinical examination and 12 lead ECG. Patients were initially diagnosed based on the existing evidence. Then, the LuCUS protocol was performed by the senior residents at bedside in under 30 min from the time of admission, under the supervision of ED attending physicians, who were an Iranian board-certified in Emergency Medicine specialist. All EPs had participated in the training course on POCUS. For the purposes of this study, a SonoSite ultrasound machine (Fujifilm SonoSite, Inc., USA) was used. The LuCUS protocol has two parts – lung and cardiac:

In the pulmonary section of LuCUS, four anterior/lateral lung regions were examined in each hemithorax using curvilinear and linear probes. Next, the number of B-lines between two ribs was recorded in each lung region [9]. B-line is defined as vertical, hyperechogenic, reverberation artifacts that arise from the pleural line to the bottom of the screen moving synchronously with lung sliding [10]. <3 B-lines in each region is considered as the Focal B-profile with differential diagnoses of pneumonia and cancer, and presence of 3 and over 3 B-lines in transverse intercostal plane is categorized under the B-profile (positive region). Observation of A-line indicates pulmonary causes, such as COPD and asthma. Also, existence of pleural effusion (PE) in the midaxillary line was examined in a bilateral position. The cardiac section involved the following items:

A. Subxiphoid view: Assessment of inferior vena cava (IVC) diameter size and collapsibility in the long axis during inhalation. IVC with maximum diameter $\geq$2 cm and collapsibility <50% was considered plethoric, and IVC with maximum diameter <2 and collapsibility >50% was deemed collapsible. If IVC did not meet any of the mentioned criteria, it was considered as intermediate.

B. Parasternal long- and short-axis views: Left ventricular ejection fraction (LVEF) was determined by observing the contractions and wall thickness in the parasternal long-axis view [9].

2.5. Measurements

After discharge, patient files (including laboratory data, radiograms, echocardiograms, admission notes and discharge summary) were reviewed separately by two independent specialists (an emergency medicine specialist and a cardiologist), and their opinions on the etiology of dyspnea were recorded (if it was cardiac or non-cardiac), and final diagnosis as gold standard, and then the results of LuCUS were compared to it. Meanwhile, none of these 2 specialists were aware of the LuCUS results. If there was any disagreement between the reviewers, a third blinded reviewer would determine the final diagnosis. It should be noted that combination of the following observations would be defined as ADHD, sonographically: 1) one plethoric IVC plus; 2) at least one bilateral B-profile or any PE plus; 3) moderately - severely depressed LVEF (<40%).

2.6. Statistical analysis

The statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 22.0 and Medcalc software for Windows were used for statistical analysis, through descriptive and analytical tests such as; *independent t-test* and *Chi Square* tests. Results are presented as mean (Standard Deviation) (SD) for continues variables and are summarized in number (percentage) for categorical variables. Two-sided *P*-value <0.05 and Confidence Interval (CI) of 95% was considered to be statistically significant. For calculating the diagnostic tests, such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and accuracy, the Medcalc software was used. Receiver operating characteristics (ROC) curve was drawn for LuCUS protocol to obtain the area under the curve. Furthermore, we performed a sub-analysis to determine the variables with the highest accuracy, including B-lines, pleural effusions and IVC evaluation. Kappa was used to assess the agreement between initial and final diagnosis.

2.7. Ethical consideration

The current study was supported by Shiraz University of Medical Sciences (grant No. 94.01.01.9435), which was conducted in accordance to the Declaration of Helsinki, and was approved by the vice-chancellor of research and technology, as well as the local ethics committee (IR.SUMS.MED.REC.1395.s44) of Shiraz University of Medical Sciences.

3. Results

In the current study from Jan 2016 to Dec 2016, 100 patients were assessed, which 47 (47%) were male and 53 (53%) were female ($P = 0.48$). The mean (SD) of age was 58.44 (12.23) years. The most common comorbidities were cigarette smoking (55%), diabetes (37%) and coronary artery diseases (36%). Regarding vital signs, 64% had tachycardia, 55% had hypotension and 46% had hypoxia (Table 1).

Based on initial diagnosis, 46 cases (64%) were diagnosed as AHF and 18 (18%) as COPD. Meanwhile, in the final diagnosis, 28 cases (28%) received an AHF diagnosis and 27 cases (27%) were diagnosed as COPD. Interpreter agreement (kappa) between initial and final diagnoses was obtained as 0.484 ($P < 0.0001$) (Table 2). Sensitivity and specificity of the pre-US diagnosis were 100% (95%CI, 88%–100%) and 75% (95%CI, 63%–84%) ($P < 0.0001$).

Pulmonary ultrasound findings revealed that 47% of all participants were positive B-lines, and 46% were positive for PE. Among the 28 patients with final diagnosis of AHF, 18 (64%) were positive B-lines and 28 (100%) had positive PE ($P = 0.031$ vs. $P < 0.0001$). In regard to the cardiac ultrasound results, LVEF was between 50 and 55% in 27 patients (27%) and between 30 and 35% in 19 cases (19%). In all 28 patients with final diagnosis of AHF (100%), LVEF was <40% ($P < 0.0001$) (Table 3).

Based on the LuCUS protocol, 18 patients with AHF were true positives (TP), 2 patients were false positives (FP), 10 were false negatives (FN), and 70 cases were true negatives (TN) (Fig. 1). The sensitivity, specificity, PLR, NLR, PPV, NPV, and accuracy of the LuCUS protocol equaled to 64% (95%CI, 44%–82%), 97% (95 CI, 90%–100%), 23.14 (95%CI, 5.74–93.3), 0.37 (95%CI, 0.22–0.6), 90% (95%CI, 69%–97%), 88% (95%CI, 81%–92%), and 88% (95%CI, 80%–94%), respectively (Table 4). Fig. 2 shows ROC curve of LuCUS protocol for the diagnosis of AHF. The area under the curve is 0.808 (95%CI, 0.694–0.921, $P < 0.0001$).

Table 1
Patient characteristic.

Characteristic	Total ($n = 100$)	AHF ($n = 28$)
Age (year) mean (SD)		
Total	58.44 (12.23)	60.43 (10.84)
Male	60.40 (12.55)	
Female	56.70 (11.79)	
Gender No. (%)		
Male	47 (47)	12 (42.9)
Female	53 (53)	16 (57.1)
Medical comorbidities No. (%)		
Smoking	55 (55)	19 (67.9)
Diabetes	37 (37)	19 (67.9)
CAD	36 (36)	9 (32.1)
Hypertension	27 (27)	9 (32.1)
COPD	18 (18)	9 (32.1)
Lung cancer	9 (9)	0 (0)
CHF	9 (9)	0 (0)
Vital signs No. (%)		
Tachycardia (HR > 100 beat/min)	64 (64)	19 (67.9)
Hypotension (SBP < 100 mmHg)	55 (55)	19 (67.9)
Hypoxia (<92%)	46 (46)	19 (67.9)
Tachypnea (RR > 20 beat/min)	37 (37)	19 (67.9)
Fever (>100.4 °F)	18 (18)	0 (0)

CAD = Coronary Artery Disease, COPD = Chronic Obstructive Pulmonary Disease, CHF = Congestive heart failure, HR = Heart Rate, SBP = Systolic Blood Pressure, RR = Respiratory Rate.

Table 2
Comparison of the initial and final diagnosis in patients with undifferentiated acute dyspnea.

Diseases	Initial diagnosis No. (%)	Final diagnosis No. (%)	Kappa	*P* value
AHF	46 (46)	28 (28)	0.484	0.0001
COPD	18 (18)	27 (27)		
Pulmonary edema	9 (9)	9 (9)		
Sepsis	9 (9)	9 (9)		
PTE	0 (0)	9 (9)		
Malignancy	0 (0)	9 (9)		
Aortic dissection	0 (0)	9 (9)		
ESRD	0 (0)	0 (0)		
Poisoning	9 (9)	0 (0)		
Undefined	9 (9)	0 (0)		

AHF = Acute Heart Failure, COPD = Chronic Obstructive Pulmonary Disease, PTE = Pulmonary Thrombi Emboli, ESRD = End Stage Renal Disease.

4. Discussion

It is a challenging task to evaluate and manage the patients visiting EDs for dyspnea, given the non-specificity of sign, as many patients with dyspnea due to HF show extremely similar signs to patients with dyspnea caused by lung disease. This shows the importance of identifying the etiology of dyspnea, as lack of an accurate diagnosis, or a misdiagnosis, would deviate the treatment from the right direction [6]. Among the differential diagnoses of dyspnea, AHF is one of the common and clinically significant ones, which needs to be detected and treated as quickly as possible [9]. Considering lack of adequate evidence in this area, this study was carried out with the aim to assess the accuracy of LuCUS protocol in AHF detection in patients with acute dyspnea referring to on ED. To the best of our knowledge, this is the first ever study on this subject in Iran, and similar research is limited in other countries.

According to our results, B-lines and PE observed in the lung ultrasound and LVEF<40% in the cardiac ultrasound were the findings associated with AHF. In this study, the protocol was performed by EPs, which was similar to the study by Russell et al., [9]. However, in the study conducted by Kajimoto et al., the protocol was performed by a trained cardiologist [18]. Patients treated with nitroglycerin and diuresis were excluded from our study, which is different from the criteria of Russell et al. Another difference is that Russell et al., also assessed diastolic dysfunction and its grid, as well as the impact of LuCUS on correct treatment, in their study [9].

In the current study, sensitivity and specificity of the pre-US diagnosis were obtained as 100% (95%CI, 88%–100%) and 75%,

Table 3
The frequency of LVEF of patients with undifferentiated acute dyspnea.

LVEF	Total (n = 100) No. (%)	AHF (n = 28) No. (%)
20–25	9 (9)	0 (0)
25–30	9 (9)	9 (32.1)
30–35	19 (19)	19 (67.9)
35–40	0 (0)	0 (0)
40–45	9 (9)	0 (0)
45–50	18 (18)	0 (0)
50–55	27 (27)	0 (0)
55–60	9 (9)	0 (0)

LVEF = Left Ventricular Ejection Fraction.

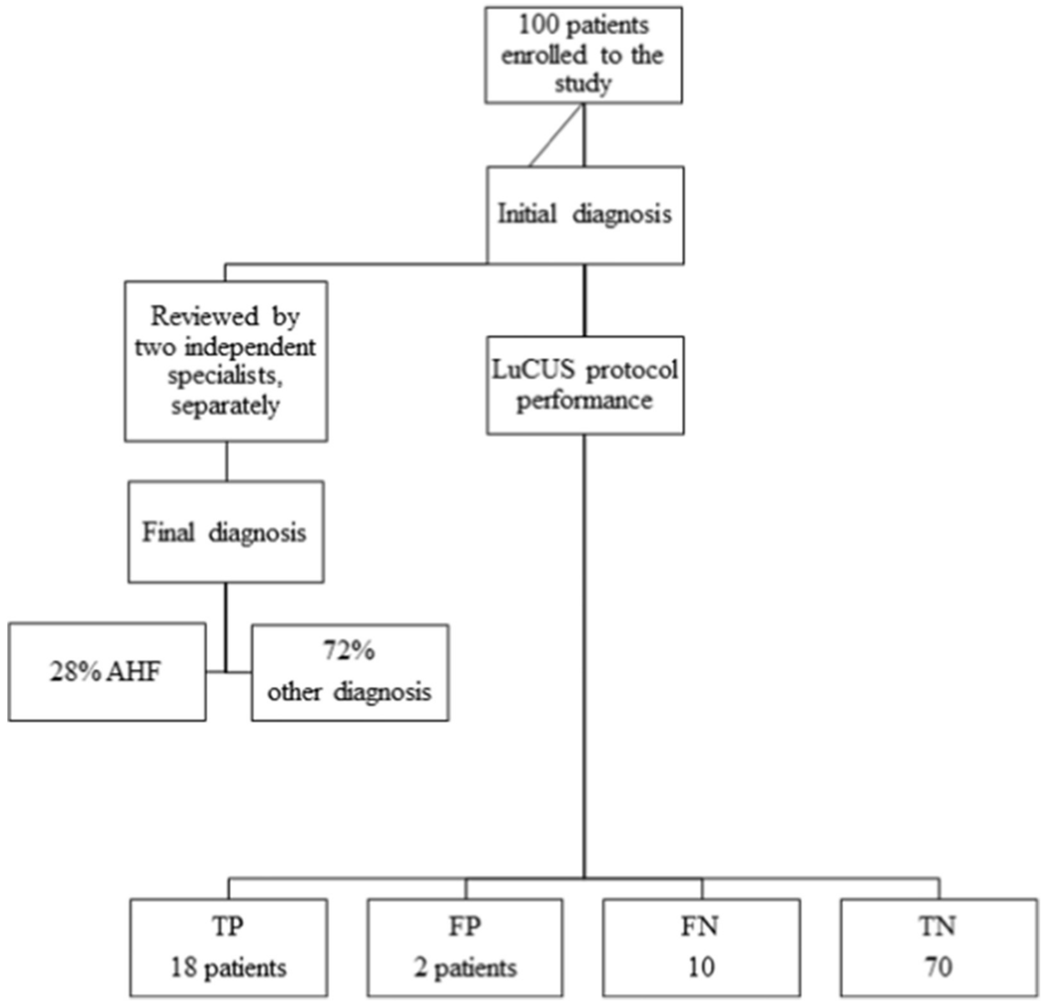

Fig. 1. The flowchart of patients with undifferentiated acute dyspnea.AHF = Acute Heart Failure, TP = True Positives, FP = False Positives, FN = False Negatives (FN), TN = True Negatives.

Table 4
Performance characteristics of tests in diagnosing AHF in patients with undifferentiated acute dyspnea.

Tool	P value	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	LR (+) (95%CI)	LR (−) (95%CI)	Accuracy % (95%CI)
Pre-US diagnosis (Clinical)	<0.0001	100 (88–100)	75 (63–84)	61 (51–70)	100	4 (2.68–5.97)	0	82 (73–89)
Lung ultrasound								
B lines	0.031	64 (44–81)	60 (48–71)	38 (30–48)	81 (72–88)	1.6 (1.08–2.37)	0.6 (0.35–1.02)	61 (51–71)
PE	<0.0001	100 (88–100)	75 (63–84)	61 (51–79)	100	4 (2.68–5.97)	0	82 (73–89)
Cardiac ultrasound								
Plethoric IVC	0.003	100 (88–100)	25 (16–37)	34 (31–37)	100	1.33 (1.17–1.52)	0	46 (36–56)
LVEF <40%	<0.0001	100 (88–100)	88 (78–94)	76 (63–85)	100	8 (4.34–14.74)	0	91 (84–96)
LuCUS	<0.0001	64 (44–81)	97 (90–100)	90 (69–97)	88 (81–92)	23.14 (5.74–93.30)	0.37 (0.22–0.6)	88 (80–94)
B line and LVEF<40%	<0.0001	64 (44–81)	86 (76–93)	64 (49–77)	86 (79–91)	4.63 (2.45–8.76)	0.41 (0.25–0.69)	80 (71–87)
PE and LVEF<40%	<0.0001	100 (88–100)	100 (95–100)	100	100	–	0	100 (97–100)
Plethoric IVC and LVEF <40%	<0.0001	100 (88–100)	88 (78–94)	76 (63–85)	100	8 (4.34–14.74)	0	91 (84–96)

AHF = Acute Heart Failure, LuCUS = Lung and Cardiac Ultrasound, PE = Plural Effusion, LVEF = Left Ventricular Ejection Fraction, IVC = Inferior Vena Cava, LR = Likelihood Ratio, CI = Confidence Interval.

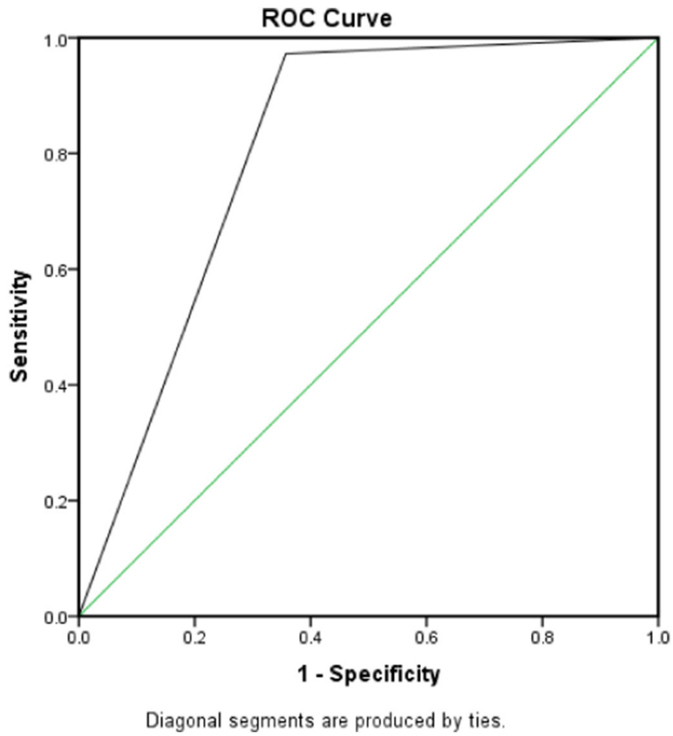

Fig. 2. Receiver operating characteristics (ROC) curve of LuCUS protocol for diagnosis of AHF in patients with undifferentiated acute dyspnea. Area under the curve is 0.808 (95%CI, 0.694–0.921, P < 0.0001).

(95%CI, 63%–84%), respectively, with an accuracy of 82% (95%CI, 73–89). Meanwhile, sensitivity and specificity of LuCUS were 64% (95%CI, 44%–81%) and 97% (95%CI, 90%–100%), respectively, with an accuracy of 88% (95%CI, 80%–94%). The higher sensitivity of the pre-US diagnosis suggested an over diagnosis of AHF in patients with acute dyspnea by senior emergency medicine residents. In addition, the higher specificity of the LuCUS protocol shows its greater power in differentiation of individuals who do not have AHF. Russell et al., obtained a sensitivity and specificity of 94.4% (95%CI, 81%–98%) and 44.4% (95%CI, 33%–56%), respectively, for clinical gestalt (pre-US), and reported the sensitivity and specificity of LuCUS as 83.3%% (95%CI, 67%–93%) and 82.5% (95%CI, 70%–91%), respectively, with accuracy of 100% [9]. Needless to say, the current study showed a higher specificity for the LuCUS protocol. Moreover, they mentioned the overdiagnosis of clinical gestalt in the pre-US phase [9]. Pivetta et al., obtained the sensitivity and specificity of lung ultrasound in acute decompensated heart failure (ADHF) diagnosis as 97% (95%CI, 95%–98%) and 97.4% (95%CI, 95.7%–98.6%), respectively, which had a higher accuracy than clinical workup, chest radiograms and natriuretic peptides. At the end, they recommended the use of lung ultrasound to improve the accuracy of ADHF diagnosis in patients with acute dyspnea visiting the ED [17]. Furthermore, Kajimoto et al., reported the sensitivity and specificity of lung ultrasound as 96.2% and 54%, respectively [18]. In the study conducted by Gallard et al., cardiopulmonary ultrasound performed by EPs during 12 min after admission, had higher accuracy compared to clinical examination in patients with acute dyspnea (90% vs. 81%, $P = 0.04$) [16]. Sartini et al., showed that lung ultrasound had the sensitivity and specificity of 57.73% and 87.97%. Also, in combination with chest radiogram had the sensitivity and specificity of 84.69% and 77.69%, respectively [10].

In this study, sensitivity and specificity of B-lines were 64% (95% CI, 44%–81%) and 60% (95%CI, 48%–71%) alone, and 64% (95%CI, 44%–81%) and 86% (95%CI, 76%–93%) in combination with LVEF<40%, respectively. Sensitivity and specificity of PE were 100% (95%CI, 88%–100%) and 75% (95%CI, 63%–84%) alone and 100% (95%CI, 88%–100%) and 100% (95%CI, 95%–100%) in combination with LVEF<40%, respectively, with 100% (95%CI, 97–100) accuracy. It shows that a combination of PE and LVEF<40% is an extremely powerful factor for AHF diagnosis. In line with our study, Russell et al., also investigated the role of B-profile and PE detection in AHF diagnosis. They obtained a sensitivity and specificity of 69.4% (95%CI, 53%–82%) and 93.7%, (95%CI, 84%–97%), respectively, for B-profiles in combination with EF < 40%, and a sensitivity and specificity of 79.4%% (95%CI, 63%–89%) and 98.4% (95%CI, 92%–99%) for a combination of PE and EF < 40%, which reveals higher sensitivity and specificity in the present study [9]. In another study by Russell et al., they reported that modified LuCUS protocol, which was defined as positive B-lines in both the right and left antrosuperior lung regions plus LVEF<45% had 25% (95%CI, 14%–41%) sensitivity and 100% (95%CI, 94%–100%) specificity [19].

In the study by Liu et al., B-line score and numbers were higher in patients with pulmonary infection and LVHF comparing to patients with pulmonary infection alone. Their results showed the B-line score with cutoff point of 8 had a sensitivity of 80.7% and a specificity of 100% [20]. It was revealed in the study by Coiro et al., that presence of over 30 B-lines in the lung ultrasound is the best tool to predict the risk of readmission within 3 months in HF patients [21].

In the current study, plethoric IVC had a sensitivity of 100% (95% CI, 88–100) and a specificity of 25% (95%CI, 16%–37%) in patients with AHF. In combination with LVEF<40%, these values changed to 100% (95%CI, 88%–100%) and 88% (95%CI, 78%–94%), respectively. Russell et al., reported the same values as 70.6% (95%CI, 54%–83%) and 81.5% (95%CI 70–89) [9]. Moreover, in the research by Kajimoto et al., sensitivity and specificity of <50% IVC collapsibility were equal to 83% and 81.1% [18].

In this study, cardiac ultrasound showed that LVEF<40% alone can strengthen the cardiac etiology of dyspnea, with sensitivity and specificity of 100% (95%CI, 88%–100%) and 88% (95%CI, 78%–94%). Russell et al., reached similar results to our findings [9]. However, results presented by Kajimoto et al., indicated a lower sensitivity and specificity (26.4% vs. 86.5%) [18].

Finally, our study suggested that the LuCUS protocol performed by EPs would have a higher accuracy than clinical diagnosis, and can be used as a useful tool in EDs to differentiate the cardiac and non-cardiac causes of acute dyspnea, especially AHF, and thereby improve the quality of emergency care.

5. Limitations

This study faced a number of limitations, such as the fact that our study setting only included one ED. As systolic heart failure is more common than diastolic heart failure [22,23], we did not differentiate systolic and diastolic heart failure, which is one of the limitation of this study. Furthermore, even though a sample size bigger than the calculated value was considered, our results were significant and the study had a power of 90%, it seems necessary to select a bigger sample size in future studies to achieve higher clinical significance and generalizability. Moreover, RCTs can be designed and conducted to arrive at a more accurate result. Researches to determine the cost-effectiveness and efficacy of this method are recommended.

6. Conclusions

With a sensitivity of 64%, a specificity of 97% and an accuracy of 88%, the LuCUS protocol can be used by EPs as a practical tool to differentiate the cardiac and non-cardiac etiologies of acute dyspnea, specifically AHF, as it is more accurate than clinical diagnosis alone. Since ultrasound is a relatively risk-free intervention for patients, we recommend that while conducting further studies to achieve more generalizable results, EPs receive training on the LuCUS protocol, and employ it alongside their clinical evaluations aiming at faster and more accurate diagnoses.

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