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Diagnostic accuracy and reproducibility of pleural and lung ultrasound in discriminating cardiogenic causes of acute dyspnea in the Emergency Department

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Abstract Dyspnea is a common symptom in patients admitted to the Emergency Department (ED), and discriminating between cardiogenic and non-cardiogenic dyspnea is often a clinical dilemma. The initial diagnostic work-up may be inaccurate in defining the etiology and the underlying pathophysiology. The aim of this study was to evaluate the diagnostic accuracy and reproducibility of pleural and lung ultrasound (PLUS), performed by emergency physicians at the time of a patient's initial evaluation in the ED, in identifying cardiac causes of acute dyspnea. Between February and July 2007, 56 patients presenting to the ED with acute dyspnea were prospectively enrolled in this study. In all patients, PLUS was performed by emergency physicians with the purpose of identifying the presence of diffuse alveolar-interstitial syndrome (AIS) or pleural effusion. All scans were later reviewed by two other emergency physicians, expert in PLUS and blinded to clinical parameters, who were the ultimate judges of positivity for diffuse AIS and pleural effusion. A random set of 80 recorded scannings were also reviewed by two inexperienced observers to assess inter-observer variability. The entire medical record was independently reviewed by two expert physicians (an emergency medicine physician and a cardiologist) blinded to the ultrasound (US) results, in order to determine whether, for each patient, dyspnea was due to heart failure, or not. Sensitivity, specificity, and positive/negative predictive values were obtained; likelihood ratio (LR) test was used. Cohen's kappa was used to assess inter-observer agreement. The presence of diffuse AIS was highly predictive for cardiogenic dyspnea (sensitivity 93.6%, specificity 84%, positive predictive value 87.9%, negative predictive value 91.3%). On the contrary, US detection of pleural effusion was not helpful in the differential diagnosis (sensitivity 83.9%, specificity 52%, positive predictive value 68.4%, negative predictive value 72.2%). Finally, the coexistence of diffuse AIS and pleural effusion is less accurate than diffuse AIS alone for cardiogenic dyspnea (sensitivity 81.5%, specificity 82.8%, positive predictive value 81.5%, negative predictive value 82.8%). The positive LR was 5.8 for AIS [95% confidence interval (CI) 4.8–7.1] and 1.7 (95% CI 1.2–2.6) for pleural effusion, negative LR resulted 0.1 (95% CI 0.0–0.4) for AIS and 0.3 (95% CI 0.1–0.8) for pleural effusion. Agreement between experienced and inexperienced operators was 92.2% ($p < 0.01$) and 95% ($p < 0.01$) for diagnosis of AIS and pleural effusion, respectively. In early evaluation of patients presenting to the ED with dyspnea, PLUS, performed with the purpose of identifying diffuse AIS, may represent an accurate and reproducible bedside tool in discriminating between cardiogenic and non-cardiogenic dyspnea. On the contrary, US detection of pleural effusions does not allow reliable discrimination between different causes of acute dyspnea in unselected ED patients.

Keywords Dyspnea · Ultrasonography · Diagnosis

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Introduction

Dyspnea is a common symptom in patients admitted to the Emergency Department (ED) [1]. Discrimination between cardiac and non-cardiac causes of dyspnea can sometimes be challenging. Initial work-up including history, physical examination, electrocardiography (EKG), and laboratory results may be inconclusive [1]. The chest radiograph does not show signs of congestion in about 20% of patients with cardiogenic dyspnea [2]. Many serological markers, such as serum Brain-type Natriuretic Peptide (BNP), can be altered in a variety of clinical settings irrespective of the presence of heart failure [3]. In addition, the chest X-ray study and serum markers are seldom immediately available. Hence, approximately 20% of patients with dyspnea in ED are misdiagnosed, and treated inappropriately with increased mortality [4].

The alveolar-interstitial syndrome (AIS) of the lung includes several heterogeneous conditions with diffuse involvement of the interstitium, impairment of gas exchange, and subsequent respiratory failure. Such conditions are either chronic (e.g., pulmonary fibrosis) or acute [e.g., acute respiratory distress syndrome (ARDS), cardiogenic pulmonary edema, interstitial pneumonia]. During the past few years, pleural and lung ultrasound (PLUS) has emerged as a non-invasive technique potentially useful in detecting AIS at the bedside, especially due to its wide availability, real-time results and low costs. Sonographic diagnosis of AIS relies on the detection of multiple and diffuse ultrasound (US) artifacts in both lungs, which have been called B-lines [5, 6].

The US detection of B-lines shows high accuracy in discriminating pulmonary edema from chronic obstructive pulmonary disease (COPD) in ICU patients with acute dyspnea and severe respiratory failure [5]. In a previous study performed in an ED setting, lung US (LUS) shows high sensitivity and specificity in AIS recognition [6]. However, one of the major limitations of this study includes a delay of LUS up to 48 h after the patient's first evaluation in the ED [6]. Moreover, LUS is inexpensive, widely available, and can be repeated without added radiation to patient. Directed Acyclic Graph (DAG) is a graphical tool for epidemiological research that allows one to directly specify the model, in order to try to avoid biased estimates of the covariate effects on the outcome [7]. Figure 1 shows the DAG illustrating the possible framework of "dyspnea pathway" in the ED. In our opinion, the detection of specific PLUS patterns, either AIS or pleural effusions, may help in discriminating between cardiogenic and non-cardiogenic dyspnea. On the contrary, we hypothesized that both the timing of US evaluation, i.e., the time between patient arrival in the ED and US assessment, and the level of US expertise of the operator may affect the detection of these US specific signs of cardiogenic dyspnea, having an indirect effect on diagnosis.

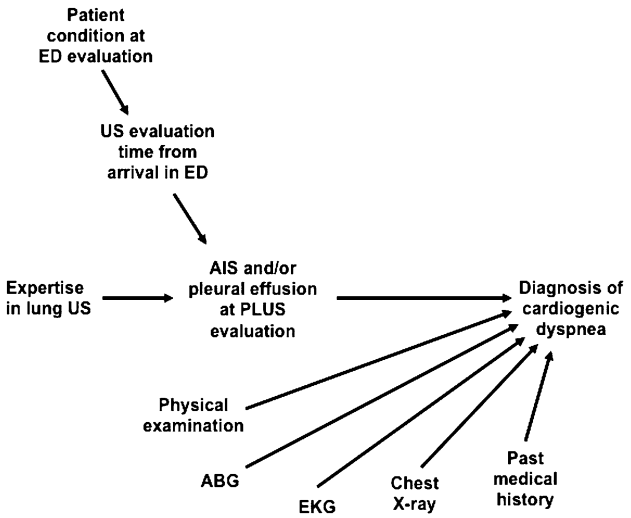

Fig. 1 Directed Acyclic Graph (DAG) for "dyspnea pathway" in the ED. A directed path is a sequence of *arrows*, a graph is acyclic if no directed path forms a closed loop. An *arrow* between two variables represents the possible presence of causal influence. *ED* Emergency department, *US* ultrasound, *PLUS* pleural and lung ultrasound, *AIS* alveolar-interstitial syndrome, *ABG* arterial blood gas, *EKG* electrocardiography

The aim of this study was to evaluate the diagnostic accuracy of PLUS in discriminating between cardiogenic and non-cardiogenic acute dyspnea in an ED setting. PLUS has been performed by emergency physicians at the time of a patient's initial presentation to the ED. A secondary aim was to evaluate the inter-observer reproducibility of PLUS between experienced and inexperienced physicians.

Methods

Study design

This was a prospective US study in ED patients. All patients gave informed consent for the performance of PLUS, which is routinely carried out in our department. The study was conducted in accordance with the principles of the declaration of Helsinki for clinical research involving human subjects. The study protocol was approved by the Hospital Ethics Committee.

Patients

Between February and July 2007, we prospectively enrolled 56 non-consecutive patients admitted to the ED of the "EdoardoAgnelli" Hospital (Pinerolo, Turin, Italy). To be eligible for the study, patients had to present to the ED with a principal complaint of shortness of breath, defined as

either the sudden onset of dyspnea with no history of chronic dyspnea, or an increase in the severity of chronic dyspnea in the prior 48 h irrespective of the presence of fever [8]. The presence of at least one emergency physician expert in PLUS was required for patient enrollment.

Lung ultrasound

A general electric LOGIQ 3 (GE Healthcare, Milwaukee, WI, USA) with 3.5 MHz convex probe, not phased array, was used. PLUS was performed by emergency physicians at the time of the initial evaluation in the ED, immediately after the initial work-up was completed. In all patients in whom US time was shorter than 30 min, emergency physician knew, at the time of US evaluation, only the vital signs, including body temperature, the patient's history, physical examination findings, EKG, and arterial blood gas analysis, but neither the results of laboratory tests nor of a chest X-ray study.

Patients were investigated in supine or semi-recumbent position. We followed a scanning protocol adapted from Volpicelli et al. [6], in which eight regions of the lungs are explored (Fig. 2). The presence of B-lines was evaluated in anterior and lateral regions, whereas pleural effusion was evaluated in the basal regions. B-lines were defined as an echogenic, coherent, dynamic, wedge-shaped signal with a narrow origin in the near field of the image, arising from the pleural line and extending to the edge of the screen, according to Liteplo et al. [9] (Fig. 3). A single region was considered positive for AIS if 3 or more B lines were detected within an intercostal space between ribs. Diffuse AIS was defined by the bilateral presence of 2 or more positive regions [6]. Pleural effusion was identified by the presence, on either chest side, of an anechogenic/hypoechogenic fluid collection immediately above diaphragm and adjacent structures (Fig. 3). All US images were saved onto a hard drive [10].

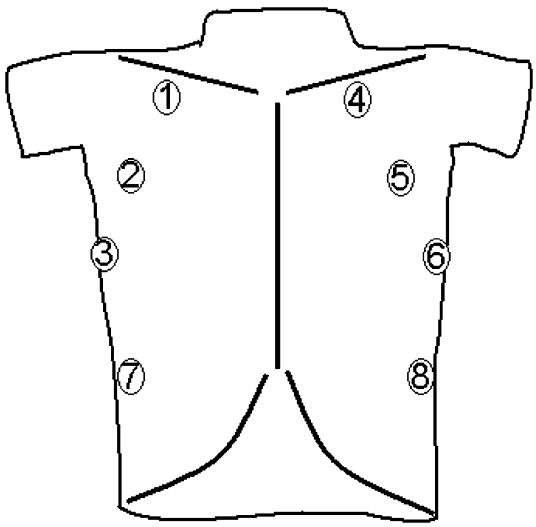

Fig. 2 PLUS scanning scheme, adapted from Volpicelli et al. [6]. The chest wall was divided in four areas for each side. Two areas were localized anteriorly in the 2° intercostal space on the hemiclavicular line (scan 1 and 4, respectively, for right and left side) and the 4° intercostal space on the hemiclavicular line (scan 2 and 5, respectively); one area was localized laterally in the 5° intercostal space on the medium axillary line (scan 3 and 6, respectively); a further area was localized basally on the posterior axillary line (scan 7 and 8, respectively)

Study protocol

All patients were hospitalized, and treatment was implemented by the treating physician who was blinded to the results of PLUS. Each patient underwent echocardiography in order to assess systolic and diastolic ventricular function. After discharge, the patients' charts were independently reviewed by two expert physicians (an emergency physician and a cardiologist), also both blinded to the PLUS results. They ultimately determined if the patient's dyspnea on presentation was related to heart failure or not, using the entire medical record (laboratory, radiography, and echocardiography results, admission notes, consultations, discharge summaries).

All PLUS scannings were later reviewed by two emergency physicians with large experience in PLUS (more than 200 PLUS evaluations performed in the ED) blinded to clinical data, who ultimately determined positivity for diffuse AIS and pleural effusion. A random scan set of 10 patients, for a total of 80 PLUS scannings, was also reviewed by two inexperienced emergency physicians, with limited training on PLUS, in order to assess inter-observer variability.

Data analysis

Sensitivity, specificity, and positive/negative predictive values were obtained using a 2×2 table fashion. Likelihood ratio (LR) tests were used to assess the change in the odds of having or not having cardiogenic dyspnea when diffuse AIS or pleural effusion (either unilateral or bilateral) were present or absent. Inter-observer agreement was assessed using Cohen's kappa (statistical significance $p < 0.05$). Analyses were carried out using Stata 9.2 (Stata Corporation, College Station, TX, USA)

Results

A total of 56 patients were enrolled (35 men, 21 women), with a median age of 82.1 years [interquartile range (IQR) 13.7 years, range 38.7–94.3 years]. Patients' clinical characteristics are summarized in Table 1.

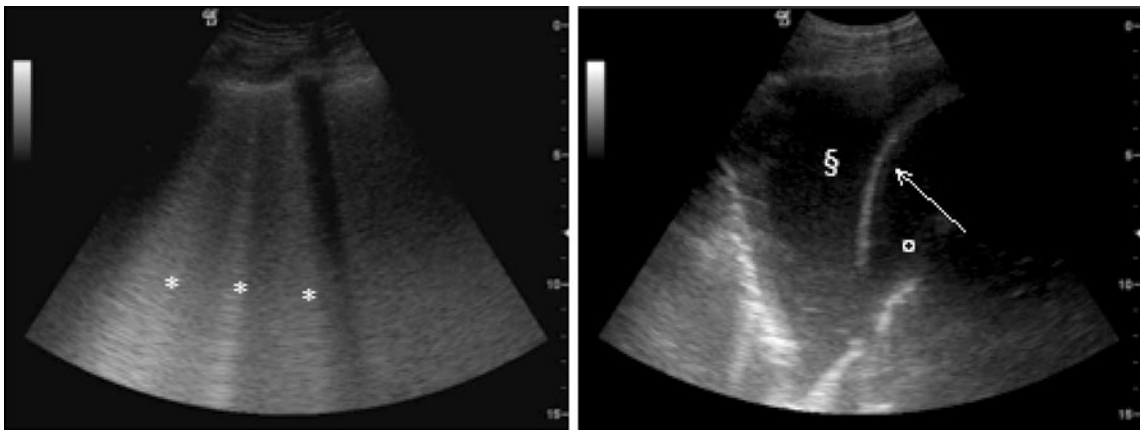

Fig. 3 PLUS: typical B-lines artifacts (* in the *left* panel) and pleural effusion (§ in the *right* panel). The *arrow* shows the diaphragm and the ° the liver

Table 1 Patients' clinical characteristics

	Total
Age; median year (IQR)	82.1 (13.7)
Gender, M/F (ratio)	35/21 (1.6)
Door-to-US time, minutes (IQR)	30 (45)
Cardiac dyspnea, *n* (%)	27 (48.2%)
Pulmonary dyspnea, *n* (%)	25 (44.6%)
Cardio-pulmonary dyspnea, *n* (%)	4 (7.1%)
EKG alterations, *n* (%)	39 (69.6%)
History of COPD, *n* (%)	22 (39.3%)
History of heart failure, *n* (%)	27 (48.2%)

yr year, *IQR* interquartile range, *EKG* electrocardiography, *COPD* chronic obstructive pulmonary disease

Cardiogenic dyspnea represented the final diagnosis in 27 patients (48%), whereas pulmonary dyspnea in 25 patients (45%); in 4 patients (7%) the cause of dyspnea was considered mixed (both cardiogenic and pulmonary). Among all patients with a final diagnosis of pulmonary or mixed dyspnea, 11 cases were due to pneumonia (in 4 cases associated with COPD), 8 to acute exacerbation of COPD, 5 to pulmonary embolism, 2 to malignancies, 2 to acute bronchitis (in a patient with a history of chronic respiratory failure secondary to interstitial lung disease, and in a patient with severe kyphoscoliosis), and 1 to severe kyphoscoliosis (associated with cardiogenic dyspnea).

An US evaluation was feasible in all patients, with an examination time of less than 5 min. The median time from patient assessment in the ED to US examination (door-to-US time) was 30 min (IQR 45, range 1–720); 75 and 90% of examinations were performed within 60 and 120 min, respectively.

The presence of diffuse AIS had a sensitivity of 93.6% and a specificity of 84% for the diagnosis of cardiogenic dyspnea, with a positive predictive value of 87.9% and a negative predictive value of 91.3%. US detection of pleural effusion had a sensitivity of 83.9% and a specificity of 52% for the diagnosis of cardiogenic dyspnea, with a positive predictive value of 68.4% and a negative predictive value of 72.2%. The coexistence of AIS and pleural effusion had a sensitivity of 81.5% and a specificity of 82.8% with positive predictive value of 81.5% and negative predictive value of 82.8%. Positive LR was 5.8 for AIS [95% confidence interval (CI) 4.8–7.1] and 1.7 (95% CI 1.2–2.6) for pleural effusion, negative LR resulted 0.1 (95% CI 0.0–0.4) for AIS and 0.3 (95% CI 0.1–0.8) for pleural effusion.

When 80 randomly selected recorded PLUS scannings were reviewed by two inexperienced observers, agreement between experienced and inexperienced operators was 92.2% ($p < 0.01$) and 95% ($p < 0.01$) for the diagnoses of AIS and pleural effusion, respectively.

Discussion

The aim of the present study was to evaluate the diagnostic accuracy of PLUS, performed by emergency physicians at the time of a patient's initial evaluation in the ED, in discriminating between cardiac and non-cardiac causes of acute dyspnea.

An US evaluation was feasible in all patients, with a very short examination time (lower than 5 min). We ideally performed US examination immediately after the patient's initial evaluation to prevent the risk of obtaining a negative test as a consequence of appropriate treatment. B-lines are dynamic artifacts that can disappear rapidly after edema resolution [11]. We did not plan to perform repeated US evaluation in patients with cardiogenic dyspnea because this was beyond the scope of the present study; therefore, we have no data concerning US resolution of

AIS in those patients with cardiogenic dyspnea enrolled in our study. In our cohort, 75 and 90% of the US examinations were performed within 60 and 120 min, respectively. Only one patient was studied after more than 8 h from ED admission, and two after about 4 h (220 and 240 min, respectively). In these cases, the etiology of dyspnea was thought to be pulmonary after the standard ED work-up, but given that they were not improving after a few hours of treatment, the ED physician decided to perform PLUS at that time to rule out mixed dyspnea. These patients were neither treated with IV diuretics nor with non-invasive ventilation before PLUS, and the final diagnosis for all of them was pulmonary dyspnea.

48% of the 56 patients presenting with acute dyspnea (appeared or worsened in the prior 48 h) had a final diagnosis of cardiogenic dyspnea. In similar studies, the prevalence of cardiogenic dyspnea ranges from 37 to 61% [5, 6]. Although other studies have previously evaluated US accuracy for the diagnosis of cardiogenic dyspnea, no data are currently available on the accuracy of PLUS performed early in the ED setting. In our study, we find that the detection of diffuse AIS by PLUS is highly predictive for cardiogenic dyspnea, confirming the results of previous studies performed in different clinical settings [5, 6, 9, 12]. Positive and negative LR values make this sonographic finding a rule-in and rule-out test. We emphasize that almost all of these results were obtained in ED patients evaluated shortly after their arrival in the ED, i.e., before the results of other commonly used diagnostic tests (chest X-ray and serological markers, in particular) were available.

On the contrary, US detection of pleural effusion showed high sensitivity but low specificity for cardiogenic dyspnea. Positive and negative LR values indicate that this sonographic finding cannot be used as a rule-in and rule-out test. Our results are apparently in contrast with those obtained by Kataoka and Takada [13], who report a similar sensitivity but higher specificity. These discordant findings may be at least partially related to the different study settings. In patients with known chronic heart failure, US detection of pleural effusion may indeed be helpful in diagnosing decompensated disease. On the contrary, in the ED, the presence of a pleural effusion may be secondary to various diseases. Finally, we estimated the diagnostic accuracy of PLUS for cardiogenic dyspnea in patients with coexistence of diffuse AIS and pleural effusion. As expected, the coexistence of diffuse AIS and pleural effusion increased the specificity of PLUS compared to pleural effusion alone, but decreased sensitivity of our technique, given that not all patients with acute cardiogenic dyspnea have a pleural effusion [14].

Analysis of discordant cases provided interesting information. We had only one false-positive and 2 false-negative US tests (both obtained within 30 min from arrival). The false-positive patient had lung consolidation in the left lower lobe surrounded by a pattern of localized AIS; localized AIS was found also in the right lower lobe. The final diagnosis was bilateral pneumonia. In the first false-negative patient, severe pleural effusion hampered a correct examination with non-interpretable US lateral scannings. We suggest that, in presence of abundant pleural effusion, it may be useful to obtain different scannings in areas more easily evaluable. The second false-negative patient had biventricular heart failure with a severe right heart dysfunction; in these cases AIS would not be present.

Finally, a secondary aim of our study was to evaluate the inter-observer reproducibility of PLUS for the detection of AIS between experienced and inexperienced operators. In our study, inexperienced operators are able to interpret the test with good correlation with experienced physicians. These findings confirm those obtained in other studies, showing that thoracic US is easy to learn [9, 13].

This study has some limitations. First, it enrolled a small number of patients. Furthermore, only a single patient had interstitial lung disease, and none had inflammatory pulmonary edema (i.e., acute lung injury/acute respiratory distress syndrome). Pulmonary diseases with interstitial involvement have an US pattern similar to cardiogenic pulmonary edema; thus, the low number of patients with these clinical conditions enrolled in our study may have artificially increased and at least partially accounts for the high specificity of sonographic AIS detection [12, 14, 15]. High resolution CT scan is the gold standard for lung interstitium; however, this test is ordinarily neither available nor feasible in common ED practice. Therefore, we chose to compare the US diagnosis to the final clinical diagnosis. A further limitation of our study is the impossibility to reach a complete blinding of the ED physician performing the PLUS to the clinical status of the patient, in comparison with other imaging techniques (X-ray, CT). We tried to partially overcome this limitation recording all the scannings, and asking to two emergency physicians blinded to clinical data to review the scannings. Finally, although BNP has a well-defined role in the diagnosis of cardiogenic dyspnea, we were not able to compare BNP with PLUS results, because BNP measurement was not available in our laboratory in 2007.

In conclusion, the detection of diffuse AIS by PLUS, performed at the bedside and early during the evaluation of patients presenting to the ED with acute dyspnea, may represent an accurate and reproducible test in discriminating between cardiogenic and non-cardiogenic dyspnea in the ED. On the contrary, US detection of a pleural effusion does not allow reliable discrimination between different causes of acute dyspnea in unselected ED patients.

Conflict of interest None.

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