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Original Article

Correlation analysis between lung ultrasound scores and pulmonary arterial systolic pressure in patients with acute heart failure admitted to the emergency intensive care unit

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ABSTRACT

Background: No convenient, inexpensive, and non-invasive screening tools exist to identify pulmonary hypertension (PH) - left heart disease (LHD) patients during the early stages of the disease course. This study investigated whether different methods of lung ultrasound (LUS) could be used for the initial investigation of PH-LHD.

Methods: This was a single-center prospective observational study which was performed in the Zigong Fourth People's Hospital. We consecutively enrolled patients with heart failure (HF) admitted to the emergency intensive care unit from January 2018 to May 2020. Transthoracic echocardiography and LUS were performed within 24 h before discharge. We used the Spearman coefficient for correlation analysis between ultrasound scores and pulmonary arterial systolic pressure (PASP). Bland-Altman plots were generated to inspect possible bias, and receiver operating characteristic (ROC) curves were calculated to assess the relationship between ultrasound scores and an intermediate and high echocardiographic probability of PH-LHD.

Results: Seventy-one patients were enrolled in this study, with an overall median age of 79 (interquartile range: 71.5–84.0) years. Among the 71 patients, 36 (50.7%) cases were male, and 26 (36.6%) had an intermediate and high echocardiographic probability of PH. All four LUS scores in patients with an intermediate and high probability of PH were significantly higher than in patients with a low probability of PH (P <0.05). The correlation coefficient (r) between different LUS scoring methods and PASP was moderate for the 6-zone (r=0.455, P <0.001), 8-zone (r=0.385, P=0.001), 12-zone (r=0.587, P <0.001), and 28-zone (r=0.535, P <0.001) methods. In Bland-Altman plots, each of the four LUS scoring methods had a good agreement with PASP (P <0.001). The 8-zone and 12-zone methods showed moderately accurate discriminative values in differentiating patients with an intermediate and high echocardiographic probability of PH (P <0.05).

Conclusions: LUS is a readily available, inexpensive, and risk-free method that moderately correlates with PASP. LUS is a potential screening tool used for the initial investigation of PH-LHD, especially in emergencies or critical care settings.

Introduction

Acute heart failure (HF) is a common critical illness caused by sudden onset or rapid deterioration of abnormal cardiac functions. The clinical symptoms and signs of acute HF are related to systemic and pulmonary congestion and hypoperfusion of tissues and organs. Pulmonary hypertension (PH) - left heart disease (LHD), also known as World Health Organization group 2 PH, is the most common type of PH worldwide, defined as a mean pulmonary artery pressure (mPAP) of >20 mmHg and pulmonary capillary wedge pressure (PCWP) >15 mmHg during right heart catheterization (RHC).[1–3] Patients with PH-LHD have more severe symptoms and a worse prognosis in response to a passive increase in left-sided filling pressures than LHD pa-

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tients without PH.[1,4,5] Thus, PH-LHD is a clinical phenomenon that warrants mandatory attention.

According to the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension, the gold standard for diagnosing PH-LHD relies on RHC.[6] RHC is an invasive diagnostic method and poses safety risks for patients, so the decision to perform RHC should depend on the presence of an intermediate and high echocardiographic probability of PH.[6,7] Therefore, echocardiography is an effective approach routinely used for the initial evaluation of PH. Nevertheless, diagnosing PH using echocardiography is challenging for physicians in the emergency department and intensive care unit (ICU) due to the specialty, diversity, and complexity of echocardiographic parameters.

Lung ultrasound (LUS) is gaining popularity as a ready-available, inexpensive, and risk-free method for detecting and quantifying pulmonary congestion. LUS is mainly used to diagnose and evaluate lung and cardiovascular diseases in emergencies or critical care settings,[8]and it is an efficient bedside tool for evaluating patients with pulmonary congestion or acute HF.[9–11]

A recent study demonstrated that one of the LUS methods could help to identify the intermediate and high probability of PH, consistent with the 2015 ESC/ERS Guidelines, but the exact LUS scoring method was not elucidated.[12-14] To the best of our knowledge, no study has evaluated the relationship between LUS and pulmonary arterial sys tolic pressure (PASP) and compared the different LUS scoring methods in predicting the intermediate and high echocardiographic probability of PH-LHD based on the 2022 ESC/ERS Guidelines. We hypothesized that the severity of pulmonary congestion based on LUS may be related to the echocardiographic probability of PH-LHD. This study, therefore, investigated and assessed the relationship between different LUS scoring methods and PASP, as well as the association between LUS scoring methods and the probability of PH.

Method

Study design and setting

This was a single-centre prospective observational study conducted in the Zigong Fourth People's Hospital, a tertiary referral hospital in Zigong with 1600 beds. We consecutively enrolled patients admitted to the emergency intensive care unit (EICU) for newly diagnosed or decompensated HF. The study protocol was approved by the human research ethics committee of the Zigong Fourth People's Hospital (180,002) and managed following the ethical guidelines of the 1975 Declaration of Helsinki.[15,16] All patients provided written informed consent for the enrollment in the study.

Participants

We enrolled patients admitted with acute HF to the EICU from January 2018 to May 2020. The diagnosis of acute HF was established based on medical history, clinical symptoms, physical examination, chest imaging, B-type natriuretic peptide levels, and echocardiography.

In this study, we included all patients fulfilling the following criteria: (1) Patients with acute HF or acute exacerbation of chronic HF who were admitted to the EICU of the Zigong Fourth People's Hospital from January 2018 to May 2020; (2) Age ≥18 years old; (3) The diagnosis met the 2016 ESC criteria,[17] regardless of the etiology and systolic function; (4) Patients did not require the use of a ventilator or underwent ventilator weaning procedures. We excluded patients with the following: (1) Pulmonary fibrosis, significant pleural effusion, severe emphysema, pleurisy, previous pneumectomy or lobectomy, lung cancer or metastases, and breast prosthesis; (2) Pregnancy; (3) Features that would influence follow-up (planned revascularization, the patient's home, and emergencies care setting).[18,19]

Echocardiography

Transthoracic echocardiography (blinded reading) was performed using the Mindray M7 Diagnostic Ultrasound System (Shenzhen Mindray Bio-Medical Electronics Co., Ltd, Guangdong, China) with a Phased Array transducer within 24 h before discharge. Referring to the recommendations for cardiac chamber quantification by echocardiography, we measured the left ventricular ejection fraction (EF), PASP, inferior vena cava diameter (IVC), and IVC collapsibility index (IVC–CI).[13,20,21] PASP was estimated using continuous wave Doppler echocardiography by assessing the peak tricuspid regurgitation velocity (TRV) and considering right atrial pressure (RAP). PASP was calculated using the modified Bernoulli equation: PASP = $4[TRV_{max}]^2$ + RAP.[13,20]

Lung ultrasound

All patients underwent LUS (blinded reading) after immediate echocardiography within 24 h before discharge. According to the recommendations for point-of-care LUS, we selected four different approaches (Figure 1) as follows:

The 6-zone method: We counted the number of B-lines bilaterally in three zones, including the second intercostal space on the midclavicular line, the fourth intercostal space on the anterior axillary line, and the fifth intercostal space on the midaxillary line.[8,22]

The 8-zone method: We considered four chest areas on each side for a complete eight-zone LUS examination. The anterior chest wall was delineated from the sternum to the anterior axillary line and was subdivided into upper and lower halves (from the clavicle to the second intercostal spaces and from the third space to the diaphragm). The lateral zone was delineated from the anterior axillary line to the posterior axillary line and subdivided into upper and basal halves. The total score was obtained by summing the number of positive zones recorded across all eight scanning sites.[23–25] A positive zone indicated the presence of ≥3 B-lines simultaneously or pleural effusion on a frozen image.

The 12-zone method: All intercostal spaces of the upper and lower parts of the anterior, lateral, and posterior regions of the left and right chest walls were examined. The worst ultrasound pattern for each region was characterized using the following grading: 0: normal aeration; 1: moderate loss of aeration (interstitial syndrome defined by multiple spaced B-lines, or localized pulmonary edema defined by coalescent B-lines in less than

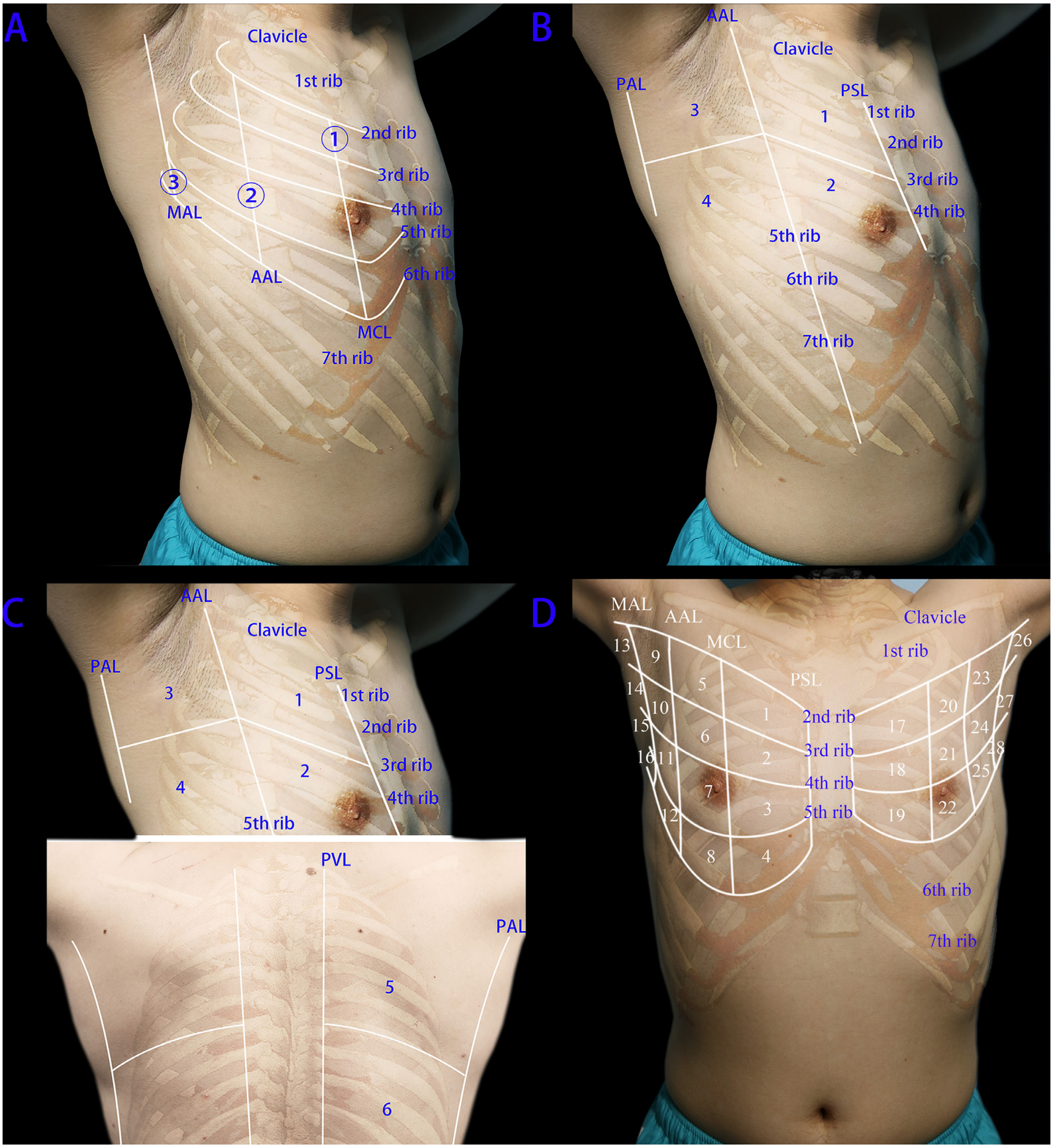

Figure 1. The areas of the four LUS scoring methods. A: LUS scoring 6-zone methods. B: LUS scoring 8-zone methods. C: LUS scoring 12-zone methods. D: LUS scoring 28-zone methods.
AAL: Anterior axillary line; LUS: Lung ultrasound; MAL: Mid-axillary line; MCL: Midclavicular line; PAL: Posterior axillary line; PSL: Parasternal line; PVL: Paravertebral line.

50% of the intercostal space examined in the transversal plane, or subpleural consolidations); 2: severe loss of aeration (alveolar edema defined by diffused coalescent B-lines occupying the entire intercostal space); and 3: complete loss of lung aeration (lung consolidation defined as a tissue pattern with or without air bronchogram). The 12-zone LUS score was calculated as the sum of the 12 regional scores, ranging from 0 to 36.[26,27]

The 28-zone method: we scanned the right and left hemithorax from the second to the fourth on the left side (or fifth on the right side) intercostal spaces along four anatomical lines—parasternal line, midclavicular line, anterior axillary line, and mid-axillary line. The number of B-lines recorded in the 28 scanning sites was added to obtain the total score, which ranged from 0 to 280, representing the degree of pulmonary congestion.[19,28]

Data collection

We queried the hospital information system, laboratory information system, and medical record system to create a database. We included variables on demographic characteristics, clinical conditions, clinical examination, laboratory results, echocardiography, LUS at EICU discharge, and therapy. The primary end-

Table 1
Baseline characteristics of study population.*

Parameters	All patients (n=71)	Patients with low-risk PH (n=45)	Patients with intermediate/high-risk PH (n=26)	P-value
Demographics				
Age (years)	79 (71.5, 84.0)	79 (72.0, 83.0)	81.5 (69.5, 85.0)	0.689
Male	36 (50.7)	22 (48.9)	14 (53.8)	0.876
Clinical conditions				
Previous HF admission	25 (35.2)	14 (31.1)	11 (42.3)	0.488
Length of EICU stay (days)	4 (2, 8)	5 (3, 8)	3 (2, 6)	0.139
Coronary heart disease	50 (70.4)	34 (75.6)	16 (61.5)	0.329
Hypertensive heart disease	3 (4.2)	2 (4.4)	1 (3.8)	>0.999
Valvular heart disease	11 (15.5)	7 (15.6)	4 (15.4)	>0.999
Clinical examination at EICU discharge				
Temperature (°C)	37 (36.5, 37.5)	37 (36.5, 37.4)	36.7 (36.2, 37.6)	0.350
Systolic blood pressure (mmHg)	113 (97.5, 142.5)	114 (99.0, 148.0)	109 (92.0, 125.8)	0.400
Diastolic blood pressure (mmHg)	67.3±14.8	67.4±15.6	67.2±13.7	0.935
Atrial fibrillation	11 (15.5)	6 (13.3)	5 (19.2)	0.516
Jugular vein distention	26 (36.6)	15 (33.3)	11 (42.3)	0.617
Rales	64 (90.1)	41 (91.1)	23 (88.5)	0.701
Peripheral edema	20 (28.2)	14 (31.1)	6 (23.1)	0.652
NYHA functional class				0.991
III	45 (63.4)	28 (62.2)	17 (65.4)	NA
IV	26 (36.6)	17 (37.8)	9 (34.6)	NA
Laboratory results at EICU discharge				
Potassium (mmol/L)	4.0±0.6	4.1±0.6	4.0±0.6	0.543
TC (mmol/L)	3.8±1.0	3.8±1.0	3.7±1.1	0.577
LDL (mmol/L)	1.9 (1.4, 2.2)	1.8 (1.4, 2.1)	1.9 (1.4, 2.3)	0.825
TG (mmol/L)	1.0 (0.8, 1.5)	1.0 (0.8, 1.5)	1.0 (0.8, 1.7)	0.694
Creatinine (μmol/L)	84.6 (54.9, 149.2)	80.7 (52.4, 156.0)	87.4 (58.9, 128. 7)	0.691
D-Dimer (ng/mL)	3.0 (1.8, 7.8)	3.0 (1.8, 8.9)	2. 9 (1.9, 6.8)	0.633
Troponin (ng/mL)	0.23 (0.1, 0.9)	0.2 (0.1, 0.7)	0.3 (0.1, 1.5)	0.567
Echocardiography at EICU discharge				
EF	50 (38.4, 55.8)	48 (38.5, 57.0)	50.86 (38.1, 54.1)	0.420
IVC diameter (cm)	2.1±0.4	2.0±0.4	2.2±0.5	0.102
IVC–CI	22 (14.0, 37.0)	24.0 (15.5, 39.0)	17.5 (12.0, 29.2)	0.051
Lung ultrasound at EICU discharge				
6-zone	14 (13, 16)	13 (11, 15)	14.5 (13, 17)	0.008
8-zone	3 (2, 5)	3 (2, 4)	5 (3, 6)	0.002
12-zone	10 (8, 12)	8 (6, 12)	12 (10, 13)	0.001
28-zone	51.8±16.8	47.9±16.5	58.5±15.4	0.009
Therapy				
β-blockers	2 (2.8)	1 (2.2)	1 (3.8)	>0.999
ACEI/ARBs	10 (14.1)	7 (15.6)	3 (11.5)	0.736
Furosemide	67 (94.4)	42 (93.3)	25 (96.2)	>0.999
Aldosterone receptor antagonists	20 (28.2)	14 (31.1)	6 (23.1)	0.652
Digoxin or cedilanid	35 (49.3)	21 (46.7)	14 (53.8)	0.736
Outcome				
Readmission to the ICUs or death within 180 days	38 (53.5)	19 (42.2)	19 (73.1)	0.024

Data were presented as mean±standard deviation, median (interquartile range) or n (%).
ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; EF: Ejection fraction; EICU: emergency intensive care unit; ERS: European Respiratory Society; ESC: European Society of Cardiology; HF: Heart failure; ICU: Intensive care unit; IVC: Inferior vena cava; IVC–CI: Inferior vena cava collapsibility index; LDL: Low-density lipoprotein cholesterol; LHD: Left heart disease; NA: Not available; PH: Pulmonary hypertension; TC: Total cholesterol; TG: Triglyceride.
* The primary endpoint was the intermediate and high echocardiographic probability of PH-LHD based on the 2022 ESC/ERS guidelines.

point was intermediate and high echocardiographic probability of PH-LHD based on the 2022 ESC/ERS Guidelines.[6]

Statistical methods

Normally distributed quantitative data were expressed as mean±standard deviation, while non-normally quantitative data were summarized using the median (interquartile range [IQR]). We presented categorical variables as counts and percentages. Spearman coefficients were performed for correlation analysis between ultrasound scores and PASP, and scatter plots were used for visualization. The correlation was considered good if the correlation coefficient (r) was ≥0.6, moderate if r was ≥0.3 but <0.6, and poor if r was <0.3[29] Bland-Altman plots were generated to check for possible bias. Receiver operating characteristic (ROC) curves were used to assess the relationship between ultrasound scores and intermediate and high echocardiographic probability of PH. According to an arbitrary guideline, the discriminative ability of a test is considered non-informative if the area under the curve (AUC)=0.5, has low accuracy if 0.5<AUC ≤0.7, has moderate accuracy if 0.7<AUC ≤0.9, high accuracy if 0.9<AUC <1, or perfect accuracy if AUC=1.[30,31] We performed statistical analyses using MedCalc for Windows (version 18.11.6, MedCalc Software, Ostend, Belgium), GraphPad Prism (version 8.0, GraphPad Software, CA, USA), and R software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria). P <0.05 was considered statistically significant.

Results

General characteristics of the patients

Seventy-one patients were included in the present study; 36 (50.7%) were male, and the overall median age was 79 years (IQR: 71.5–84.0) (Table 1). There were 50 (70.4%) with coro-

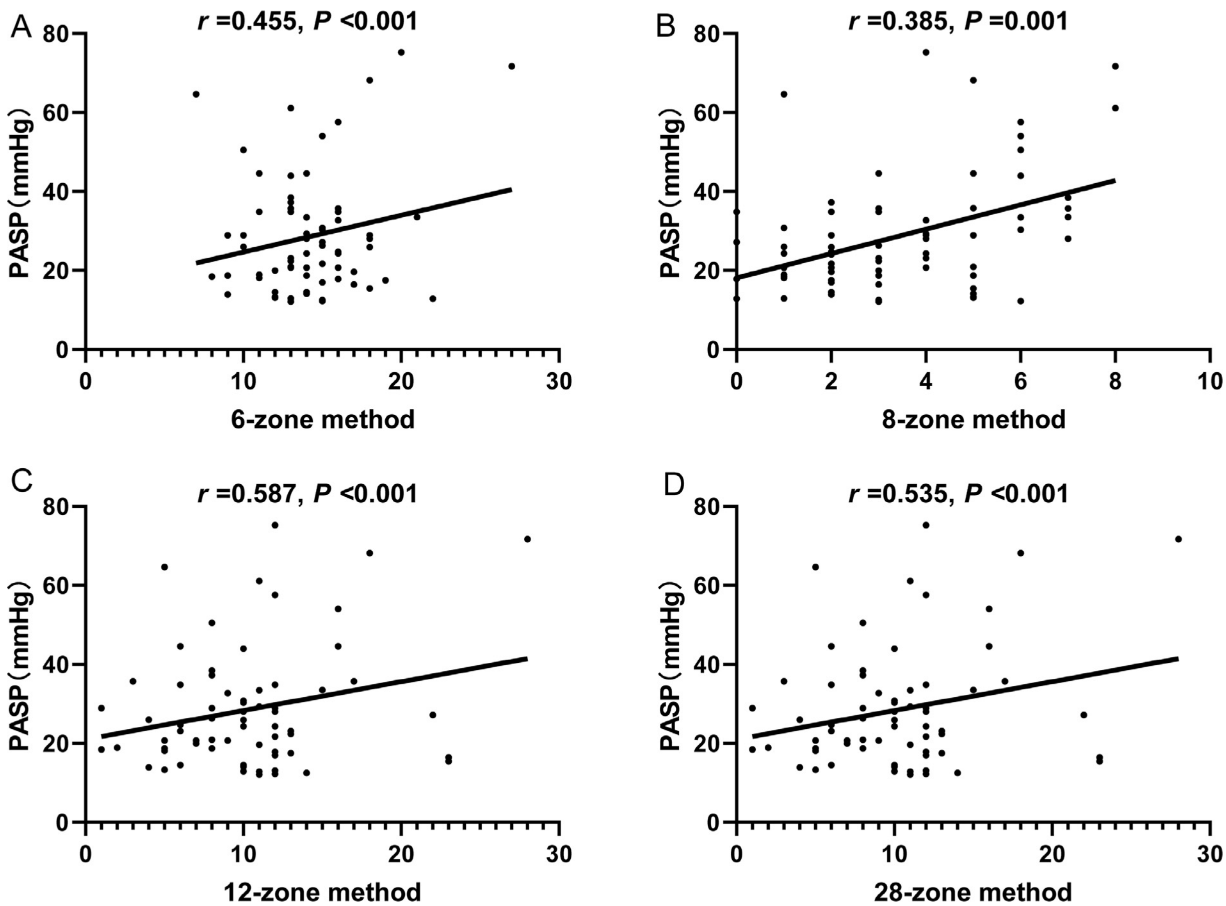

Figure 2. Scatter plot for the correlations between PASP and LUS scores. A: LUS scoring 6-zone methods. B: LUS scoring 8-zone methods. C: LUS scoring 12-zone methods. D: LUS scoring 28-zone methods.
LUS: Lung ultrasound; PASP: Pulmonary arterial systolic pressure.

nary heart disease, 11(15.5%) with valvular heart disease, 3 (4.2%) with hypertension heart disease, and 26 (36.6%) with intermediate and high echocardiographic probability of PH.

Regarding the results of different LUS scoring methods (Table 1), the median LUS scores of the 6-, 8-, and 12-zone methods were 14 (IQR: 13–16), 3 (IQR: 2–5), and 10 (IQR: 8–12), respectively; the mean LUS score of the 28-zone method was 51.8±16.8. All four LUS scores in patients with an intermediate and high echocardiographic probability of PH were significantly higher than in patients with a low echocardiographic probability of PH (P <0.05).

Correlation between different LUS scoring methods and PASP

The scatter plot in Figure 2 shows the correlation between different LUS scoring methods and PASP, and the correlation coefficients (r) were moderate for the 6-zone (r=0.455, P <0.001), 8-zone (r=0.385, P=0.001), 12-zone (r=0.587, P < 0.001), and 28-zone (r=0.535, P <0.001) method.

Bland-Altman plots were calculated to assess potential bias by comparing different LUS scoring methods and PASP (Figure 3). We observed that 2.8% (2/71), 4.2% (3/71), 4.2% (3/71), and 4.2% (3/71) of the points were outside the 95% limits of agreement using the 6-zone, 8-zone, 12-zone, and 28-zone methods, respectively. Hence, each of the four LUS scoring methods and PASP had a good agreement (P <0.001).

Discriminative value of different LUS scoring methods for identifying intermediate and high echocardiographic probability of PH

There was a mildly or moderately good discriminative value between the four LUS scoring methods and intermediate and high probability of PH. The 6-zone (AUC=0.688, 95% confidence interval [CI]: 0.567 to 0.792, P=0.009) and 28-zone method (AUC=0.679, 95% CI: 0.558 to 0.785, P=0.012) had low discrimination accuracy, while the 8-zone (AUC=0.721, 95% CI: 0.602 to 0.821, P=0.002) and 12-zone method (AUC=0.727, 95% CI: 0.609 to 0.826, P=0.001) showed moderate discrimination accuracy (Figure 4).

Discussion

Among the 71 patients enrolled in this study, only 26 (36.6%) had an intermediate and high echocardiographic probability of PH. The significant findings of this study included a moderately strong correlation and good agreement between the LUS scores of each method and PASP. There was also significantly accurate discrimination between the LUS scoring methods and intermediate and high echocardiographic probability of PH. Additionally, the 8-zone and 12-zone methods correlated better with PASP and had more accurate discriminatory ability than the 6-zone

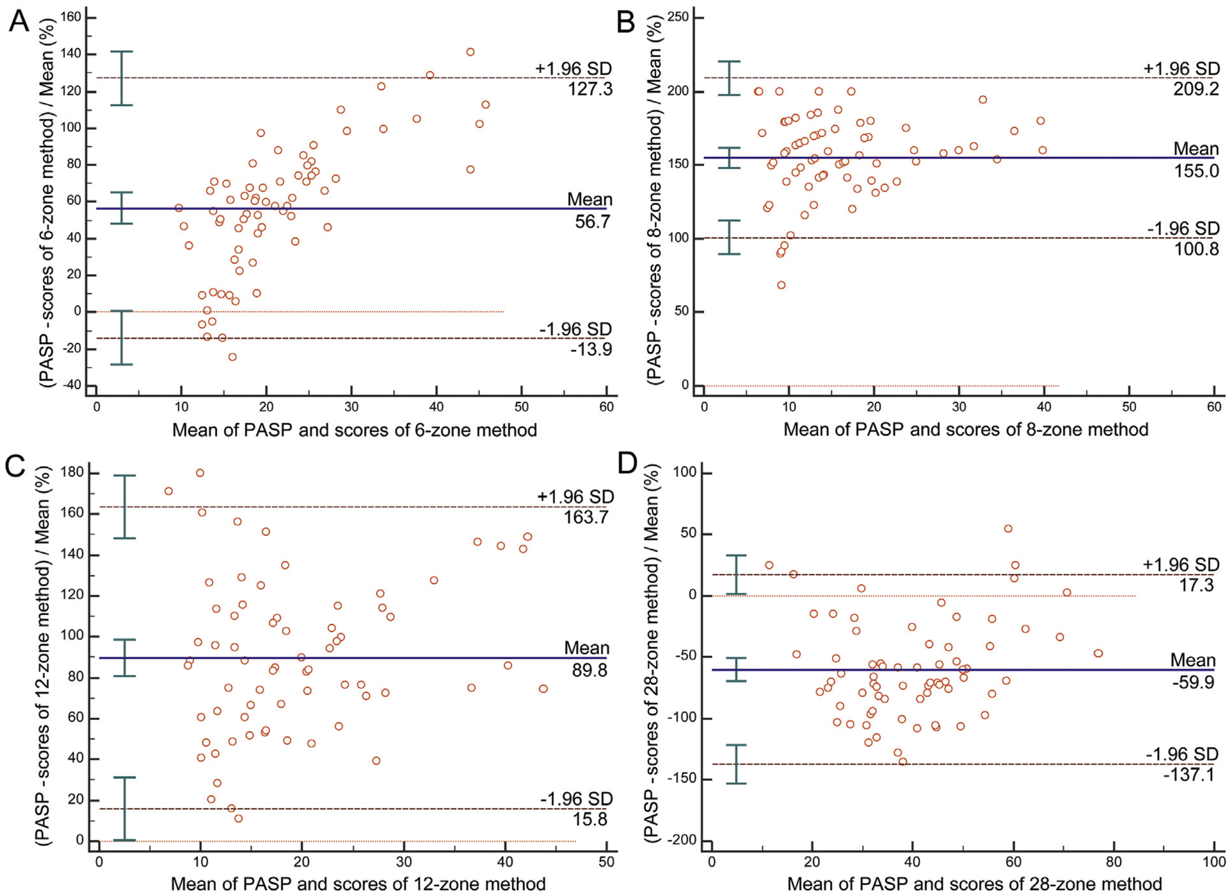

Figure 3. Bland-Altman plot comparing the difference between PASP and LUS scores (PASP–LUS scores) with the average of PASP and LUS scores. A: LUS scoring 6-zone methods. B: LUS scoring 8-zone methods. C: LUS scoring 12-zone methods. D: LUS scoring 28-zone methods.
LUS: Lung ultrasound; PASP: Pulmonary arterial systolic pressure; SD: Standard deviation.

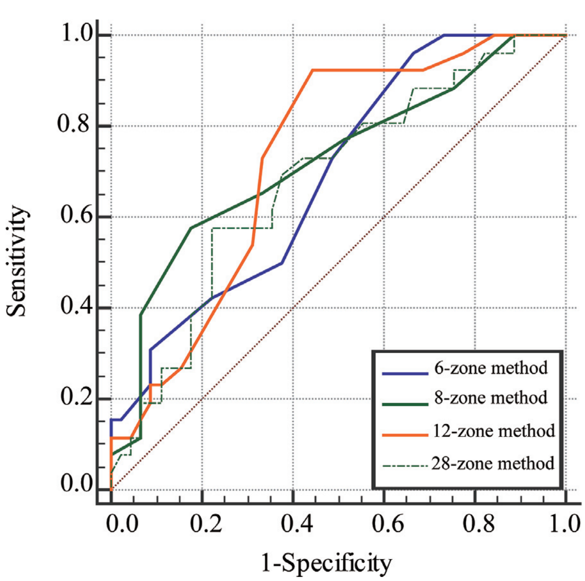

Figure 4. ROC curves for the four LUS scoring methods (the 6-, 8-, 12-, and 28-zone methods) and intermediate and high echocardiographic probability of PH.
LUS: Lung ultrasound; PH: Pulmonary hypertension; ROC: Receiver operating characteristic.

and 28-zone methods in differentiating patients with the intermediate and high echocardiographic probability of PH.

The incidence of PH-LHD was 11.7%, and delays in diagnosis and initiation of treatments could lead to higher morbidity and mortality.[7] Adusumalli et al.[32] reported that the incidence of PH is high in patients with acute HF and demonstrated a positive relationship between the severity of the impairment of left ventricular systolic and diastolic function and the incidence of PH. Another study of 2343 patients hospitalized for HF with preserved EF observed a significant increase in the rehospitalization rate of acute HF patients with severe PH compared to those with normal pulmonary artery pressure.[33] Barywani et al.[34] studied 302 patients with HF and PH in three hospitals of Sahlgrenska University. They found that PH >35 mmHg was considered a risk factor of increased 5-year all-cause mortality in elderly HF patients (Hazard ratio [HR]=1.7, 95% CI: 1.1 to 2.6, *P*=0.013). They also reported a 10% increased risk of all-cause mortality for each 5 mmHg increase in PH. In our study, the proportion of ICU readmission or death within 180 days in patients with an intermediate and high echocardiographic probability of PH was higher than in patients with a low echocardiographic probability of PH (73.1% *vs.* 42.2%, *P*=0.024). Thus, our results were in line with the above results.

A recent study found that LUS scores (AUC=0.839, *P*=0.008) showed significant discriminative values in identifying intermediate and high PH.[14] Kagami et al.[35] studied 41 patients with interstitial pneumonia and 24 controls and found a significant positive correlation between the number of total B-lines at rest and higher PASP (r=0.52, P <0.0001). Furthermore, the number of resting B-lines predicted the development of exercise-induced PH with an AUC of 0.79 (P=0.0003). The study also analyzed patients with connective tissue disease, explicating that B-lines might reflect the coexisting left HF. Similarly, our results showed that LUS scores positively correlated with PASP. The potential mechanisms between LUS scores and PASP correlation remain speculative. However, they might be related to factors including changes in PASP affected by the deleterious effects of passive backward transmission of left atrial pressures on pulmonary arterial vascular resistance associated with left HF.[2] LUS is a rapid and non-invasive method to assess lung congestion in patients with acute left HF, which is a beneficial tool for early detection of acute HF.[36–38]

Sonographic findings of cardiogenic pulmonary edema are characterized by a uniform distribution of alveolar-interstitial syndrome.[39,40] Occasionally, the distribution may not be peripheral or uniform due to the gravitational effect, concomitant pulmonary infections, or other underlying pulmonary diseases. Therefore, images of LUS may differ due to the positions of the front chest, axilla, and back, as well as the imaging depths of LUS examinations. In this study, the correlation coefficient or AUC of the 8-zone and the 12-zone methods was higher than in other methods. We hypothesize that these findings may be because patients admitted to ICUs are usually in the supine position due to severe illnesses—physicians should bear in mind the importance of the axilla and back when choosing the regions of LUS. Additionally, although the 8-zone and the 12-zone methods do not have the highest number of examination areas among the four LUS scoring methods, both involve multiple regions, such as the front chest and axilla, and the 12-zone method also includes the back, allowing for relatively more accurate reflection of pulmonary congestion bilaterally in an all-around way. The 6-zone method has relatively fewer axillary areas, and body positioning may affect predictions. The 28-zone method includes the front chest and axilla but does not include the back—this may introduce confounding bias due to excessive zones in the front chest, which may affect the accuracy of the results. We, therefore, inferred that the 8-zone and the 12-zone methods could be recommended as the LUS scoring methods in predicting PH, especially in emergencies or critical care settings.

The present study had two strengths. First, to the best of our knowledge, this study was the first to comprehensively investigate the correlation and agreement between different LUS scoring methods and PASP. Such methods are relatively easy to grasp and are accurately measured by physicians in emergencies or intensive care settings. Consequently, abnormalities in LUS could attract the attention of doctors to confirm PH diagnosis by echocardiography or RHC, preventing delays in diagnosis and treatment. Second, the study also adopted several approaches, including the 6-, 8-, 12-, and 28-zone LUS scoring methods, most of which were recommended by the expert consensus document.[8,11]

This study had some limitations, including that transthoracic echocardiographic parameters were used to define PH, but RHC is the optimal standard to confirm the diagnosis of PH.[2,20,41] Moreover, this was a single-center observational study with a relatively small sample size. Further multicentre studies are needed to validate these results, especially in patients with left heart disease undergoing RHC.

Conclusions

PH-LHD is a clinical phenomenon that must be diagnosed and treated effectively. LUS is a readily available, inexpensive, and risk-free method that moderately correlates with PASP. LUS, especially the 8-zone and the 12-zone methods, is likely to become a screening tool commonly used for the initial investigation of PH-LHD, particularly in emergencies or critical care settings.

CRediT authorship contribution statement

Ping Xu: Conceptualization, Methodology, Formal analysis, Writing – original draft, Funding acquisition. **Basma Nasr:** Writing – review & editing, Visualization, Project administration. **Liang Li:** Investigation, Resources, Data curation. **Wenbin Huang:** Resources, Data curation. **Wei Liu:** Resources, Data curation. **Xuelian Wang:** Resources.

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Ethics Statement

The study protocol is approved by the human research ethics committee of Zigong Fourth People's Hospital (180002).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets used and analyzed during this study are available from the corresponding author upon reasonable request.

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