



OPEN Value of lung ultrasound scores in assessing extravascular lung water in septic shock patients

Xueyan Zhang & Zhifeng Li✉

The aim of this study was to explore the clinical value and accuracy of lung ultrasound in evaluating extravascular lung water (EVLW) in septic shock patients. Twenty-four septic shock patients who required mechanical ventilation and pulse indicating continuous cardiac output (PiCCO) monitoring in the Department of Critical Care Medicine of our hospital were included. Basic laboratory and demographic data for these patients were recorded. PiCCO monitoring was employed to measure EVLW at 0, 2, 6, 12, 24, and 48 h. The lung ultrasound score (LUS) was obtained via bedside transthoracic lung ultrasound (TTE), and the correlation between these two variables was analysed. Of 24 patients, 22 had satisfactory Doppler lung ultrasound results, and a strong correlation was detected between the LUS and EVLW measurements at the 0, 2, 6, 12, 24, and 48 h time points (all $P < 0.001$; ICC (interclass correlation coefficients) = 0.92, 0.91, 0.92, 0.90, 0.88, 0.71, respectively; all $P < 0.001$). The Bland–Altman analysis revealed that only 4 (3.03%) points exceeded the limits of agreement. These findings suggest that pulmonary ultrasound scores can be utilized as an auxiliary metric for identifying EVLW in septic shock patients, suggesting that this technique is well suited for clinical application.

Keywords Lung ultrasound scoring, Septic shock, PiCCO, EVLW

Septic shock is an extremely critical condition that can progress rapidly and is associated with high rates of mortality, making it a key area of focus for clinical research worldwide. To maximize the survival rate of septic shock patients, the haemodynamic parameters of patients must be optimized¹. PiCCO monitoring is frequently used in clinical settings to accurately and objectively assess haemodynamics and EVLW in patients, but such monitoring is expensive, albeit minimally invasive, and associated with the potential for catheter-related infection². Ultrasonography can serve as a multi-objective approach for assessing dynamic changes in critically ill patients, providing important guidance for the fine-tuning of haemodynamic management and other therapeutic interventions. These ultrasound-based approaches have been used to assess pulmonary B lines, consolidation, and pleural effusion and comprehensively evaluate the severity of pulmonary lesions to therefore guide patient care³. Previous research has suggested that lung ultrasound scores are more sensitive than X-ray measurements are and are comparable to those of chest computed tomography (CT) scans when used to detect pulmonary oedema³. Given the diagnostic and therapeutic value of PiCCO as a means of quantitatively assessing the degree of EVLW in critically ill patients^{2,4,5}, further studies of the correlations between the LUS and PiCCO-measured EVLW are warranted. Accordingly, the aim of the present study was to compare bedside ultrasound scores and PiCCO-based EVLW measurements in patients with septic shock to ascertain the clinical value of bedside ultrasonography as a means of evaluating the severity of pulmonary lesions.

Methods and materials

Research participants

The present study specifically focused on septic shock patients undergoing mechanical ventilation who required PiCCO monitoring due to their condition. Eligible patients were individuals who were hospitalized in the intensive care unit (ICU) of Henan Provincial People's Hospital between January 1, 2021, and December 31, 2021. All experiments were conducted with the approval of the Henan Provincial People's Hospital Medical Ethics Committee [(2020) Ethics No. (176)], and all experiments were performed in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants and/or their legal guardians, and all procedures were performed in accordance with the Helsinki Declaration.

Department of Critical Care Medicine, Henan Key Laboratory for Critical Care Medicine, Zhengzhou Key Laboratory for Critical Care Medicine, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Henan University People's Hospital, Zhengzhou 450003, Henan, China. ✉email: lizhifeng153@163.com

Inclusion and exclusion criteria

Patients who (1) were male or female, at least 18 years old, and were diagnosed with septic shock according to SEPSIS 3.0⁶; (2) required PiCCO monitoring and mechanical ventilation, and (3) themselves or their authorized representatives were able to understand and comply with the study requirements, voluntarily participated in the study and provided written informed consent.

Patients were excluded if (1) they exhibited contraindications for PiCCO monitoring or catheterization; (2) they were suffering from end-stage diseases, tumour cachexia, or other severe diseases or were likely to die in the immediate future; (3) they required emergency interventions not compatible with PiCCO monitoring, including cardiopulmonary resuscitation for cardiac and respiratory arrest or extracorporeal membrane oxygenation (ECMO); or (4) they were pregnant.

Sample size calculations

The sample size was calculated using PASS 21.0 software on the basis of correlation coefficients between LUS and EVLW as the primary index for study evaluation. According to a previous study exploring the clinical value of lung ultrasound as a means of assessing EVLW and prognostic outcomes in acute respiratory distress syndrome patients published by Yu K et al.³, an estimated correlation coefficient of 0.745 is necessary to define the relationship between the LUS and EVLW, with α being set to 0.05 and a test efficiency ($1-\beta$) of 90%. When a two-sided test was performed, a total of 14 patients was needed, but the goal was to recruit 20 participants to account for the possibility of missing data.

Research approach

Following enrolment, the researchers obtained general clinical and demographic data for the study participants, including age, sex, height, weight, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, major disease status upon intensive care unit (ICU) admission, and vital signs. At 0, 2, 6, 12, 24, and 48 h after enrolment (The completion time of the PiCCO catheter insertion is defined as the 0-hour time point), bedside ultrasound and PiCCO were used to collect relevant data, as detailed below:

PiCCO analyses: The same specialist analysed data from all patients included in this study. A total of 2–3 luminal internal carotid or subclavian central venous catheters were placed in all the patients, while a PiCCO catheter was placed in the femoral artery using the Seldinger method. The measurement approach was as follows: (1) 15 mL of cold ($<5^{\circ}\text{C}$) saline was added; (2) the cardiac output (CO) calculation page of the monitor monitoring system was opened, and basic patient information [height, weight, central venous pressure (CVP), etc.] was collected; (3) following baseline stabilization, 15 mL of cold saline was injected as quickly as possible (<5 s); and (4) these thermal-dilution measurements were repeated three times, after which the PiCCO measurements were calculated and recorded.

Bedside ultrasound analyses^{7–9}: Patients were placed in the supine position under deep sedation and analgesia without spontaneous breathing, and the target examination site was fully exposed. Following the connection of the conventional ultrasound equipment, a lung ultrasound examination was conducted with an abdominal convex array probe. LUS were computed for 12 areas on the basis of measured ultrasonic signs (2020, The Lung, Paradigm of point-of-care ultrasound). The axillary front and midline were each used to separate the chest wall into three regions (before, during, and after), with the nipple level serving as the upper lung boundary. These boundaries and the lower lung boundary were used to separate the lung into 12 zones. Using ultrasonographic signs, areas with A lines or <2 separate B lines were scored as 0 points, areas with moderately reduced ventilation (≥ 3 B lines) were scored as 1 point, areas with severely reduced ventilation (diffuse coalescent B lines) were scored as 2 points, and sections exhibiting lung consolidation without air bronchograms were scored as 3 points. The most severe score for each of the 12 regions was recorded, and these 12 scores were summed together for a total value ranging from 0 to 36.

Instruments and equipment

The equipment used in this study was as follows: a PC4000 core output measurement instrument (PiCCO) monitoring module for monitoring the PiCCO Pulsion (Germany); a PiCCO femoral artery indwelling catheter (Shanghai McCorvair Medical Equipment Co., Ltd.); central venous catheters placed in the internal jugular vein (Guangdong Baihe Medical Technology Co., Ltd.); and an M9 portable colour Doppler ultrasound system (Shenzhen Mindray Biomedical Electronics Co., Ltd.).

Statistical methods

The data were analysed using SPSS 25.0 and MEDCALC 15.0. Normally distributed continuous data are reported as the means $\pm$ standard deviations, whereas nonnormally distributed data are reported as medians and interquartile ranges (P25–P75). Differences in indices over time were analysed via repeated-measures ANOVAs with Bonferroni correction. Correlation analyses for nonnormally distributed data were performed via Spearman's correlation coefficient (R_s). Analysis of Bland–Altman limits of agreement and interclass correlation coefficients was performed to evaluate consistency. Regression analysis was used to compute the weight of the LUS on the EVLW. A P value <0.05 indicated statistical significance.

Results

General information

A total of 24 septic shock patients from the Department of Critical Care Medicine of Henan Provincial People's Hospital were enrolled in this study. Among these patients, one died during the study period, and satisfactory ultrasound images could not be obtained for one patient. The average age of the remaining 22 patients (13 males, 9 females) was 54.27 ± 19.18 years (range: 23–76), and their body mass index (BMI) ranged from 21.91 to

Index		M ± SD/N(%)
Age (years)		54.27 ± 19.18
Sex	Male	13(59.1%)
	Female	9(40.9%)
BMI (kg/m ²)		24.36(21.91–25.56)
APACHE II		23 ± 11.78
Albumin (g/L)		29.64 ± 1.12
Serum creatinine (μmol/L)		169.73 ± 23.15
Oxygenation index (mmHg)		198.50 ± 11.21
Blood lactic acid (mmol/L)		6.65 ± 0.88

Table 1. General data of the enrolled patients.

Index	0 h	2 h	6 h	12 h	24 h	48 h	F	P
HR	116.82 ± 19.82	106.00 ± 16.93	103.05 ± 16.69	100.23 ± 18.55	94.32 ± 13.86* ^{&}	90.36 ± 15.35* ^{&} [@]	12.92	<0.001
MAP	58.82 ± 9.85	66.36 ± 7.44*	70.77 ± 9.12*	77.82 ± 12.65* ^{&} ^s	82.82 ± 11.90* ^{&} [@]	87.82 ± 11.06* ^{&} [@]	37.17	<0.001
Oxygen Saturation (SpO ₂)	95.27 ± 2.78	95.68 ± 2.25	95.95 ± 3.58	95.95 ± 3.58	96.73 ± 2.43	97.14 ± 1.98	2.83	0.05
Temperature	37.47 ± 0.91	37.45 ± 0.73	37.61 ± 0.64	37.61 ± 0.64	37.36 ± 0.61	37.25 ± 0.53	2.33	0.097

Table 2. Comparison of different biometric indices in enrolled patients over time. *: significant vs. 0 h; &: significant vs. 2 h; \$: significant vs. 6 h; @: significant vs. 12 h; #: significant vs. 24 h.

Index	0 h	2 h	6 h	12 h	24 h	48 h	F	P value
EVLW	9.64 ± 6.02	10.41 ± 5.72	11.27 ± 6.12	10.82 ± 5.29	13.45 ± 5.80* ^{&}	9.14 ± 4.78 [#]	7.79	<0.001
LUS	12.59 ± 7.30	13.73 ± 6.95	14.82 ± 6.99	14.45 ± 6.46	16.64 ± 6.15* ^{&}	12.23 ± 6.3 [#]	6.08	0.002

Table 3. Comparison of the LUS and EVLW measurement at different time points. * Significant vs. 0 h; & significant vs. 2 h; \$ significant vs. 6 h; @ significant vs. 12 h; # significant vs. 24 h.

Index	0 h	2 h	6 h	12 h	24 h	48 h
r _s	0.95(0.86–1.00)*	0.97(0.88–1.00)*	0.95(0.82–0.99)*	0.95(0.82–0.99)*	0.79 (0.47–0.96)*	0.82(0.44–0.97)*
ICC	0.92(0.82–0.97)*	0.91(0.80–0.96)*	0.92(0.82–0.97)*	0.90(0.78–0.96)*	0.88(0.72–0.95)*	0.71(0.42–0.87)*

Table 4. Coefficients of the correlation and interclass correlation between LUS and EVLW. r_s: Spearman correlation coefficient; ICC: interclass correlation coefficient; *: $p < 0.001$.

25.56 kg/m². The average APACHE II score for this patient cohort was 23 ± 11.78 (Table 1). All patients provided written informed consent. Patients were informed about the study and signed informed consent forms. Trends in the basal heart rate (HR), mean arterial pressure (MAP), body temperature (T), CO, and other indicators were recorded in these patients and were consistent with those of patients with septic shock (Table 2).

Correlation between the LUS and EVLW

The LUS and EVLW measurements are compiled in Table 3. Correlation analyses revealed a strong correlation between these two values at the different study time points (Table 4). The interclass correlation coefficients at each time point revealed that the two indicators were highly consistent (Table 4). Similarly, a scatter plot revealed a strong correlation between the LUS and the EVLW measurement (Fig. 1).

In addition, we analysed the Bland-Altman limits of agreement, and the results revealed that the limits of agreement between the two indicators were −3.3 (−9.2, 2.6), and only 4 (3.03%) points exceeded the limits (Table 5; Fig. 2).

The regression analysis of the two indicators revealed that the coefficient was 0.76, with a 95% CI of 0.70–0.83 ($t = 23.40$, $p < 0.001$), and the equation was $EVLW = 0.76 \times LUS + 0.08$ (Table 6).

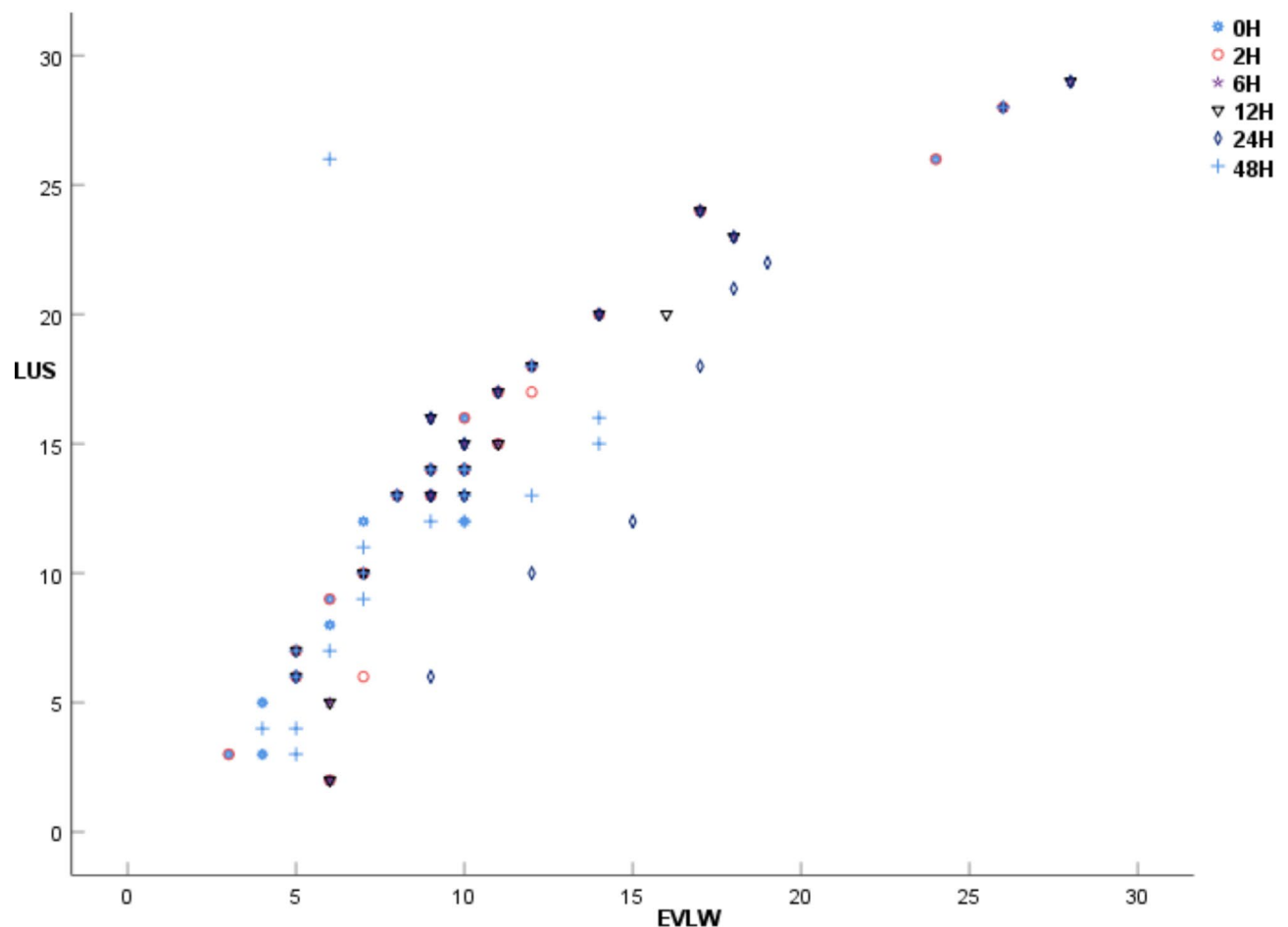


Fig. 1. Scatter plot analysis of overall correlations between LUSs and EVLW measurements.

Index	M ± SD	95% LOA	Lower than 95% LOA	Upper than 95% LOA
EVLW and LUS	−3.30 ± 3.01	(−9.2, 2.6)	1(0.76%)	3(2.27%)

Table 5. Bland–Altman limits of agreement between the EVLW and LUS. LOA: limits of agreement, SD: standard deviation.

Discussion

Sepsis is one of the leading causes of mortality among patients in the ICU, with mortality rates estimated to range from 18–55%¹⁰. Septic shock is a form of severe sepsis that is the focus of current research in the field of critical care. However, reliable approaches for reducing the risk of mortality in septic shock patients have yet to emerge, and there is controversy surrounding the use of goal-oriented fluid resuscitation strategies in clinical settings¹¹.

Septic shock results from a decrease in circulating blood volume due to changes in vascular tone coinciding with a sharp decrease in tissue perfusion, contributing to tissue hypoxia and organ dysfunction owing to the disruption of the normal homeostatic balance between oxygen supply and demand. Restoring appropriate tissue perfusion is a primary goal of fluid resuscitation and a criterion for the discontinuation of fluid resuscitation¹². However, septic shock patients often exhibit simultaneous acute respiratory distress syndrome (ARDS), the treatment of which necessitates restricted fluid resuscitation. Accurately gauging the severity of pulmonary oedema in these critically ill patients is thus essential for guiding treatment. While CT and magnetic resonance imaging (MRI) approaches can be used for accurate, semiquantitative assessment of the degree of pulmonary lesions¹³, these techniques are poorly suited for critically ill patients in need of dynamic real-time monitoring. In contrast, PiCCO is a haemodynamic monitoring technique that is repeatable and suitable for continuous monitoring, allowing accurate assessment of pulmonary oedema status. However, PiCCO monitoring is minimally invasive but expensive, thus its use in primary hospitals is limited. In recent years, ultrasonography has been increasingly favoured by clinicians in critical care settings because of its rapid, noninvasive, radiation-free properties. Jambrik et al.¹⁴ conducted an experimental analysis of acute lung injury in pigs in which tissue samples were analysed using a mass method, revealing a significant correlation between the number of B

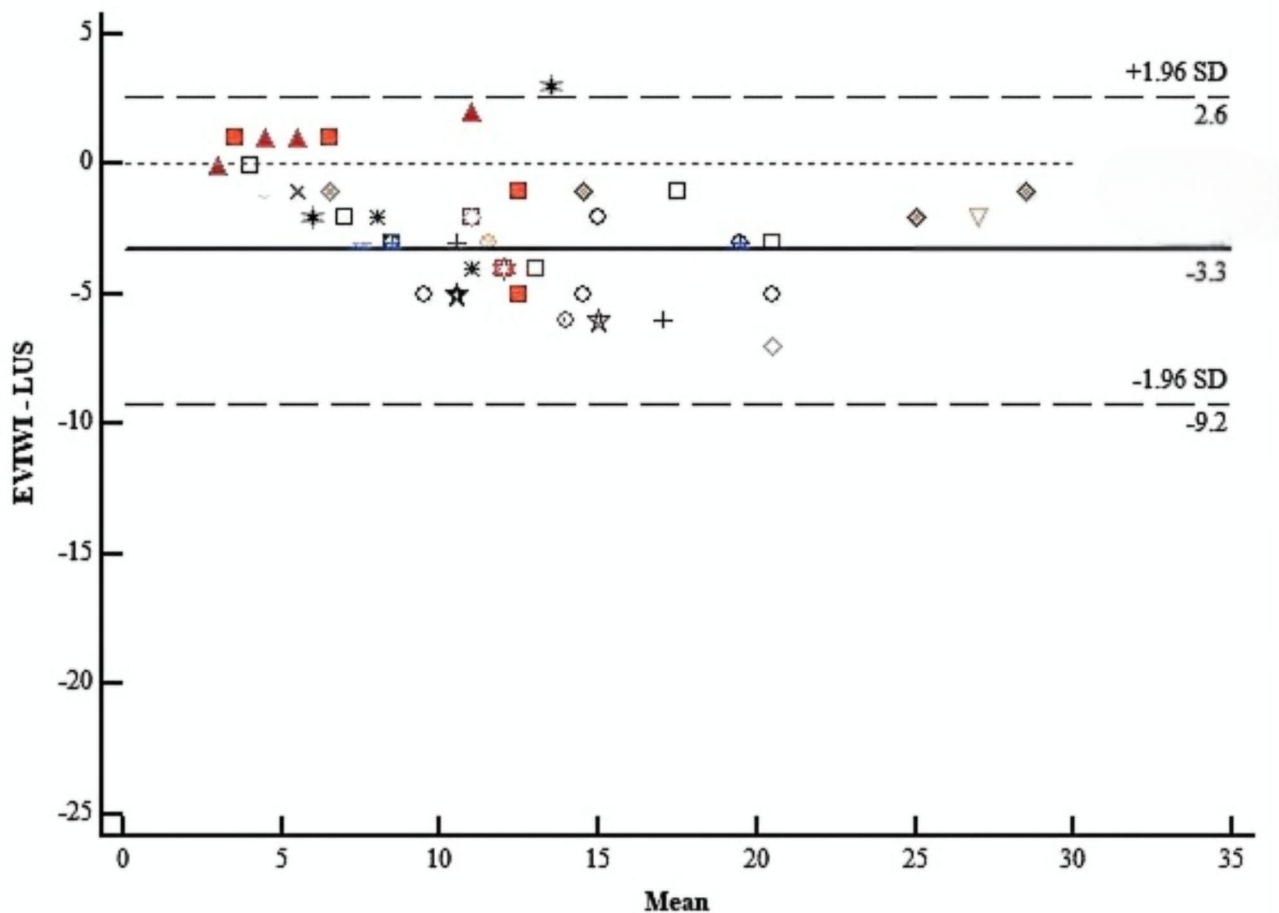


Fig. 2. Bland–Altman limits of agreement between the EVLW measurement and LUS.

Item	β	Se	95% CI	t	p	Equation
LUS	0.76	0.03	0.70–0.83	23.40	<0.01	$EVLW = 0.76 \cdot LUS + 0.08$
intercept	0.08	0.51	−0.92–1.08	0.16	0.87	

Table 6. Regression analysis of the EVLW and LUS.

lines detected via ultrasonography and the dry/wet ratio measured by the mass method, thus suggesting that ultrasound scans can be used for noninvasive evaluation of EVLW. Pulmonary ultrasound analyses are used to assess severely impaired lung function in patients with various lung diseases¹⁵, and Speidel et al.¹⁶ reported the value of pulmonary ultrasonography as an approach to detect severe COVID-19 in its early stages.

With respect to EVLW analyses, prior research clearly revealed the superiority of lung ultrasound examinations over chest X-rays for evaluating pulmonary oedema status. Yu et al.³ reported that, relative to chest CT, the LUS has accuracy, sensitivity, and specificity values of 93.12%, 91.33%, and 95.31%, respectively, suggesting that the LUS can be used for early prognostic evaluation of ARDS. Anile et al.¹⁷ reported a significant correlation between B line-positive lung quadrants and EVLW index values in patients with critical lung disease, whereas Emperador et al.¹⁸ reported that more B lines were correlated with poorer oxygenation and more difficult extubation in 73 patients following cardiac surgery, which is consistent with the value of ultrasonography as a tool for monitoring EVLW.

PiCCO can measure EVLW with a high degree of quantitative accuracy. Here, PiCCO-based monitoring was used to assess EVLW over time, whereas the LUS was computed using a previously published approach¹⁹. These two indices were strongly correlated with one another, with a correlation coefficient of 0.902 ($P < 0.001$), indicating that lung scores increase as the amount of water in the lungs increases, which is consistent with prior research. These results also confirmed that pulmonary scores can be used to accurately gauge the severity of pulmonary lesions in septic shock patients. Theerawit et al.²⁰ reported that for every 120 mL increase in positive balanced fluid volume in the lungs, the number of measured B lines increased by 1, and the oxygenation index

(PaO₂/FiO₂) was negatively correlated with the rate at which the number of B lines in the lungs changed ($R = -0.704$, $P < 0.05$), underscoring the value of pulmonary ultrasound as a tool that can guide fluid resuscitation in septic shock patients.

While these results highlight the promise of the LUS as a tool for assessing EVLW, these results are subject to several limitations. Hasan and Makhoul²¹ conducted analyses of interstitial lung disease and determined that while the B-line distance can be utilized to differentiate between interstitial pulmonary oedema and alveolar pulmonary oedema, these B-lines often move with respiration and can be difficult to identify. Ventilators, wound dressings, obesity, and other factors can also impact ultrasound examination results, and the results lack any established quantitative standards such that the findings are somewhat subjective, complicating efforts to implement lung ultrasound scoring more broadly²². Although PiCCO is advantageous in terms of precise haemodynamic assessment, the challenges associated with its widespread adoption can be partially mitigated through the utilization of pulmonary ultrasound scoring, and a combination of both techniques may thus more effectively guide clinical decision-making, emphasizing the need for further research to better guide clinical care efforts.

In summary, the pulmonary ultrasound score was strongly correlated with PiCCO in assessing EVLW, highlighting the promise of the former approach as a tool for assessing pulmonary status in septic shock patients.

Limitations

In line with the views of most scholars, lung ultrasound will impact acute care, leading to tangible results if used in the right way. However, lung ultrasound is currently limited in assessing alveolar-interstitial syndrome and ascertaining the differential diagnosis of lung dilatation and consolidation. Moreover, lung ultrasound has high interoperator variability, which primarily depends on clinician skill^{23,24}. The LUS is commonly used to determine the degree of lung aeration loss in each of the six zones on each side of the chest in ICU patients²⁵. The lung ultrasound scoring system needs to be further standardized to improve its repeatability. Additionally, diagnostic methods and scoring techniques are not interchangeable. Diagnosing lung conditions and quantifying their disease using scoring systems may result in fallacies that could invalidate the study results^{23,24}. Finally, the small sample size is a limitation of this study, which may affect the accurate estimation of the validity. Future multicenter study with larger sample size is needed for a better validation and generalization.

Data availability

The data that support the findings of this study are available upon request from the corresponding author.

Received: 12 April 2024; Accepted: 28 March 2025

Published online: 04 April 2025

References

- Kuhn, S. O., Meissner, K. & Rehberg, S. Fluid resuscitation in sepsis: Get the balance right. *Crit. Care Med.* **45**, 555–556 (2017).
- Litton, E. & Morgan, M. The PiCCO monitor: A review. *Anaesth. Intensive Care.* **40**, 393–408 (2012).
- Yu, K. et al. Application of critical care ultrasound in hemodynamic monitoring of septic shock. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* **31**, 248–251 (2019).
- Kopp, S. et al. Injection site matters: A comparative analysis of transpulmonary thermodilution via simultaneous femoral and jugular indicator injections under veno-venous extracorporeal membrane oxygenation therapy. *J. Clin. Med.* **13**, 2334 (2024).
- Katzenelson, R. et al. Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water. *Crit. Care Med.* **32**, 1550–1554 (2004).
- Singer, M. et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* **315**, 801–810 (2016).
- Mongodi, S. et al. Modified lung ultrasound score for assessing and monitoring pulmonary aeration. *Ultraschall Med.* **38**, 530–537 (2017).
- Sayed, M. S., Elmeslmany, K. A., Elsayy, A. S. & Mohamed, N. A. The validity of quantifying pulmonary contusion extent by lung ultrasound score for predicting ARDS in blunt thoracic trauma. *Crit. Care Res. Pract.* 3124966 (2022).
- Mongodi, S. et al. Quantitative lung ultrasound: Technical aspects and clinical applications. *Anesthesiology* **134**, 949–965 (2021).
- Devia Jaramillo, G. & Menendez Ramirez, S. USER protocol as a guide to resuscitation of the patient with septic shock in the emergency department. *Open. Access. Emerg. Med.* **13**, 33–43 (2021).
- Investigators, P. R. I. S. M. et al. Early, goal-directed therapy for septic shock—A patient-level meta-analysis. *N Engl. J. Med.* **376**, 2223–2234 (2017).
- Liu, D. Shock management: Bridging microcirculation and cellular function (in Chinese). *Chin. Crit. Care Med.* **25**, 2–4 (2013).
- Leiser, P. et al. A quantitative CT parameter for the assessment of pulmonary oedema in patients with acute respiratory distress syndrome. *PLoS ONE* **15**, e0241590 (2020).
- Jambrik, Z. et al. B-lines quantify the lung water content: A lung ultrasound versus lung gravimetry study in acute lung injury. *Ultrasound Med. Biol.* **36**, 2004–2010 (2010).
- Zhang, C. et al. Clinical significance of bilateral lung asymmetry signs of bedside ultrasound in severe patients. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* **32**, 1118–1120 (2020).
- Speidel, V., Conen, A., Gislser, V., Fux, C. A. & Haubitz, S. Lung assessment with point-of-care ultrasound in respiratory coronavirus disease (COVID-19): A prospective cohort study. *Ultrasound Med. Biol.* **47**, 896–901 (2021).
- Anile, A., Russo, J., Castiglione, G. & Volpicelli, G. A simplified lung ultrasound approach to detect increased extravascular lung water in critically ill patients. *Crit. Ultrasound J.* **9**, 13 (2017).
- Emperador, F. 4th et al. Extravascular lung water and effect on oxygenation assessed by lung ultrasound in adult cardiac surgery. *Cureus* **12**, e9953 (2020).
- Macho, J. T. & Sánchez, G. G. D. C. The lung, paradigm of point-of-care ultrasound. *Rev. Clin. Esp. (Engl. Ed.)*. **221**, 281–282 (2021).
- Theerawit, P., Touman, N., Sutherasan, Y. & Kiatboonsri, S. Transthoracic ultrasound assessment of B-lines for identifying the increment of extravascular lung water in shock patients requiring fluid resuscitation. *Indian J. Crit. Care Med.* **18**, 195–199 (2014).
- Hasan, A. A. & Makhoul, H. A. B-lines: Transthoracic chest ultrasound signs useful in assessment of interstitial lung diseases. *Ann. Thorac. Med.* **9**, 99–103 (2014).
- Romero-Bueno, F., Rodríguez-Nieto, M. J. & Naredo, E. Education and use of lung ultrasound in rheumatology and pneumology in Spain: A SER-SEPAR survey. *Reumatol. Clin. (Engl. Ed.)*. **18**, 94–99 (2022).

23. Lichtenstein, D. A. Current misconceptions in lung ultrasound: A short guide for experts. *Chest* **156**, 21–25 (2019).
24. Volpicelli, G. & Rovida, S. Clinical research on point-of-care lung ultrasound: Misconceptions and limitations. *Ultrasound J.* **16**, 28 (2024).
25. Demi, L. et al. New international guidelines and consensus on the use of lung ultrasound. *J. Ultrasound Med.* **42**, 309–344 (2023).

Author contributions

All the authors helped with the study conception and design. Zhifeng Li helped with volunteer recruitment. Data collection and analysis were performed by Xueyan Zhang. The first draft of the manuscript was written by Xueyan Zhang, and all the authors commented on previous versions of the manuscript. All the authors have read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Consent for publication

All the authors have consented to publication.

Additional information

Correspondence and requests for materials should be addressed to Z.L.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2025