

# Evaluating Extravascular Lung Water in Sepsis: Three Lung-Ultrasound Techniques Compared against Transpulmonary Thermodilution

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## Abstract

**Background:** Excessive extravascular lung water (EVLW) is associated with increased morbidity and mortality. We compared three lung-ultrasound (L-US) techniques against the reference-standard transpulmonary thermodilution (TPTD) technique to access EVLW. **Materials and Methods:** This was a prospective, single-blind, cross-sectional study. Forty-four septic patients were enrolled. EVLW index was measured by the TPTD method, and an index of  $\geq 10$  mL/kg was considered diagnostic of pulmonary edema. EVLW index was then compared to three established bedside L-US protocols that evaluate sonographic B-lines: (1) a 28-zone protocol (total B-line score [TBS]) (2) a scanning 8-region examination, and (3) a 4-point examination. **Results:** Eighty-nine comparisons were obtained. A statistically significant positive correlation was found between L-US TBS and an EVLW index  $\geq 10$  mL/kg ( $r = 0.668$ ,  $P < 0.001$ ). The 28-zone protocol score  $\geq 39$  has a sensitivity of 81.6% and a specificity of 76.5% to define EVLW index  $\geq 10$  mL/kg. In contrast, the positive 4-point examination and scanning 8-regions showed low sensitivity (23.7% and 50.0%, respectively) but high specificity (96.1% and 88.2%, respectively). Ten patients with a total of 21 comparisons met criteria for acute respiratory distress syndrome (ARDS). In this subgroup, only the TBS had statistically significant positive correlation to EVLW ( $r = 0.488$ ,  $P = 0.025$ ). **Conclusion:** L-US is feasible in patients with severe sepsis. In addition, L-US 28-zone protocol demonstrated high specificity and better sensitivity than abbreviated 4- and 8-zone protocols. In ARDS, the L-US 28-zone protocol was more accurate than the 4- and 8-zone protocols in predicting EVLW. Consideration of limitations of the latter protocols may prevent clinicians from reaching premature conclusions regarding the prediction of EVLW. **Trial Registration:** ISRCTN11419081. Registered 4 February 2015 retrospectively.

**Keywords:** Acute interstitial syndrome, B-lines, extravascular lung water, lung ultrasound, transpulmonary thermodilution

## INTRODUCTION

Following sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, fluid resuscitation can be acutely lifesaving.<sup>[1]</sup> However, excessive extravascular lung water (EVLW) is associated with subsequent organ dysfunction and increased mortality.<sup>[2]</sup> Accordingly, clinicians need to be able to detect excessive EVLW if they are to achieve clinical balance in order to maximize the likelihood of patient rescue. Several techniques exist, but all have limitations. For example, chest X-ray and physical examination are limited by their

inability to detect EVLW during early stages<sup>[3]</sup> and because of substantial interobserver variability.<sup>[4]</sup> Transpulmonary thermodilution (TPTD),<sup>[5]</sup> the current reference standard, detects water accumulated in the interstitium, lymphatics, and alveoli, and an extravascular lung water index (EVLWI)

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of  $\geq 10$  mL/kg suggests pulmonary edema.<sup>[6,7]</sup> Elevated EVLW by TPTD has been shown to be predictive of 28-day mortality in septic shock patients after initial fluid resuscitation.<sup>[8]</sup> However, TPTD is costly, requires proprietary equipment, and is invasive. Lung-ultrasound (L-US) offers the putative advantages of being noninvasive, repeatable, portable, and low cost.<sup>[9-12]</sup> However, there are several protocols (see below). To date, there is insufficient data to recommend a single L-US technique, or whether an algorithmic L-US approach could be employed, or whether EVLW determination is feasible in a low-resource setting.

Sonographic evaluation of lung parenchyma for interstitial edema is based on visualizing B-lines. These are discrete, laser-like vertical hyperechoic reverberation artifacts. B-lines arise from the pleura, extend to the bottom of the image without fading, and move synchronously with respiration.<sup>[13]</sup> Sonographic B-lines are biophysically correlated to EVLW and their number correlates with the degree of pulmonary interstitial edema.<sup>[11,14,15]</sup> Studies have compared L-US and determination of lung water by chest X-ray,<sup>[14,16]</sup> chest computed tomography (CT),<sup>[17]</sup> and pulmonary capillary wedge pressure.<sup>[11,18]</sup> L-US has also been compared to TPTD in a variety of studies<sup>[9,11,18,19]</sup> and it demonstrates strong positive correlation with the amount of EVLW. Enghard *et al.* demonstrated a strong correlation between a 4-zone L-US protocol and EVLW by TPTD in a heterogeneous group of critically ill patients.<sup>[9]</sup> Volpicelli *et al.* compared an 8-zone qualitative L-US protocol to EVLW by TPTD and found that patients with an elevated EVLWI ( $\geq 10$  ml/kg) almost invariably also displayed a B-line-dominant pattern.<sup>[18]</sup> Both Enghard and Volpicelli included patients with sepsis and septic shock, respectively, but did not perform predefined subgroup analyses. To our knowledge, ours is the first study which compares three common L-US techniques against TPTD and focuses on intensive care unit (ICU) patients with sepsis.<sup>[9,11,20]</sup> This study would add more information on the sensitivity and specificity of each method of L-US in detecting pulmonary edema. This would aid the intensivists to select the appropriate method for the patients.

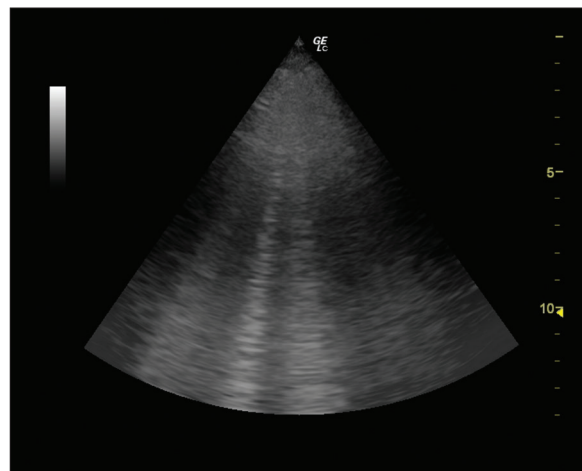
## MATERIALS AND METHODS

This prospective, single-blind, cross-sectional study of medical ICU sepsis patients compares a TPTD-derived measurement of EVLWI against three L-US techniques. Between May 2014 and November 2015, we enrolled patients admitted to the medical ICU of a tertiary care hospital who met the following criteria for diagnosis of sepsis: as defined by the third international consensus definitions of sepsis and septic shock<sup>[21]</sup> and requiring fluid boluses and continuous blood pressure monitoring. Due to its prevalence in sepsis patients, acute respiratory distress syndrome (ARDS) was not an exclusion criterion. However, patients with conditions that can lead to inaccurate EVLW measurement by either L-US or TPTD were excluded from the study. These included pulmonary embolism, prior lung resection, interstitial lung diseases, and pleural

diseases. For the sample size calculation, we were expecting a population correlation between EVLWI  $< 10$  ml/kg and  $\geq 10$  ml/kg of around 0.66, a sample size of forty patients generating approximately eighty comparisons between L-US and TPTD will give us approximately 90% power ( $\alpha = 0.05$ , one sided) to reject the null hypothesis of zero correlation. Ethical approval was obtained from the Institutional Review Board of Royal Thai Army Medical Department (R032 h/56), and consent was obtained from the patients or the patients' next of kin. This study was conducted according to the principles of the Declaration of Helsinki.

L-US examinations (LOGIQ e ultrasound, GE Healthcare, China) were performed using a 2.5–3.5 MHz phased array probe. We utilized this probe because it is commonly used by bedside clinicians. We also turned off tissue harmonics in order to maximize the visualization of lung artifacts. Current evidence-based recommendations for L-US suggest that, although a microconvex probe is preferred, linear and phased array probes are acceptable alternatives with no difference in visualization in the number of B-lines.<sup>[11,12]</sup> All patients were studied supine and with the US transducer-oriented cephalad. The pleural line was identified (between and deep to two rib shadows) and used as an indicator of the visceral and parietal pleural layers.

The B-line was defined by seven features: a comet-tail artifact, arising from the pleural line, hyperechoic, well defined, spreading out indefinitely, erasing A-lines, and moving in concert with lung sliding when present [Figure 1]. Per rib space, the number of B-lines ranged from 0 to 10, with 10 designated as “white lung” and three or more indicative of subpleural interstitial edema. According to 2012 international L-US recommendations,<sup>[10]</sup> there are three methods for assessing interstitial syndrome. We performed each of these methods on each patient, each day, and until hemodynamic support was discontinued. As the focus of this study was on quantification and correlation between B-lines and EVLW, we did not record pleural- or other parenchymal-based abnormalities. B-line determination was made with strict adherence to criteria previously mentioned. The absence of an independent reviewer



**Figure 1:** B-lines detected by lung-ultrasound

for US images also reflected resource constraints. Instead, one experienced investigator scored all scans.

### Total B-line scores

The anterior and lateral chest was scanned on the left from the second to the fourth intercostal space (and on the right side from the second to the fifth), plus along the parasternal, mid-clavicular, anterior-axillary, and mid-axillary lines. The total number of B-lines was counted and recorded at each of the 28 sites, from which a total B-line score (TBS) is determined.<sup>[14]</sup>

### 4-point examination

Four sites were scanned, namely, the upper and lower points of each hemithorax. Placement was determined using the clinician's hands: the fifth finger of the upper hand touches the lower border of the patient's clavicle and fingertips touch the midline. The lower hand was applied below, and both thumbs were excluded. The upper point is in the middle of the hand (the root of the middle and ring fingers). The lower point is in the middle of the palm of the lower hand. This method avoids the cardiac window. A scan with at least three artifacts at each point is considered abnormal.<sup>[4,22]</sup>

### Scanning 8-regions

The chest wall is divided into eight areas (four from each hemithorax: two anterior and two lateral), and one scan is obtained from each area.<sup>[16]</sup> The anterior chest wall is delineated from the sternum to the anterior axillary line and subdivided into upper and lower halves (approximately from the clavicle to the second–third intercostal spaces, and from the third space to the diaphragm). The lateral zone is between the anterior and posterior axillary lines and is subdivided into upper and basal halves. An abnormal pattern has all three of the following features: (1) multiple artifacts per scan (at least three), (2) positive findings in more than one scan per side, and (3) positive findings bilaterally.

### Extravascular lung water measurement methods

The EV1000 (VolumeView Set, EV1000, Edwards Lifesciences, Irvine, CA, USA) measures cardiac output (CO), preload, and lung water. It computes CO utilizing an arterial pulse contour analysis algorithm and a TPTD method. In all patients, a 5F thermistor-tipped catheter was placed into the right or left femoral artery, and then connected to the EV1000 System and calibrated. Arterial input impedance to arterial pressure is calculated by determining the area under the systolic portion of the arterial pulse wave. A 15–20 mL bolus of cold 0.9% saline was injected through a central venous catheter, and the thermodilution curve was evaluated with the arterial catheter in the femoral artery. The mean of three consecutive boluses was used to obtain the intrathoracic thermal and intrathoracic blood volume. From the difference of these two parameters, the device could determine the EVLW. Normally, EVLWI is <10 mL/kg, whereas an EVLWI of  $\geq 10$  mL/kg suggests pulmonary edema.<sup>[6,7]</sup> EVLW measurements were done promptly after L-US by the principal investigator. The results of EVLW were blinded to the investigator who did L-US.

### Statistical analysis

Data were expressed as mean value  $\pm$  standard deviation, median (interquartile range), or percentages. The correlations between TBS, 4-point examination, scanning 8-regions, and EVLWI were analyzed by the Spearman's correlation coefficient analysis ( $r$ ) and coefficient of determination ( $r^2$ ). Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of each method of L-US using one-sided  $P$  value. The ROC curves were compared using proportion tests. All tests were two sided and  $P < 0.05$  was considered statistically significant. Similar subgroup analysis was done in the patients meeting ARDS criteria according to the Berlin definition.<sup>[23]</sup> All data were analyzed and graphs were generated with Stata/IC 13.0 (StataCorp, TX, USA).

### RESULTS

Eighty-nine comparisons between L-US and TPTD were obtained from 44 patients (28 men and 16 women,  $67.3 \pm 17.4$  years of age). Baseline patient characteristics are displayed in Table 1. The median TBS was 36 (22–67) and the mean EVLWI was  $9.1 \pm 2.6$  mL/kg. Intraobserver variability of TBS was 3.5%.

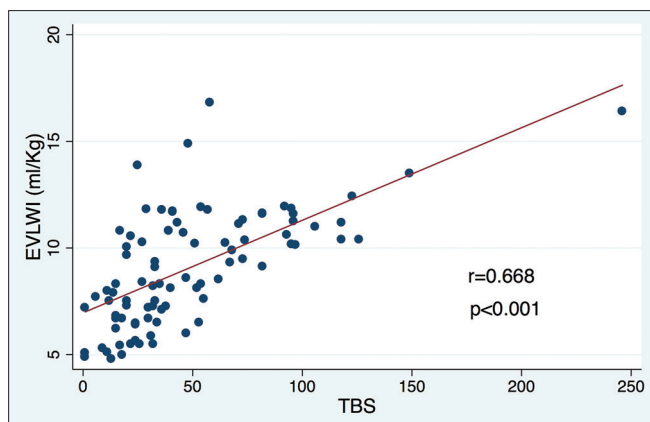
There was a statistically significant positive linear correlation between TBS and EVLWI ( $r = 0.668$ ,  $P < 0.001$ ) [Figure 2], 4-point examination, and EVLWI ( $r = 0.558$ ,  $P < 0.001$ ) and also between scanning 8-regions and EVLWI ( $r = 0.640$ ,  $P < 0.001$ ). The coefficient of determination between TBS, 4-point examination, scanning 8-regions, and EVLWI was statistically significant at 0.408 ( $P < 0.001$ ), 0.254 ( $P < 0.001$ ), and 0.396 ( $P < 0.001$ ), respectively. ROC curves of each L-US-based method (TBS, 4-point examination, and scanning 8-regions) for the prediction of  $\text{EVLWI} \geq 10$  mL/kg were 0.844,

**Table 1: Baseline characteristics of the study population**

Characteristics	Value
Number of patients	44
Age (years) $\pm$ SD	67.3 $\pm$ 17.4
Male (%)	28 (63.6)
Height (cm) $\pm$ SD	167.1 $\pm$ 9.4
Weight (kg) $\pm$ SD	64.5 $\pm$ 13.0
Predicted body weight (kg) $\pm$ SD	62.6 $\pm$ 9.0
APACHE II score ( $\pm$ SD)	21.2 $\pm$ 6.4
SOFA score ( $\pm$ SD)	11 $\pm$ 4
ARDS (%)	10 (22.7)
Source of sepsis (%)	
Intra-abdominal infection	19 (43.2)
Pneumonia	8 (18.2)
Bloodstream infection	8 (18.2)
UTI	3 (6.8)
CRBSI	2 (4.5)
Soft-tissue infection	1 (2.2)
Sepsis unknown source	3 (6.8)

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; ARDS: Acute respiratory distress syndrome; UTI: Urinary tract infection; CRBSI: Catheter-related bloodstream infection; SD: Standard deviation





**Figure 2:** Significant positive linear correlation between total B-line scores and extravascular lung water index determined with the transpulmonary thermodilution technique (EV1000 System)

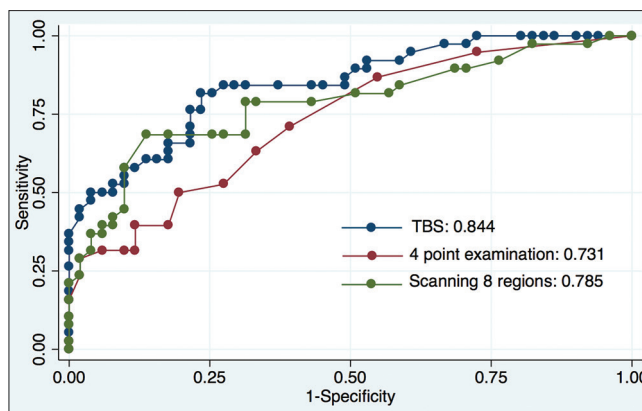
0.731, and 0.785, respectively [Figure 3]. A one-sided *P* value of the ROC curve comparison between TBS and 4-point examination was 0.008, between TBS and scanning 8-regions was 0.111, and between 4-point examination and scanning 8-regions was 0.087. For the TBS US method, using  $\geq 39$  as cutoff point had a sensitivity of 81.6% and a specificity of 76.5% for predicting  $\text{EVLWI} \geq 10$  ml/kg. The presence of  $\geq 3$  B-lines in all 4-point examination points and any two regions on each side of the 8-regions method exhibited sensitivities of 23.7% and 50.0% and specificities of 96.1% and 88.2% in predicting  $\text{EVLWI} \geq 10$  ml/kg, respectively.

Ten patients with a total of 21 comparisons met criteria for ARDS. In this subgroup, the correlation coefficients between TBS, 4-point examination, scanning 8-regions, and EVLWI were 0.488, 0.209, and 0.312, respectively, with only the TBS reaching statistical significance ( $P = 0.025$ ,  $P = 0.362$ , and  $P = 0.168$ , respectively).

## DISCUSSION

Despite limitations (see below), our study confirms the feasibility and potential clinical utility of L-US in ICU patients with sepsis and in a low-resource setting. We demonstrated a strong correlation between TBS and EVLWI ( $r = 0.668$ ,  $P < 0.001$ ). Using a cutoff point of  $\text{TBS} \geq 39$  yielded a sensitivity of over 80% and a specificity of over 75% for predicting  $\text{EVLWI} \geq 10$  ml/kg. Our findings duplicate the strong correlation between L-US and EVLW shown in other studies.<sup>[9,11,18]</sup> Next, the 4-zone and 8-zone scanning methods demonstrated both low sensitivities (23.7% and 50.0%, respectively) but high specificities (96.1% and 88.2%, respectively). This suggests that the abbreviated 4- and 8-zone protocols may be more suitable to rule in fluid overload rather than rule it out. If higher sensitivity and specificity is required or more quantitative information, then our pilot data help to justify a more time-consuming 28-zone protocol.

Our subgroup analysis of ten patients with ARDS revealed findings that contrasted with the overall study results.



**Figure 3:** Receiver operating characteristic curves for prediction of extravascular lung water index  $\geq 10$  ml/kg. (blue line = total B-line scores; red line = 4-point examination; green line = scanning 8-regions)

In this analysis, the correlation of L-US to EVLW was poor for the 4- and 8-point examination and only reached statistical significance in the TBS protocol. This disparity in L-US protocols may be a consequence of the characteristic heterogeneous topographical distribution of ARDS that may vary with inciting pathology, time, mechanical ventilation, and patient position.<sup>[24,25]</sup> The propensity of alveolar collapse, atelectasis, and consolidation to occur in a gravitationally dependent manner in the dependent (dorsal) lung areas in ARDS may limit accurate assessment by an abbreviated, predominantly ventral, L-US protocol.<sup>[24,25]</sup> The TBS protocol, by way of its comprehensiveness, may better account for both mixed topographical distribution and ventral-to-dorsal loss of parenchymal density.<sup>[17]</sup> Indeed, a study by Zhao *et al.* found that in a group of ARDS patients, a 12-region method of LUS demonstrated a strong positive correlation between L-US and EVLWI ( $r^2 = 0.906$ ) and sensitivity and specificity of 84.6% and 91.8%, respectively, by area under the curve analysis of a ROC.<sup>[26]</sup> Notably, the L-US examinations described in our study were strictly designed to assess B-line prevalence and were not designed to account for the full range of pleural and parenchymal abnormalities seen in ARDS including lack of lung sliding, subpleural consolidation, and consolidation.<sup>[27,28]</sup> Given the limitations of our subgroup analysis, including the small number of patients, and limited available literature that examines L-US in ARDS, further study is warranted.

Increased EVLW is associated with high morbidity (fewer ventilator-free days and longer hospital admission) as well as with increased mortality.<sup>[20,29,30]</sup> Chest X-ray does not typically detect EVLW until it is two to three times normal.<sup>[3]</sup> As a result, more sensitive EVLW measurements are needed. *In vivo* methods have also been validated and include quantitative CT, positron emission tomography scanning, magnetic resonance imaging,<sup>[31]</sup> and EVLW by TPTD.<sup>[20,32]</sup> Unfortunately, all these methods are costly, time-consuming, invasive, and impractical at the bedside, or limited to a single static time point. L-US, in contrast, is appealing because it is noninvasive, nonionizing, repeatable, and has a high

concordance rate even after limited training.<sup>[13]</sup> Previous research comparing L-US scoring to EVLW by TPTD has largely focused on cardiogenic pulmonary edema,<sup>[18,33,34]</sup> and an increased number of US B-lines has been used to approximate its severity. Notably, there is scant literature comparing the performance of L-US to EVLW in patients with sepsis, one of the most common conditions in ICU. Moreover, there is scant literature examining the challenges and feasibility of determining EVLW in low-resource settings.

This study has limitations, including the relatively small number of patients and single-center enrollment. This reflects the fact that the study was a pragmatic investigation of real-world L-US in a resource-limited setting. We also used a higher cutoff point than previously described in outpatients with systolic heart failure.<sup>[33]</sup> Notably, using a single operator would eliminate intra- and inter-observer variability, which has been reported as 3.1% and 4.4%, respectively, in B-line scoring (TBS protocol).<sup>[11]</sup> We believe that our developing world location, rather than being an impediment, helps to demonstrate the feasibility of L-US as a bedside test.

Using EV1000 as a reference standard for evaluating EVLW was another limitation. Currently, the PiCCO (Pulsion system) is the gold standard. More importantly, there is no human validation study for EV1000. This might lead to some error of EVLW measurement.

Our findings differ from those of Enghard *et al.*<sup>[9]</sup> who found that a novel 4-zone protocol had a strong and significant correlation with EVLW values by TPTD and could predict severely increased EVLW (>15 ml/kg), with a sensitivity of 92.3% and a specificity of 94.6%. This may reflect their heterogeneous cohort of critically ill patients integrating patients suffering from heart failure. Unfortunately, it is difficult to know exactly why given that they did not perform a predefined subgroup analysis for sepsis patients and we did not include all-comers. We chose to study sepsis in this pilot work because it is characterized by inflammatory cytokines that should enhance fluid leakage. In addition to future studies that encompass the widest range of ICU pathologies, we intend not only to see how it might supplement simple modalities such as physical examination and chest X-ray, but also to examine where its use is associated with rational changes in clinical management.

## CONCLUSION

Our research demonstrates the clinical applicability of three distinct L-US protocols for noninvasive detection of EVLW in patients with sepsis. More extensive 28-zone protocols demonstrate high specificity and better sensitivity than abbreviated 4- and 8-zone protocols. In patients with ARDS, our subgroup analysis suggests that the TBS protocol is more accurate than the abbreviated 4- and 8-zone protocols. Consideration of limitations of abbreviated 4- and 8-zone protocols may prevent clinician from reaching premature conclusions regarding the prediction of EVLW.

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## Conflicts of interest

There are no conflicts of interest.

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