

## **The potential of the ultrasound method in diagnosing pulmonary edema in critically ill patients with liver failure**

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### **Abstract**

**Background.** *Pulmonary edema is a common complication in critically ill patients. The liberal tactics of fluid therapy and pathological accumulation of extravascular lung water increase the risks of mortality in Intensive Care Unit patients. Timely and non-invasive diagnosis of pulmonary edema is a primary goal in the intensive care of patients in the Critical Care Unit. We prefer to use lung ultrasound with the registration of B-lines to diagnose lung edema. However, in our country, this method is not validated due to the lack of a sufficient number of clinical studies and necessary regulatory framework.*

**Objective.** *To assess the potential of diagnostic ultrasonography for pulmonary edema in critically ill patients.*

**Material and methods.** *A retrospective study was conducted on 27 patients, including 15 males and 12 females aged from 43 to 67 years old*

(mean age  $45.05 \pm 17.2$  years). All patients were in critical condition due either to acute liver failure, or acute-on-chronic liver failure, or early post-transplant liver graft failure, or posthepatectomy liver failure. Some patients had a systemic inflammatory response syndrome with the development of multiple organ failure and clinical signs of redistribution shock. All patients underwent ultrasound examination of the lungs, and had hemodynamic parameters measured using the transpulmonary thermodilution technique. The data obtained by the two diagnostic modalities were compared.

**Results.** A significant correlation ( $p < 0.05$ ) was found between the extravascular lung water index and the presence of lung edema. We identified a significant correlation ( $p < 0.05$ ) between the number of B-lines and the presence of pulmonary edema. In assessing the relationship between the "B-line" parameter and the "EVLWI" parameter, a strong positive correlation was identified. The area under the ROC curve (AUC) was  $0.9 \pm 0.06$  with a 95% CI [0.77–1.00].

**Conclusions.** Ultrasound data in diagnosing pulmonary edema have a significant correlation with the level of extravascular pulmonary water. Lung ultrasound is an accurate, non-invasive method for assessing extravascular lung water. It can be used for the rapid and accurate diagnosis of pulmonary edema.

**Keywords:** pulmonary edema, diagnostic ultrasound, extravascular lung water

**Conflict of interests** Authors declare no conflict of interest

**Financing** The study was performed without external funding

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ACLF, acute-on-chronic liver failure  
ALF, acute liver failure  
BMI, body mass index  
CI, cardiac index  
CVC, central venous catheter  
CVP, central venous pressure  
EVLW, extravascular lung water  
GEDVI, global end-diastolic volume index  
EGF, early graft failure  
PEEP, positive end expiratory pressure  
PHLF, post-hepatectomy liver failure  
SIRS, systemic inflammatory response syndrome  
TPTD, transpulmonary thermodilution  
USE, ultrasound examination

## **Introduction**

Pulmonary edema is a common complication in critically ill patients [1–3]. This is most often associated with fluid overload, increased pulmonary capillary permeability, or acute left ventricular heart failure [4]. Liberal tactics of fluid therapy for critical illness and abnormal accumulation of extravascular lung water increase the mortality risks of patients in the intensive care unit [5]. The volume of fluid accumulated in the alveolar, interstitial and intracellular compartments of the lungs is defined by the general term “extravascular lung water” (EVLW) and can be measured by determining the extravascular lung water index (EVLWI) using the transpulmonary method thermodilution (TPTD), which is the “gold standard” in the quantitative assessment of pulmonary edema worldwide. However, this method is invasive, traumatic, expensive, requires appropriate training of personnel and the availability of special equipment; when using it, there is a high risk of developing life-threatening complications [6].

Timely and non-invasive diagnosis of pulmonary edema is an important task during intensive care of a patient in the Intensive Care

Unit [7]. In the treatment of critical illnesses, we prefer to use lung ultrasound (US) with B-line recording instead of ELWI to diagnose pulmonary edema. Since the ultrasound diagnostic method is safe, informative, accessible, simple, and cheap, its use practically does not depend on patient's condition [8]. Ultrasound has become widely used in intensive care practice around the world [9, 10]. However, in our country, as well as in neighboring countries, due to the lack of a sufficient number of clinical studies and the necessary regulatory framework, this method has not been validated; therefore, in the Republic of Belarus, the use of ultrasound for bedside diagnosis of pathological conditions of the lungs is not yet widespread.

**The objective** was to evaluate the feasibility of ultrasound diagnosis of pulmonary edema by comparing correlations between B-line recording protocol and the extravascular lung water index (EVLWI) parameter in patients with liver failure.

### **Material and methods**

A retrospective study included 27 patients. All patients were in critical condition due to acute liver failure (ALF), or acute-on-chronic liver failure (ACLF), or early liver graft failure (EGF), or post-hepatectomy liver failure (PHLF). Some patients had systemic inflammatory response syndrome (SIRS) with the development of multiple organ failure and clinical pattern of redistribution shock according to the Sequential Organ Failure Assessment (SOFA) and Model for End-Stage Liver Disease (MELD) score; the ratios are presented in Table 1.

**Table 1. Anthropometric and clinical characteristics of patients**

<b>Criterion</b>	<b>Value</b>
Gender (male/female ratio, %)	15/12 (55.5%/44.4%)
Age, years, Me (Q1;Q3)	55 (19;67)
Weight, kg, Me (Q1;Q3)	75 (51;94)
Height, cm, Me (Q1;Q 3)	171 (162;186)
Diagnosis, n (%)	ALF 10 (37.0%) ACLF 7 (25.9%) EGF 2 (7.4%) PHLF 8 (29.6%) Of these, 19 (70%) had SIRS
Mechanical lung ventilation mode, n (%)	BiLevel 26 (96.3 %) SIMV (VC) 1 (3.7 %)
FiO <sub>2</sub> %, Me (Q1;Q3)	47 (35;60)
PEEP cm H <sub>2</sub> O, Me (Q1;Q3)	9.5 (5;14)
SOFA, n (%)	II – 4 (14.8%) III – 7 (25.9%) IV – 16 (59.2%)
MELD, n (%) (had End-stage ALF, ACLF, EGF, total 19 patients)	< 9 – 1 (5.26%) 10–19 – 3 (15.7%) 20–29 – 7 (36.8%) 30–39 – 5 (26.3%) >40 – 3 (15.7%)

Notes: BiLevel, a spontaneous ventilation mode at two PEEP levels with switching from one pressure level to another at preset intervals; SIMV (VC), Synchronized Intermittent Mandatory Ventilation (volume controlled)

The study was conducted on the base of the Department of Anesthesiology and Intensive Care Unit No. 2 of the Minsk Scientific and Practical Center for Surgery, Transplantology and Hematology, Minsk, Republic of Belarus, in the period from 09.27.21 to 01.04.24, in agreement with the approval of the Institutional Ethics Committee.

The study inclusion criteria for the patients were the following:

1. All patients in serious condition with clinical signs of redistribution shock due to acute liver failure and systemic inflammatory response syndrome.
2. Patients in whom the transpulmonary thermodilution technique was used to assess hemodynamic parameters.

The exclusion criteria from the study were the following:

1. Patients with concomitant pathology, such as: hydrothorax with a volume of more than 400 ml, pneumothorax, pneumonia, cardiogenic shock, cancer patients with widespread metastatic invasion, tense ascites.

2. Patients with constitutional features that made ultrasound visualization difficult, such as those with a body mass index (BMI) exceeding 30, with a subcutaneous fat thickness of more than 10 cm that induced the absorption and attenuation of ultrasound waves and limited the ability to reliably assess the affected areas of the lungs.

3. The sites of impaired skin integrity in the study areas, which prevented the visualization of the necessary zones of the lungs.

Interpretation of ultrasound results based on the number of B-lines was made using the following scale:

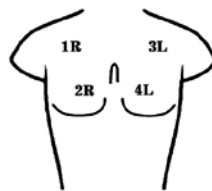
- Lung parenchyma with a normal number of B-lines in the amount of up to 4 lines in the intercostal space (regarded as normal).
- Lung parenchyma with an increased amount water and the number of B-lines from 5 to 8 lines in the intercostal space (considered as moderate edema of the pulmonary tissue).
- Lung parenchyma with an excessive amount of water and the number of B-lines of 9 or more lines in the intercostal space (interpreted as severe edema of the lung parenchyma).

All patients meeting the inclusion criteria underwent pulmonary ultrasound examination according to the 4-point protocol (4-sector B-lines) (Fig. 1), and also their hemodynamic parameters were measured with EVLWI recording by using the transpulmonary thermodilution technique (Table 2).

**Protocol of pulmonary ultrasound examination  
(4-sector B-line score)**

Patient \_\_\_\_\_  
Case history No. \_\_\_\_\_ Department \_\_\_\_\_  
Ultrasonic sensor type \_\_\_\_\_  
Study in patient supine position

Date/ time	T, S	FiO <sub>2</sub> / SpO <sub>2</sub> %	RR	1R	2R	3L	4L



**Fig. 1. A sample of 4-sector B-line (4-s BL) protocol of ultrasound examination is presented**

Diagnostic ultrasound examination was performed by one investigator who used a GE Logiq device (General Electric, USA); TPTD was performed on an Intellivue MX 550 Philips modular patient monitor (Philips, USA) with the option of advanced hemodynamic monitoring.

To assess changes in lung tissue and record B-lines, a linear sensor with a frequency of 7–10 MHz was used. The examination was performed with patients lying on their back. Ultrasound of the lungs was performed up to the modified Bedside Lung Ultrasound-in-Emergency technique, according to a 4-point scheme, designed for rapid diagnosis of urgent conditions [11]. B-lines were defined as hyperechoic vertical lines originating from the pleural line and extending down into the lung parenchyma (Fig. 2).

The TPTD technique was used to register ELWI. For this purpose, all patients were fitted with an arterial thermodilution PiCCO catheter 5 F into one of aa. femoralis with its connection to the system for measuring

and recording the thermodilution curve by Philips Intellivue MX 550 monitor, then bolus injections of a cold indicator were performed through a temperature sensor on the central venous catheter (CVC) placed in superior vena cava. Measurements were taken 3 times, averaged and automatically indexed to obtain the extravascular lung water index (EVLWI), global end-diastolic volume index (GEDVI) and cardiac index (CI). Central venous pressure (CVP) was measured through the CVC at end expiration.

**Table 2. Central hemodynamics parameters measured by transpulmonary thermodilution**

Hemodynamic calculations					
Height	175 cm			Calculation time	
Weight	95.0 kg	BSA, Body surface area	2.10 m <sup>2</sup>	1 Mar 1:29	
CO, Cardiac output	3.45 l/min			CI, Cardiac index	1.64 l/min/m <sup>2</sup>
HR, Heart rate	78 beats/min	SV, Stroke volume	44.2 ml	SI, Stroke[volume] index	21.1 ml/m <sup>2</sup>
BP <sub>syst.</sub> , Blood pressure, systolic	*119 mm Hg	SVR, Systemic vascular resistance	1669 dyn*s/cm <sup>5</sup>	SVRI, Systemic vascular resistance index	3504 DSm <sup>2</sup> /cm <sup>5</sup>
BP <sub>diast.</sub> , Blood pressure, diastolic	*67 mm Hg	LVF, Left ventricular function	4.0 kg*m	LVFI, Left ventricular function index	1.9 kg*m/m <sup>2</sup>
MAP, mean arterial pressure	*85 mm Hg	LVS <sub>W</sub> , Left ventricular stroke work	51.1 g*m	LVS <sub>W</sub> I, Left ventricular stroke work index	24.3 g*m/m <sup>2</sup>
CVP <sub>mean</sub> , Central venous pressure, mean	13 mm Hg				
FEV, forced expiratory volume	18%	EVLW, Extravascular lung water	264 ml	EVLWI, Extravascular lung water index	4.0 ml/kg
SVV, Stroke volume variability	11%	ITBV, Intrathoracic blood volume	1320 ml	ITBVI, Intrathoracic blood volume index	733 ml/m <sup>2</sup>
PPI, Pulse pressure index	%	GEDV, Global end-diastolic volume	1056 ml	GEDVI, Global end-diastolic volume index	587 ml/m <sup>2</sup>
dP <sub>max</sub> , maximal change of arterial pressure per second	574	CFI, Cardiac Function Index	3.2	PVPI, Pulmonary vascular permeability index	1.0

Notes: BSA, Body surface area; CO, Cardiac output; CI, Cardiac index; HR, Heart rate; SV Stroke volume; SVI Stroke [volume] index; SVR, Systemic vascular resistance; SVRI, Systemic vascular resistance index; BP<sub>syst.</sub>, Blood pressure, systolic; BP<sub>diast.</sub>, Blood pressure, diastolic; LVF, left



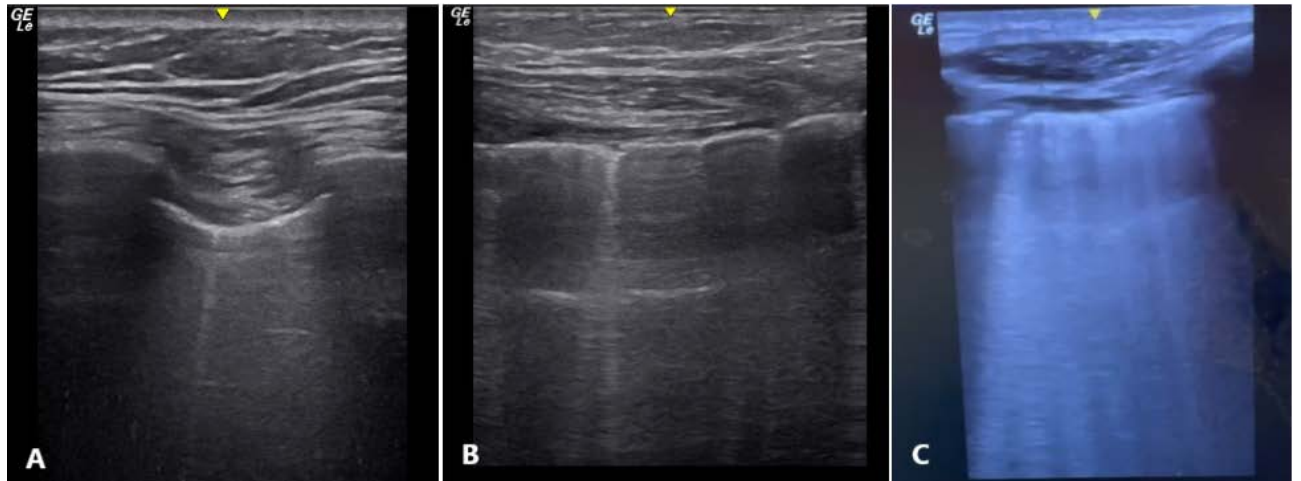
ventricular function; LVFI, left ventricular function index; MAP, mean arterial pressure; LVSW, left ventricular stroke work; LVSWI left ventricular stroke work index; CVPmean, Central venous pressure, mean; FEV, Forced expiratory volume; EVLW, Extravascular lung water; EVLWI, Extravascular lung water index; SVV, Stroke volume variability; ITBV, Intrathoracic blood volume; ITBVI, Intrathoracic blood volume index; PPI, Pulse pressure index; GEDV, Global end-diastolic volume; GEDVI, Global end-diastolic volume index; dPmax, maximal change of arterial pressure per second; CFI, Cardiac Function Index; PVPI, Pulmonary vascular permeability index

Data obtained by two methods (ultrasound and TPTD) were compared with each other in terms of the number of B-lines and the EVLWI value.

Statistical data analysis was performed using StatTech software v 3.1.8 (Russian Federation). The data differences were considered statistically significant at p value lower 0.05. The quantitative data were described using the median (Me) and lower and upper quartiles (Q1;Q3). Comparison of two groups for quantitative parameters which distribution differed from normal was performed using the Mann–Whitney U test. The direction and strength of the correlation between two quantitative variables was assessed using the Spearman rank correlation coefficient (r). To assess the diagnostic significance of quantitative characteristics in predicting a specific outcome, the ROC curve analysis method was used. The value dividing the quantitative characteristic at the cut-off point was determined up to the maximum value of the Youden index.

The results of TPTD measurements were interpreted by using the following scale:

- An EVLWI lower 7 was considered to be within the normal range, without increased extrapulmonary water (considered normal).
- EVLWI from 8 to 11 was regarded as developing or moderate pulmonary edema (regarded as moderate edema of the pulmonary tissue).
- EVLWI from 12 and higher was considered as indicating severe pulmonary edema with excess extravascular lung water in the lung parenchyma (interpreted as severe pulmonary edema) (Fig. 2).



**Fig. 2. Example of an ultrasound screen when visualizing B-lines:** (A) Normal lung parenchyma with up to 4 B-lines in the intercostal space; (B) Lung parenchyma with excess extrapulmonary water and the number of B-lines from 4 to 8; (C) Excessive number of B-lines (above 8), indicating a critically high amount of water in the lung parenchyma

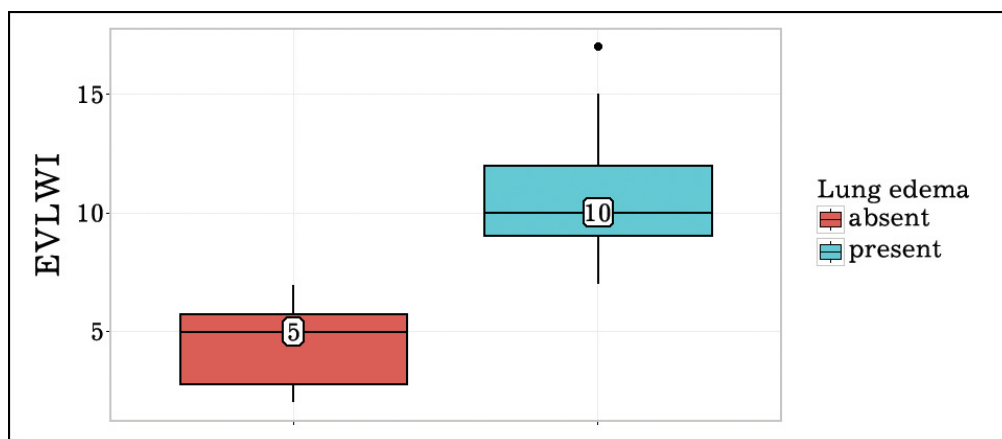
### Study results

A statistically significant relationship ( $p < 0.05$ ) was found between the extravascular lung water index and the presence of pulmonary edema (Table 3, Fig. 3).

**Table 3. Relationship between "EVLWI" and patients with pulmonary edema**

Pulmonary edema	EVLWI			p
	Me	Q <sub>lower</sub> ;Q <sub>upper</sub>	n	
Absent	5	2;7	10	<0.001*
Present	10	9;12	17	

\* statistically significant differences in parameters ( $p < 0.05$ )



**Fig. 3. Analysis of the "EVLWI" parameter in relation to the "Pulmonary edema" parameter**

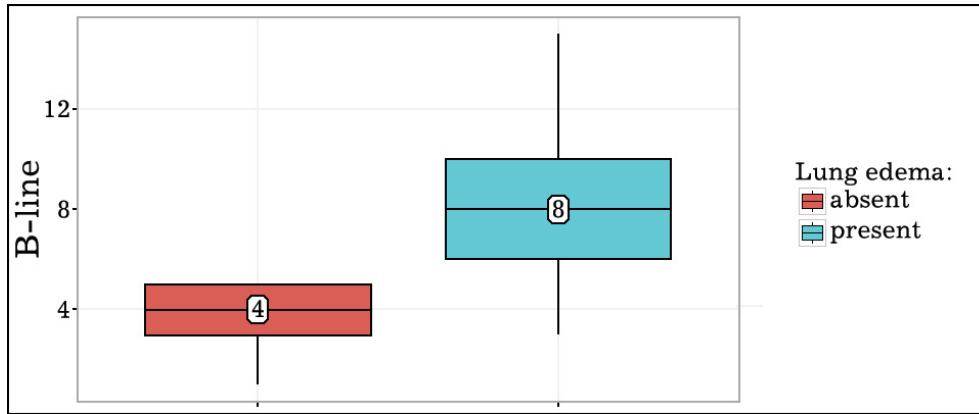
We also found a significant relationship ( $p < 0.05$ ) between the number of B-lines and the presence of pulmonary edema (Table 4, Fig. 4).

**Table 4. Analysis of the "B-line" parameter in relation to the "Pulmonary edema" parameter**

Pulmonary edema	B-line			p
	Me	Q <sub>lower</sub> ; Q <sub>higher</sub>	n	
Absent	4	2;5	10	<0.004*
Present	8	6;10	17	

\* statistically significant differences in parameters ( $p < 0.05$ )

According to the presented Table, when comparing the "B-line" parameter in relation to the "Pulmonary edema" parameter, statistically significant differences were established ( $p = 0.004$ ).



**Fig. 4. Analysis of the "B-line" parameter in relation to the "Pulmonary edema" parameter**

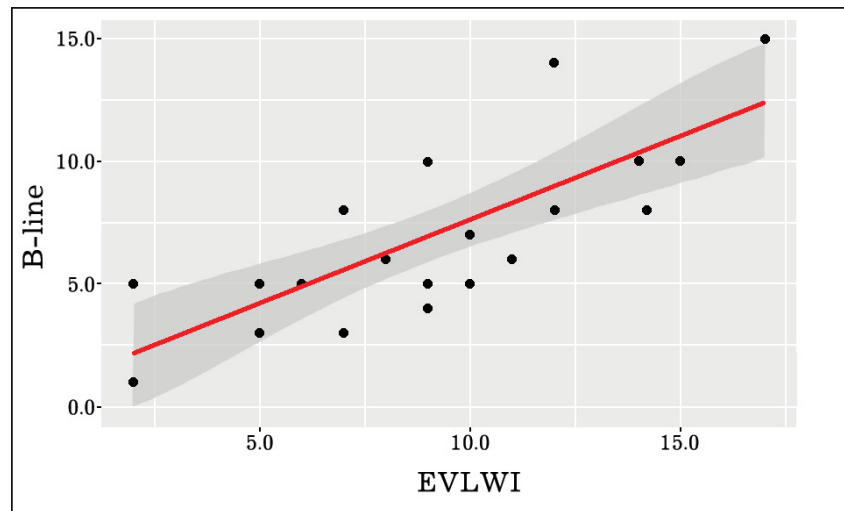
We conducted a correlation analysis for the relationship between the “EVLWI” parameter in transpulmonary thermodilution and the “B-line” parameter determined using the ultrasound examination (Table 5, Fig. 5).

**Table 5. Results of the analysis for correlation relationship between the "EVLWI" parameter and the "B-line" parameter**

Parameter	Correlation characteristics		
	$r_{xy}$	The tightness of correlation on the Chaddock scale	p
EVLWI – B-line	0.742	High	<0.001*

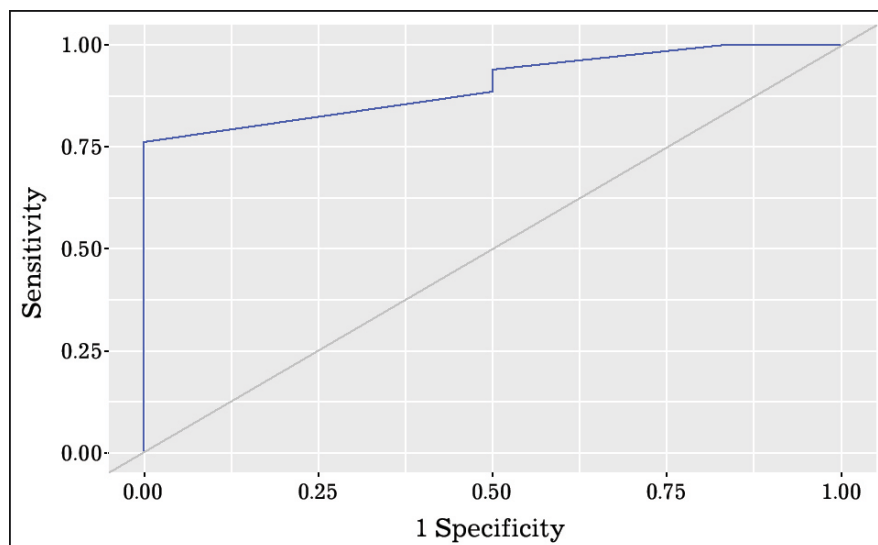
\* – statistically significant differences in parameters (p<0.05)

When assessing the relationship between the “B-line” parameter and the “EVLWI” parameter, a direct relationship of high degree was found.



**Fig. 5. The regression function graph characterizing the relationship of the "B-line" parameter to the "EVLWI" parameter**

When assessing the relationship the pulmonary edema probability to the “B-line” parameter using ROC analysis, the following curve was obtained (Fig. 6).

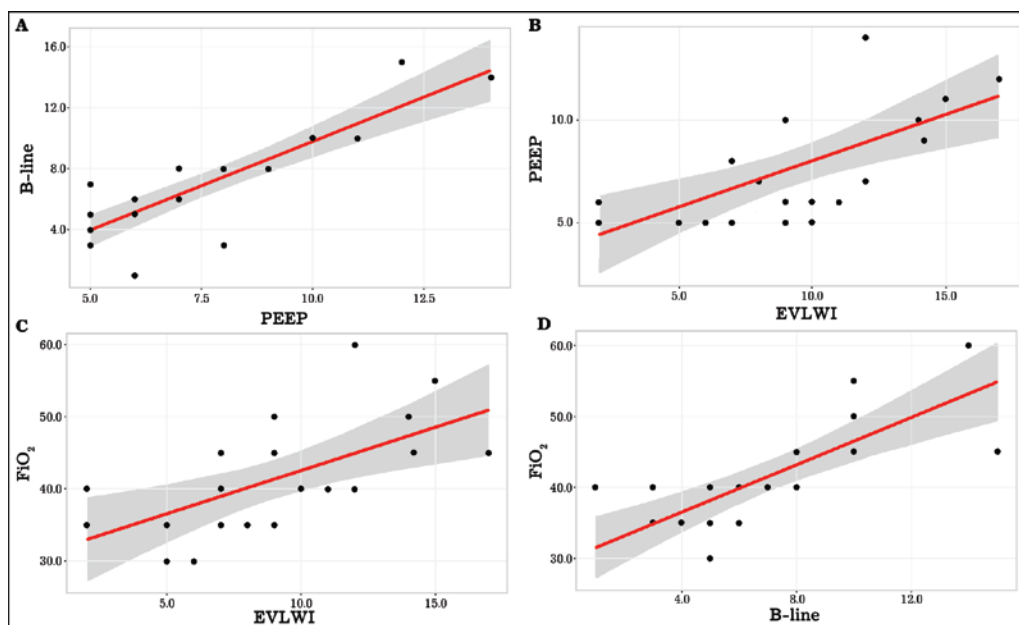


**Fig. 6. The ROC curve characterizing the relationship probability of the “Pulmonary edema” parameter from the “B-line” parameter**

The area under the ROC curve (AUC) was  $0.9 \pm 0.06$  with 95% CI [0.77–1.00]. The resulting model was statistically significant ( $p=0.004$ ). The threshold value of the "B-line" parameter at the cut-off point was

6.000. The presence of pulmonary edema was predicted when the B-line parameter was higher than or equal to that value. The sensitivity and specificity of the model were 76.5% and 96.4%, respectively. Analyzing the results obtained, we see that the final AUC values do not fall beyond the interval [0.5–1.0] for the above-described model, which means they have sufficient diagnostic value.

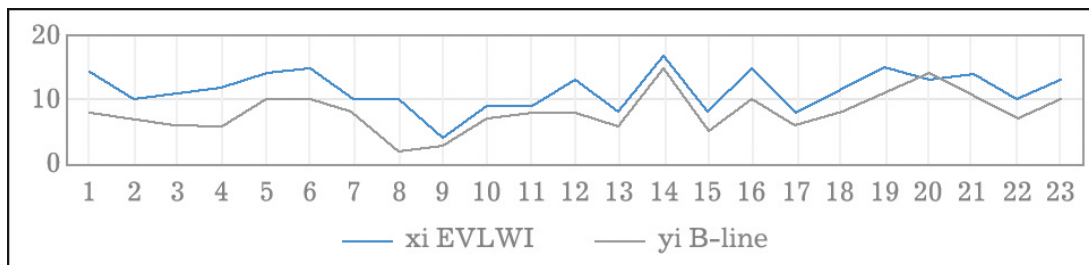
Analysis of additional respiratory parameters of the patients allowed us to identify other important regular patterns. We also found statistically significant correlations between the level of positive end expiratory pressure (PEEP) and EVLWI ( $r=0.82$ ,  $R^2=0.58$ ,  $p<0.001$ ) (Fig. 7A), between the PEEP level and the number of B-lines ( $r=0.88$ ,  $R^2=0.76$ ,  $p<0.001$ ) (Fig. 7B), as well as statistically significant correlations between the number of B-lines and  $FiO_2$  (percentage of oxygen in the inhaled air) ( $r=0.79$ ,  $R^2=0.65$ ,  $p<0.001$ ) (Fig. 7C), as well as a significant correlation between EVLWI and  $FiO_2$  ( $r=0.82$ ,  $R^2=0.70$ ,  $p<0.001$ ) (Fig. 8 D).



**Fig. 7. Scatterplots showing a significant correlation between respiratory ultrasound examinations and transpulmonary thermodilution parameters in patients: A. PEEP and B-line; B. PEEP and EVLWI; C. EVLWI and  $FiO_2$ ; D. B line and  $FiO_2$**

## Discussion

Our study has shown that the sonographic method for diagnosing pulmonary edema in critically ill patients has great diagnostic capabilities. We should note that we have found a significant correlation between B-line parameter and EVLWI, and also determined the significant accuracy and specificity of pulmonary ultrasound in the diagnosis of pulmonary edema. When plotting the relationship graph, a direct relationship is visible between the B-line parameters and EVLWI (Fig. 8).



**Fig. 8. Relationship between the EVLWI and B-line parameters**

In Fig. 8 on the Cartesian plane, the coordinate points corresponding to the results of our measurements obtained by the two methods described above are indicated. One can see that the measurement data from two independent investigational methods have a clear relationship, which confirms the presence of a correlation between them.

It is well known that TPTD is one of the accurate methods for quantitatively determining the extravascular lung water; this technique is indispensable for monitoring central hemodynamic parameters in critically ill patients, but it is invasive, traumatic (when additional catheterization of the central artery and vein is required), expensive, and also requires availability of special equipment and experience of personnel; therefore, for assessing the pulmonary parenchyma edema, ultrasound is a reasonable

alternative, and is also a non-invasive, accessible, easy-to-use, fast, and inexpensive method of investigation. The results of our study correspond to the results obtained by other authors [12, 13]. Moreover, a number of authors believe that the ultrasound method can be used to diagnose an acute respiratory distress syndrome [14].

In addition, we identified significant regularities between EVLWI, the number of B lines and other respiratory parameters of patients. Thus, we determined strong correlations between such variables as PEEP and EVLWI, B-lines and  $\text{FiO}_2$ ,  $\text{FiO}_2$  and EVLWI, which confirms once again the possibility of diagnosing pulmonary edema using the ultrasound method.

Further studies of this topic will allow us to more accurately determine the role of ultrasound in the bedside diagnosis of pulmonary edema in patients in Intensive Care Units.

Despite its advantages, the disadvantages of this method should also be noted. Since each specialist interprets the ultrasound image up to his/her knowledge and practical experience; the examination results may be subjective and may differ when the examination is made by different operators. In the case of diagnosing pulmonary edema using ultrasound, the disadvantage of the method is also an impossible quantitative measurement of extravascular lung water; only a visual assessment of the lung parenchyma is possible. In addition, ultrasound examination of lungs can be performed only in case of absent air in the pleural cavity; however, in this case, although visualization of the lung parenchyma is impossible, diagnosis of pneumothorax is nevertheless possible [15]. The limitations of our study are a small patient sample size, and the operator-dependent subjective nature of result interpretation when performing a diagnostic ultrasound examination of the lungs.



## Conclusion

Diagnosis of pulmonary edema in critically ill patients with liver failure requires a rapid, simple, and noninvasive testing method. The study determined the sensitivity and specificity of ultrasound for detecting extravascular lung water. Comparison of ultrasound parameters with the transpulmonary thermodilution results showed the possibility of using ultrasound to detect pulmonary edema in patients with liver failure. It is reasonable to popularize this method for diagnosing critical conditions.

Based on the above, we can make the following conclusions:

- Ultrasound data for diagnosing pulmonary edema (number of B-lines) have a strong correlation ( $r=0.742$ ,  $p<0.001$ ) with transpulmonary thermodilution parameters (assessing the amount of extravascular lung water), as well as with PEEP ( $r=0.88$ ,  $p<0.001$ ) and  $FiO_2$  ( $r=0.79$ ,  $p<0.001$ ) parameters in patients on mechanical ventilation.
- Lung ultrasound is an accurate (AUC= $0.9\pm0.06$  with 95% CI [0.77–1.0];  $p<0.004$ ), non-invasive, safe and accessible method for assessing extrapulmonary water and can be used for rapid and accurate diagnosis of pulmonary edema in patients in critical condition.
- The use of ultrasound may change routine approaches to instrumental assessment of pulmonary edema in Intensive Care Units. It is necessary to implement the method into widespread clinical practice.

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