Risk factors and the associated limit values for abnormal elevation of extravascular lung water in severely burned adults

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ABSTRACT

Background: Increased extravascular lung water (EVLW) correlates with pulmonary morbidity and mortality in critical illness. The extravascular lung water index (EVLWI), which reflects the degree of EVLW in an individual, increases in the fluid reabsorption stage rather than the initial resuscitation stage in severe burn cases. While many factors contribute to EVLWI variation, the risk factors contributing to its abnormal elevation in severe burns remain unclear. The aim of this study was to identify the risk factors and associated limit values for abnormal elevation of EVLWI during the fluid reabsorption stage in a cohort of severely burned adults.

Method: This prospective, single-center study included only adults with burn sizes ≥ 50% of the total body surface area (TBSA) who were admitted within 24h after burn. Demographic data were collected, and transpulmonary thermodilution (TPTD) measurements and blood biochemistry tests were performed upon admission and up to day (PBD) 9. Risk factors for abnormal EVLWI were analyzed by logistic regression. Receiver operating characteristic (ROC) curves were constructed to determine the optimal cut-offs for each risk factor.

Results: Seventy-two patients were ultimately enrolled, with a mean age of 40.3 years and mean burn size of 69.4% TBSA. EVLWI began to abnormally increase (>7 ml/kg) on day 3 and up to PBD 9, indicating that a supranormal EVLWI developed in the fluid reabsorption stage.

Several relevant factors were considered, including patient age, burn size, intrathoracic blood volume index (ITBVI), pulmonary vascular permeability index (PVPI), cardiac index (CI), systemic vascular resistance index (SVRI), serum albumin, time of first excision and grafting, and number of operations and daily fluid administration. Among these factors, we found that only burn size and ITBVI were significantly correlated with EVLWI variation and were further identified as the independent risk factors for EVLWI abnormality. ROC analysis showed that the limits for predicting a supranormal EVLWI during the fluid reabsorption stage were 65.5% TBSA for burn size and 845 ml/m^2 for ITBVI. Patients with burn sizes or ITBVIs higher than the limit showed significantly longer mechanical ventilation time and substantially higher occurrences of acute respiratory distress syndrome (ARDS) and pneumonia within two weeks after burn.

Conclusions: Burn size and ITBVI are the independent risk factors for EVLWI abnormality during the fluid reabsorption stage in severely burned adults. The limit values for predicting a supranormal EVLWI in those patients are 65.5% TBSA for burn size and 845 ml/m^2 for ITBVI.

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1. Introduction

Even without inhalation injury, pulmonary complications, such as acute respiratory distress syndrome (ARDS) and pulmonary infection, remain the leading causes of death at the early stage after severe burns [1–3]. A common etiology of these pulmonary complications is the accumulation of the interstitial fluid in lung, which is termed extravascular lung water (EVLW) [4–8]. Currently, EVLW can be measured at the bedside by transpulmonary thermodilution (TPTD) using a PiCCO system. The extravascular lung water index (EVLWI), a value of EVLW indexed by the predicted body weight, reflects the degree of EVLW in an individual within a normal range of 3–7 ml/kg [7,9]. While a consensus regarding the EVLWI value to diagnosis lung edema has been not established in burn victims, abnormally elevated EVLWI has been definitively associated with mortality in severely burned children [10]. In our previous study, we showed a negative correlation between EVLWI and pulmonary dysfunction in severely burned adults [11]. Understanding the factors that contribute to an abnormal elevation of EVLWI is therefore helpful for the early prevention of pulmonary edema as well as pulmonary complications in severe burn cases.

The abnormal elevation of EVLWI is infrequent during the initial resuscitation stage in severe burns, possibly because increased fluid loss from the capillaries is compensated by lymph flow in the lung at this stage [12,13]. However, abnormal elevation of EVLWI can be observed in the subsequent fluid reabsorption stage in severe burn cases, beginning approximately postburn days (PBDs) 2–3 and lasting for 7–10 days [14,15]. Many factors correlate with EVLWI elevation during the fluid reabsorption stage in severe burns. For example, fluids initially lost into the interstitium are gradually reabsorbed into the blood in this stage, leading to elevated hydrostatic pressure. This elevated pressure can promote fluid movement towards the pulmonary interstitium [14,16]. Severe burns often result in hypoproteinemia, which is highly correlated with EVLWI elevation in critically ill patients. Other factors, such as myocardial dysfunction, microvascular hyperpermeability and inappropriate fluid management may also correlate

with EVLWI elevation in severe burns [15,17]. Nevertheless, the main clinical factors that contribute to an abnormal elevation of EVLWI during the fluid reabsorption stage after burn remain unclear.

In our burn unit, TPTD measurements are routinely performed on admission in severely burned adults. In this study, to determine the factors responsible for abnormal elevation of EVLWI, TPTD measurement data and blood biochemical tests were prospectively collected upon admission and up to PBD day 9 in a cohort of severely burned adults. Using logistic regression and ROC analysis, we identified that burn size and ITBVI were the independent risk factors for supranormal EVLWI during the fluid reabsorption stage, with associated cut-off values of 65.5% TBSA for burn size and 845 ml/m^2 for ITBVI in severely burned adults.

2. Methods

2.1. Patients

Severely burned adults admitted to a highly specialized burn unit in Southwest Hospital, Chongqing, China between January 2013 and May 2016 were enrolled in this study. Permission to conduct the study was obtained from the ethics committee of Southwest Hospital. Informed written consent was obtained from all patients or their next of kin. The following inclusion criteria were used: (1) burn size ≥50% total body surface area (TBSA); (2) admission within 24h after injury; and (3) age between 18 and 65 years. The exclusion criteria were as follows: (1) age < 18 years or > 65 years; (2) an interval from burn injury to monitoring >24h; (3) the presence of severe inhalation injury (inhalation injury severity was classified according to the Abbreviated Injury Score based on bronchoscopic findings. A score higher than 3 was defined as severe inhalation injury [18]), traumatic brain injury or pulmonary injury; (4) the presence of serious premorbid cardiac, renal or pulmonary diseases, such as coronary heart disease, heart failure, emphysema or chronic kidney disease (glomerular filtration rate lower than 60 ml/ min per 1.73 m^2 [19]); (5) the presence of unstable conditions, such as a urinary output <0.5 ml/h/kg or mean arterial blood

pressure <65 mmHg at the end of the second 24 h postburn; or (6) contraindications for central venous access or a femoral arterial line, such as severe coagulation disorders, vasculitis and infection at the puncture site.

2.2. PiCCO monitoring

A thermistor placed into a femoral arterial catheter measured the downstream temperature changes induced by the injection of a 15 ml cold saline solution (0–8°C) bolus in the superior vena cava. All indexed values were calculated with the predicted body surface area or predicted body weight. Transpulmonary thermodilution (TPTD) measurements were performed three times daily for each patient. The results were calculated as the mean of these three measurements, including EVLWI, central venous pressure (CVP), intrathoracic blood volume index (ITBVI), cardiac index (CI), left ventricular systolic index (dPmax), stroke volume index (SVI), mean arterial pressure (MAP), pulmonary vascular permeability index (PVPI) and systemic vascular resistance index (SVRI).

2.3. Routine therapy

Patients were resuscitated according to the TMMU protocol, which was developed in the 1960s and is widely used in China for fluid resuscitation in severe burn patients [20]. For adult burn patients, the expected volume in the first 24 h postburn = [1 ml (lactated Ringer's solution) + 0.5 ml (plasma)] × burn area (%) × weight (kg) + 2000 ml (5% glucose solution). Half of the calculated fluid should be administered within the first 8 h postburn, and the remainder is homogeneously administered in the following 16 h. During the next 24 h, the protocol recommends that half of the amount of crystalloid and colloid solution used during the first 24 h and 2000 ml of 5% glucose solution should be given. If urinary output was less than 0.5 ml/h/kg or greater than 1 ml/h/kg, the infusion rate was increased or decreased by 20–30%, respectively. Debridement and grafting were performed when the systemic conditions of the patients were stable (usually on PBD 3–5). During the observation, period, the patients were subjected to 1–2 operations. Tracheotomy, fasciotomy, and mechanical ventilation were performed when necessary. Blood samples were collected daily to measure biochemical values from admission to the ninth day postburn. Fibreoptic bronchoscopy was performed if inhalation injury was suspected. Initial escharectomy and skin grafting were normally performed within 3 to 5 days after burn.

2.4. Complications

Multiple organ dysfunction syndromes (MODS) were assessed according to the Marshall MODS Scoring System [21]. ARDS was diagnosed according to the Berlin ARDS definition criteria [22]. Pneumonia was defined according to the American burn association consensus conference on burn sepsis and infection group [23].

2.5. Statistical analysis

The data were analysed using the Statistical Package for Social Sciences (SPSS) 20.0 package for Windows. Continuous variables were presented as the means ± SDs. Categorical data were summarized as absolute frequencies and percentages. Continuous variables were compared using Student's t-test. To test the influence of time on haemodynamic variables, a one-way repeated measures analysis of variance was performed with the post hoc Dunnett's test. Multiple linear regression analysis with the EVLWI as the dependent variable and age, burn size, the ITBVI, PVPI, albumin (Alb), CI, SVRI, time of first debridement and grafting (TFDG), number of operations (NO) and daily fluid administration (DFA) as the independent variables was performed to evaluate the factors associated with EVLWI variations in the fluid reabsorption stage. Binary logistic regression analysis was performed to determine the independent factors associated with a supranormal EVLWI. Adjusted ORs and corresponding 95% CIs were reported for variables in the multivariable model. Area under the receiver operating characteristic (ROC) curve (AUC) analysis was used to determine the cut-off values of burn size and the ITBVI for a supranormal EVLWI. Differences in proportions, including mortality, mechanical ventilation, ARDS, pneumonia and MODS, were compared using the chi-squared test. The durations of ICU stay and ventilation were summarized as the medians and IQRs and were compared between groups using a Wilcoxon rank-sum test. A P-value less than 0.05 was considered significant.

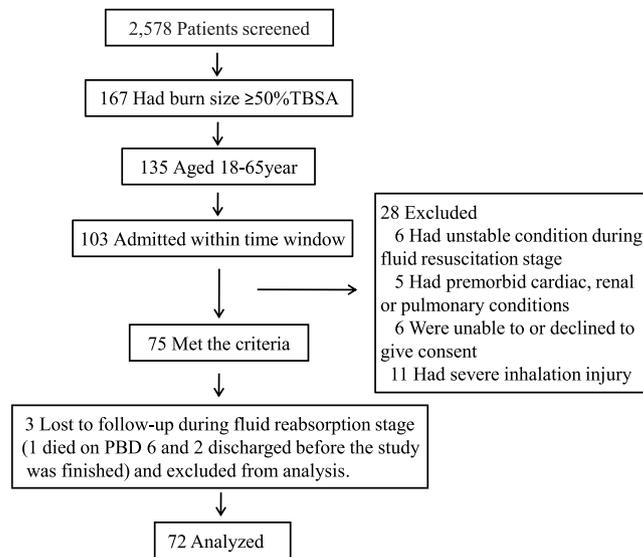## 3. Results

3.1. Enrollment and exclusion

We screened patients between Jan 2013 and May 2016. Fig. 1 shows the most common reasons for exclusion among the 2503 patients who were screened but not enrolled and presents the follow-up data for the 75 enrolled patients.

3.2. Demographics

A total of 72 extensive burn patients (3 lost due to 1 death and 2 discharges) ultimately completed this study, including 60 men and 12 women aged 40.3 ± 11.3 years with a mean burn size of 69.4 ± 16.5% TBSA. The demographics of the patients are listed in Table 1.

3.3. Variations in the EVLWI and other TPTD parameters

The EVLWI remained within the normal range (3–7 ml/kg) during the fluid resuscitation stage (PBD 1 to PBD 2) and then increased beyond the normal from PBD 3 to PBD 9, indicating abnormal EVLWI developed during the fluid reabsorption stage (Fig. 2A). PVPI decreased continually (Fig. 2B). The ITBVI was substantially lower than its normal value during the fluid resuscitation stage, and increased significantly after PBD 4 compared to PBD 2, reaching its peak on PBD 7 with a level close to the upper limit of normal (Fig. 2C). CVP increased significantly after PBD 3 compared to PBD 2 (Fig. 2D). Both the CI and SVI increased continually (Fig. 2E, F). The CI increased beyond the normal after PBD 4 (Fig. 2E), whereas the SVI remained within the normal range (Fig. 2F). dPmax was generally within the normal range (Fig. 2G). The SVRI showed a transition from a high vascular resistance on PBDs 1–2 to a low vascular resistance on PBDs 3–9 (Fig. 2H).

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2,578 Patients screened
        ↓
167 Had burn size ≥50%TBSA
        ↓
135 Aged 18-65year
        ↓
103 Admitted within time window  →  28 Excluded
        ↓                              6 Had unstable condition during
                                      fluid resuscitation stage
                                       5 Had premorbid cardiac, renal
                                      or pulmonary conditions
                                       6 Were unable to or declined to
75 Met the criteria                  give consent
        ↓                             11 Had severe inhalation injury
3 Lost to follow-up during fluid reabsorption stage
(1 died on PBD 6 and 2 discharged before the study
   was finished) and excluded from analysis.
        ↓
72 Analyzed
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Fig. 1 – Enrollment of subjects. TBSA, total body surface area; PBD 6, day 6 after burn.

Table 1 – Demographics of patients. TBSA, total burn surface area. Data are presented as the means±SD or percentages.	
Variables	
Number of patients	72
Age (yr)	40.3±11.3
Male sex [n (%)]	60 (83.3)
Height (cm)	166.3±6.7
Weight (kg)	64.4±10.4
Time of admission postburn (h)	9.7±8.6
Burn size (% TBSA)	69.3±16.5
Depth of burn	
Deep 2nd degree (% TBSA)	32.4±17.1
3rd degree (% TBSA)	26.1±23.3
Burn mechanism [n (%)]	
Flame	43 (59.7)
Flash	7 (9.7)
Scald	15 (20.8)
Other	7 (9.7)

3.4. Independent risk factors for abnormal elevation of EVLWI

Multiple linear regression analysis with EVLWI as the dependent variable and age, burn size, ITBVI, PVPI, albumin (Alb), CI, SVRI, time of first debridement and grafting (TFDG), number of operations (NO) and daily fluid administration (DFA) as the independent variables was performed. As shown in Table 2, only burn size and ITBVI had a positive linear regression relationship with EVLWI throughout the fluid reabsorption stage (PBDs 3–9), suggesting that these variables may be important for EVLWI variations. Using binary logistic regression analysis, we determined that both burn size and ITBVI were independent risk factors for the abnormal elevation of EVLWI in our cohort after adjusting for potential confounders (Table 3).

3.5. Cut-offs of burn size or ITBVI to discriminate a supranormal EVLWI

ROC curve analysis showed that burn size (AUC=0.713, 95% CI=0.592–0.833) and ITBVI (AUC=0.707, 95% CI=0.586–0.828) were the relevant predictors and had a similar ability to distinguish a supranormal EVLWI in the fluid reabsorption stage (Table 4). To determine the most relevant cut-offs, we used Youden's index because it maximized the overall discriminative powers of burn size and ITBVI for a supranormal EVLWI. The optimized cut-off values for burn size and ITBVI for predicting a supranormal EVLWI during the fluid reabsorption stage postburn were 65.5% TBSA (sensitivity, 75.0%; specificity, 62.5%) and 845 ml/m^2 (sensitivity, 80.0%; specificity, 59.4%) (Fig. 3).

3.6. Comparison of the EVLWI, pulmonary morbidity and outcomes in patients categorized by the cut-offs for burn size or ITBVI

We next sought to evaluate the potential value of the calculated limits. The patients were therefore categorized by the cut-offs for burn size or ITBVI, and the average EVLWI during the fluid reabsorption stage, pulmonary morbidity and patient outcomes were compared. The demographic data were similar between the patients in different groups. Patients with burn sizes >65.5% TBSA or with an ITBVI >845 ml/m^2 had a significantly higher EVLWI, as expected. A longer duration of mechanical ventilation and a higher occurrence of ARDS and pneumonia within 2 weeks postburn were observed in patients with either burn sizes >65.5% TBSA or an ITBVI >845 ml/m^2 (all P-values <0.05). The ICU stay was significantly longer in patients with burn sizes or ITBVIs over the cut-offs. MODS within 2 weeks showed no differences between these patients. Death within 4 weeks was significantly increased in patients with burn sizes >65.5% TBSA (Table 5).
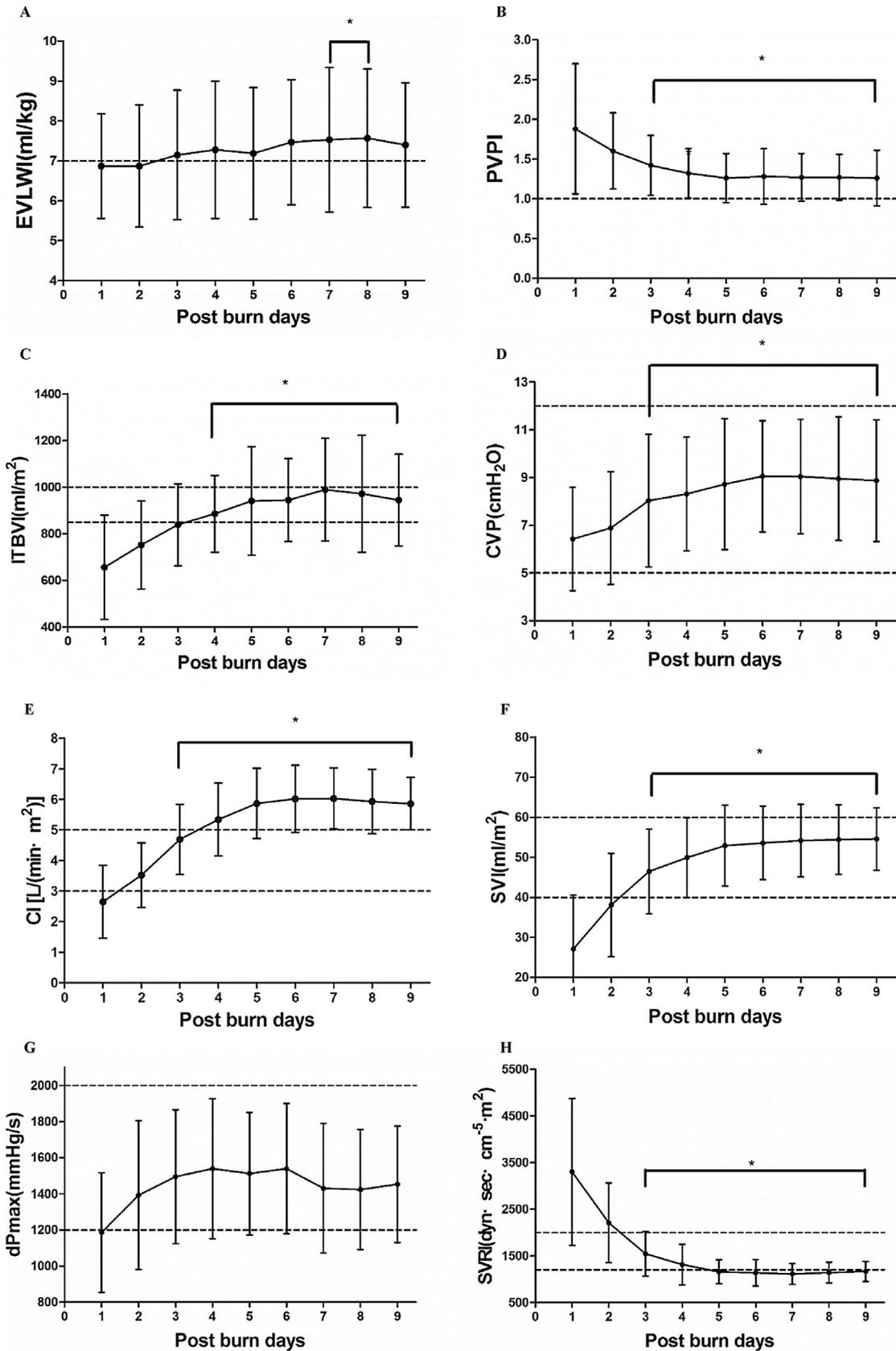
Fig. 2 – Transpulmonary thermodilution parameters. A. Extravascular lung water index; B. Intrathoracic blood volume index: The data are presented as the means±SD. *One-way analysis of variance, P<0.05 vs. PBD 2.

Table 2 – Multiple linear regression analysis to evaluate the factors associated with EVLWI variation during the fluid reabsorption stage. TFDG, time of first debridement and grafting. NO, number of operations. DFA, daily fluid administration.

Postburn days		Age	Burn size	ITBVI	PVPI	Alb	CI	SVRI	TFDG	NO	DFA
3	B	0.032	0.024	0.004	1.470	−0.026	−0.074	<0.001	0.412	−0.279	−0.114
	Standardized coefficients	0.224	0.243	0.435	0.341	−0.081	−0.052	0.073	0.206	−0.086	−0.032
	P-value	**0.024**	**0.011**	**<0.001**	**0.001**	0.391	0.742	0.640	**0.034**	0.343	0.743
4	B	0.037	0.019	0.006	4.347	0.042	0.096	<0.001	−0.226	−0.144	−0.132
	Standardized coefficients	0.242	0.189	0.567	0.777	0.125	0.066	0.062	−0.107	−0.042	−0.039
	P-value	**0.001**	**0.008**	**<0.001**	**<0.001**	0.090	0.586	0.589	0.122	0.527	0.572
5	B	0.013	0.031	0.003	−0.389	0.005	0.209	<0.001	0.283	−0.045	0.405
	Standardized coefficients	0.087	0.315	0.355	−0.150	0.017	0.146	−0.029	0.139	−0.014	0.063
	P-value	0.429	**0.002**	**0.003**	0.160	0.877	0.418	0.869	0.186	0.889	0.551
6	B	0.001	0.029	0.003	1.968	−0.009	0.175	0.001	0.222	0.056	−0.065
	Standardized coefficients	0.004	0.307	0.364	0.446	−0.029	0.123	0.161	0.115	0.018	−0.018
	P-value	0.967	**0.001**	**0.001**	**<0.001**	0.750	0.375	0.258	0.211	0.840	0.844
7	B	−0.025	0.034	0.005	0.011	−0.032	−0.040	<0.001	0.273	−0.072	0.140
	Standardized coefficients	−0.154	0.312	0.624	0.003	−0.094	−0.022	0.037	0.123	−0.020	0.030
	P-value	0.146	**0.002**	**<0.001**	0.976	0.350	0.899	0.816	0.203	0.829	0.764
8	B	−0.009	0.047	0.002	−0.316	−0.096	−0.315	−0.001	0.422	0.277	0.456
	Standardized coefficients	−0.056	0.446	0.262	−0.104	−0.242	−0.189	−0.133	0.197	0.080	0.102
	P-value	0.610	**<0.001**	**0.038**	0.334	**0.029**	0.263	0.404	0.078	0.442	0.356
9	B	0.013	0.025	0.002	2.562	0.022	0.178	<0.001	0.144	0.161	−0.216
	Standardized coefficients	0.092	0.271	0.302	0.580	0.066	0.098	0.014	0.075	0.052	−0.063
	P-value	0.378	**0.010**	**0.022**	**<0.001**	0.531	0.533	0.920	0.459	0.591	0.567

Table 3 – Binary logistic regression analysis for factors associated with an elevated EVLWI in the fluid reabsorption stage. TFDG, time of first debridement and grafting. NO, number of operations. DFA, daily fluid administration.

Variables	B	P-value	Adjusted odds ratios	95% Confidence interval	
Age	0.001	0.890	1.001	0.982	1.021
Burn size	0.055	<0.001	1.057	1.042	1.072
ITBVI	0.004	<0.001	1.004	1.002	1.005
PVPI	0.421	0.069	1.524	0.968	2.399
Alb	−0.013	0.183	0.987	0.967	1.006
CI	−0.018	0.905	0.982	0.726	1.329
SVRI	0.000	0.536	1.000	0.999	1.001
TFDG	0.096	0.462	1.100	0.853	1.420
NO	0.404	0.051	1.497	0.999	2.244
DFA	0.317	0.210	1.373	0.836	2.252

4. Discussion

Although many factors contribute to the variation of EVLWI, these are the first data showing that burn size and ITBVI are independent risk factors for EVLWI abnormality during the fluid reabsorption stage in severe burns. The cut-off values for predicting a supranormal EVLWI were 65.5% TBSA for burn size and 845 ml/m^2 for ITBVI. Patients with burn sizes or ITBVIs higher than the cut-offs showed higher occurrences of ARDS and pneumonia, indicating a clinical significance of these cut-off values in severe burn patients.

Even without inhalation injury, pulmonary complications are very common and develop earlier in severe burns [24]. Radiographic findings have shown that pulmonary complications manifest at the early stage postburn, including pulmonary edema, ARDS, pulmonary microembolism and pneumonia [25]. Liffner et al. [26] reported that in severe burns, 70% of patients developed ARDS within less than 6 PBDs and that 86% of patients developed ARDS within two weeks after burn. Furthermore, no association with inhalation injury was observed [27]. Increased EVLW is an established and important factor underlying pulmonary complications, such as ARDS and pneumonia [5,6]. Currently, the extent of EVLW can be measured at the bedside via the EVLWI using the PiCCO system, the efficiency of which has been validated in humans and experimental animals [27,28]. As suggested in the present and previous studies [14,15], the abnormal elevation of EVLWI primarily occurs after 48h postburn, indicating an increased risk of pulmonary edema in the fluid reabsorption stage in severe burns. Notably, patients with severe inhalation injury or pre-existing chronic cardiac or pulmonary disease, the known "culprits" of lung edema [29,30], were excluded from our study. Therefore, the observed supranormal EVLWI represented an inherent high risk of pulmonary edema in
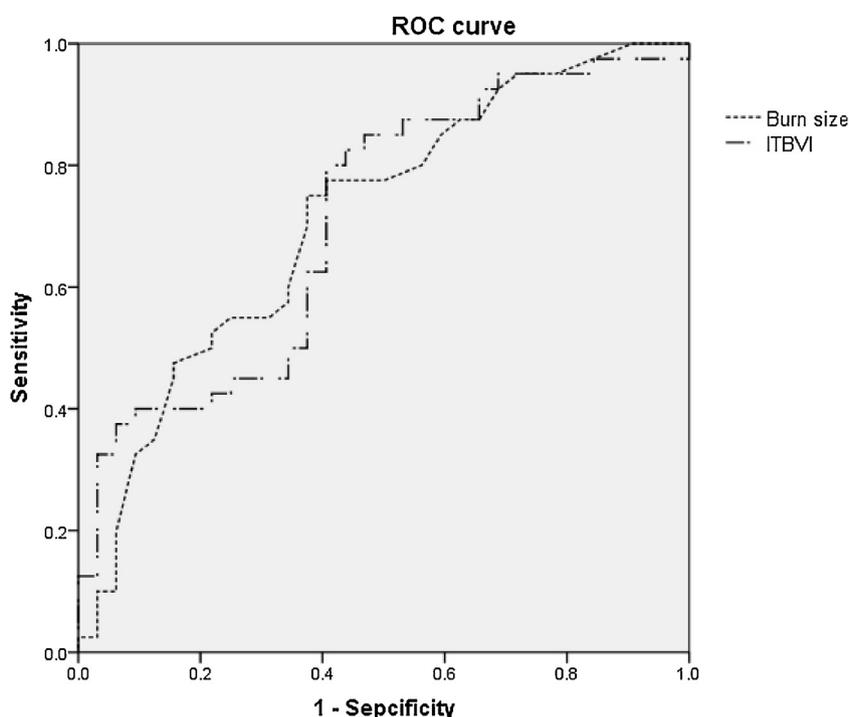
Fig. 3 – Receiver operating characteristic (ROC) curves of burn size and the ITBVI for predicting an elevated EVLWI. Receiver operating characteristic (ROC) curve analysis showed that burn size (AUC=0.713, 95% CI=0.592–0.833) and the ITBVI (AUC=0.707, 95% CI=0.586–0.828) were appropriate markers for an elevated EVLWI during the fluid reabsorption stage.

Table 4 – Burn size and the ITBVI cut-off values that predict an elevated EVLWI in the fluid reabsorption stage. AUC, area under ROC curve.

Variables	AUC	Cut-off value	Youden's index	95% Confidence interval	
Burn size	0.713	65.5	0.375	0.592	0.833
ITBVI	0.709	845	0.394	0.589	0.830

the fluid reabsorption stage in severe burn patients. Nevertheless, the primary factors contributing to the abnormal elevation of EVLWI in severe burns have not been identified.

Our results revealed that among the analyzed factors, burn size was strongly associated with abnormally elevated EVLWI in our patients. Burn injury is unique in that its severity can be quantified by the burn extent and depth. Factors relevant to the accumulation of interstitial fluid, such as vascular permeability, colloid osmotic pressure, circulation volume, and the compliance of the interstitial space, can all change due to burn injury depending on severity [31,32]. Therefore, we were not surprised to find that burn size is an independent risk factor for supranormal EVLWI throughout the entire period. Previously, burn size was identified as a predictor of morbidity and mortality in burn patients, with a cut-off value of approximately 45% TBSA for two burn wound infections/contaminations and a cut-off value of approximately 50% TBSA for sepsis from burns in adults [33]. Here, we are the first to establish a link between burn size and the EVLWI, an index of pulmonary edema, in severe burns. Using ROC curve analysis, we determined that a cut-off value of 65.5% TBSA

can predict a supranormal EVLWI in severe burns. This finding should be clinically valuable in determining whether a patient admitted with a given burn size is at a high risk for early pulmonary edema during the fluid reabsorption stage, thereby urging more careful observation or practice in clinic.

ITBVI, a cardiac preload parameter, was another factor showing a strong association with EVLWI variations in our study. The ITBVI was largely lower than normal during the fluid resuscitation stage but subsequently increased in the fluid reabsorption stage (Fig. 2C), which is consistent with other reports [12,14]. Although a larger burn size is correlated with greater fluid resuscitation requirements and greater subsequent fluid reabsorption, ITBVI was identified as an independent factor for a supranormal EVLWI in our study. This result is indirectly supported by the fact that no differences were evident in the burn sizes of the patients when categorized by ITBVI cut-offs (Table 4). In other words, patients with a higher ITBVI had higher EVLWI regardless of burn severity. We determined that a cut-off value of 845 ml/m^2 for ITBVI was associated with a supranormal EVLWI, suggesting that even if the ITBVI is within a normal range (850–1000 ml/m^2), it may still contribute to

Characteristics and outcomes	Burn size >65.5% TBSA (n=42)	Burn size ≤65.5% TBSA (n=30)	P-value	ITBVI>845 ml/m² (n=45)	ITBVI≤845 ml/m² (n=27)	P-value
Age (yr)	41.7±10.9	40.6±11.2	0.686[a]	42.9±10.7	38.6±11.2	0.106[a]
Male sex [n(%)]	35 (83.3)	25 (83.3)	0.999[b]	40 (88.9)	20 (74.1)	0.191[c]
Height (cm)	165.9±6.3	166.8±7.2	0.586[a]	166.2±7.9	166.4±7.9	0.939[a]
Weight (kg)	65.4±10.3	62.7±10.2	0.269[a]	65.2±10.7	62.7±9.5	0.311[a]
Time of admission postburn (hrs)	10.2±10.3	9.7±6.1	0.828[a]	9.8±10.7	10.3±6.1	0.814[a]
TBSA burned (%)	80.8±8.9	51.8±8.0	<0.001[a]	70.0±17.2	66.7±15.9	0.422[a]
Depth of burn (%)						
Deep 2nd degree	36.3±17.2	28.0±11.3	0.024[a]	34.0±16.7	31.0±13.4	0.428[a]
3rd degree	34.6±23.6	16.3±13.7	<0.001[a]	27.3±21.8	26.4±22.4	0.879[a]
Burn mechanism [n (%)]			–			–
Flame	21(50.0)	22 (73.3)		26(57.8)	17 (63.0)	
Flash	3 (7.1)	4 (13.3)		2 (4.4)	5 (18.5)	
Scald	12 (28.6)	3 (10.0)		11 (24.4)	4 (14.8)	
Other	6 (14.3)	1 (3.3)		6 (13.3)	1 (3.7)	
Average EVLWI in PBD 3–9 (ml/kg)	7.8±1.2	6.6±0.9	<0.001[a]	7.7±1.2	6.7±0.9	0.001[a]
Median duration of mechanical ventilation within 14 days postburn [day (IQR)]	11.5 (6.8-15.3)	4.0 (3.0-6.0)	0.006[d]	11.0 (6.0-16.0)	6.0 (3.0-11.0)	0.042[d]
Complications within 14 days postburn [n (%)]						
ARDS	23 (54.7)	9 (30.0)	0.037[b]	24 (53.3)	8 (29.6)	0.031[b]
Pneumonia	21 (50.0)	8 (26.7)	0.047[b]	22 (48.9)	7 (25.9)	0.035[b]
MODS	9 (21.4)	3 (10.0)	0.200[b]	9 (20.0)	3 (11.1)	0.449[c]
Median duration of stay in ICU [day (IQR)]	36.0 (18.8-60.3)	19.0 (12.0-29.3)	0.001[d]	26.0 (15.8-52.3)	21.5 (12.5-32.0)	0.038[d]
Death within 28 days postburn [n (%)]	12 (29.0)	2 (7.0)	0.021[b]	8 (17.8)	6 (22.2)	0.645[b]

Table 5 – Characteristics and outcomes of patients grouped by burn size or ITBVI. PBD 3–9, 3–9 days postburn. Data are presented as means±SD.

[a] Student's t-test.
[b] Pearson Chi-Square.
[c] Continuity Correction Chi-Square.
[d] Wilcoxon rank-sum test.

EVLWI abnormality in severe burns. This result highlights the importance of conservative fluid management during the fluid reabsorption stage in severe burns. Previous studies have shown that fluid resuscitation guided by PiCCO monitoring typically results in over-resuscitation, leading to exacerbation of burn edema and compartment syndromes in burn patients [15,34]. By contrast, permissive hypovolemia protocols and a below-normal ITBVI as resuscitation targets have been proven to be safe [12,35]. Our findings concurred with this notion and, more importantly suggested an ITBVI goal to help maintain a normal EVLWI and thereby reduce the risk of early pulmonary edema during the fluid reabsorption stage.

As a patient with ITBVI over 845 ml/m² has been identified "at risk", individual intervention is therefore necessary for the early pulmonary edema prevention. We found that daily fluid infusion, which decreased gradually from PBD 2 to 9 (data not shown), was not an independent risk factor for the abnormal elevation of EVLWI during the fluid reabsorption stage in severe burns. Therefore, reabsorption of the fluid that initially lost into the interstitium during the resuscitation stage may account more for ITBVI elevation in those patients. To prevent ITBVI elevation, measures that reducing fluid administration or increasing urinary output or both could be used clinically. Actually, we have performed a preliminary study to determine whether a restrictive fluid management strategy (RFMS) during the fluid reabsorption stage would be helpful for the prevention of EVLWI abnormality in severe burns [36]. RFMS is a fluid

management strategy to achieve a negative fluid balance by reducing fluid intake and/or increasing urinary output. RFMS can lead to higher serum oncotic pressures and lower intravascular pressures that would be expected to limit the accumulation of the interstitial fluid in lung. It has been shown that RFMS improves lung function and shortens intensive care in ARDS patients [37]. In our preliminary study, we performed RFMS mainly by increasing urinary output because it is difficult to reduce fluid administration largely in severe burns due to the therapeutic fluid infusion. We found that RFMS trended to lower GEDVI (ITBV=1.25×GEDV-28.4) and EVLWI in severe burns [36]. Nevertheless, a multi-center prospective, randomized clinical trial is needed to determine the possible benefits of RFMS in limiting EVLWI in severe burns.

Hypoproteinemia is very common after severe burns and is an important factor for EVLWI elevation among critically ill patients [32]. The study by Yagi et al. [17] showed that an albumin level of 2.2±0.7 g/dl was associated with a supra-normal EVLWI among ICU patients. Nevertheless, we failed to show any correlation between albumin levels and the EVLWI during the entire measurement period in severely burned adults. A possible reason for this discrepancy may be the differences in diseases or albumin levels among the patients. Albumin in our patients was maintained at a level of 3.0±0.5 g/dl by routine infusion of colloid solutions during initial resuscitation and subsequent fluid administration. These albumin levels are much higher than those reported by Yagi

(2.2±0.7 g/dl) [17]. Therefore, osmotic colloid pressure likely contributes to abnormal elevation of EVLWI only when it decreases to a relatively low level.

EVLWI >10 or 12 mg/kg has usually been regarded as a criterion of pulmonary edema in ARDS or primarily septic ICU patients [38,39]. However, this value is likely not appropriate for all patients given that differences in EVLWI have been found in critically ill patients suffering from different diseases. By meta-analysis, Eichhorn et al. found that the mean EVLWI differed significantly by 3.3 ml/kg between surgical patients and non-surgical septic patients (7.2 ml/kg vs. 11.0 ml/kg), indicating that the EVLWI is heterogeneous in critically ill patients [40]. A consensus regarding a level of EVLWI that predicts pulmonary edema has been not established for burn patients. However, accumulating evidence indicates that abnormally elevated EVLWI is definitely correlated with pulmonary morbidity and poor prognosis in critically ill patients [41–43]. Therefore, although a diagnostic EVLWI for pulmonary edema in severe burns must be conclusively determined, the identification of factors that contribute to a supranormal EVLWI (>7 ml/kg) is highly significant for the early prevention of pulmonary edema and subsequent pulmonary morbidity.

As this study was conducted at a burn specialty center, the cut-off values for burn size or the ITBVI for discriminating a supranormal EVLWI would likely be lower for a low-volume, non-specialized burn center due to differences in therapeutic methods. In addition, our conclusions were based on the TMMU resuscitation formula that is seldom used in Western country. The use of colloid and less fluid administration during the first 24h postburn underlies the major differences between the TMMU formula and the Parkland formula used in Western country. Kim et al. [44] reported that albumin in severely burned patients resuscitated according to the Parkland formula was 2.5 ±0.8 g/dl, which is lower than in our patients (3.0±0.5 g/dl). In contrast to Parkland formula, which has 4 ml kg^{-1} per 1% TBSA in 24h as a basis, the average volume of fluid administration in our study was 2.18 ml kg^{-1} per 1% TBSA during the first 24h postburn. Since more aggressive fluid resuscitation may correlate to a higher elevation of EVLWI in burn patients, the influences of different resuscitation protocols on risk factors and the associated cut-off values for elevated EVLWI require further study. These limitations, take together, may restrict the potential generalizability of our current findings.

5. Conclusion

Burn size and ITBVI are the independent risk factors for the abnormal elevation of EVLWI during the fluid reabsorption stage in severe burns. Specifically, the cut-off values for predicting a supranormal EVLWI are 65.5% TBSA for burn size and 845 ml/m^2 for ITBVI. These cut-offs are valuable in terms of identifying patients with high risks of pulmonary edema or morbidity who may require early individualized interventions.

Ethics approval and consent to participate

Permission to conduct the study was obtained from the ethics committee of Southwest Hospital. The reference number is No. 17-2012. Informed written consent was obtained from all patients or their next kin.

Consent for publication

Not applicable.

Availability of data and material

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JP Zhang supervised the work. H Ren and JP Zhang designed the experiment. WY Wang, XF Yu, FL Zuo, and SX Yu conducted the experiment with assistance from ZH Luo, J Liu, Y Wang and GQ Zhu. JP Zhang, WY Wang and H Ren drafted the manuscript. H Lin and N Xu performed the statistical analysis. WY Wang and XF Yu were the co-first authors of this article. All authors critically reviewed and approved the final manuscript.

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