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Prognostic value of extravascular lung water and its potential role in guiding fluid therapy in septic shock after initial resuscitation

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ABSTRACT

Purposes: To explore whether extravascular lung water (EVLW) provides a valuable prognostic tool guiding fluid therapy in septic shock patients after initial resuscitation.

Materials and Methods: We performed a retrospective study of septic shock patients who achieved adequate initial fluid resuscitation with extended hemodynamic monitoring, analyzing the prognostic value of EVLW and whether fluid therapy for 24 (T_{24}) or 24-48 hours ($T_{24\text{-}48}$) after initial resuscitation with a recommended value of EVLW yielded a 28-day mortality advantage.

Results: One hundred five patients with septic shock were included in this study, 60 (57.1%) of whom died after 28 days. For 48 hours after initial resuscitation, the daily fluid balance (DFB; T_{24}: 2494 ± 1091 vs 1965 ± 964 mL [$P = .011$] and $T_{24\text{-}48}$: 2127 ± 783 vs 1588 ± 665 mL [$P < .001$]) and daily maximum values of the EVLW index ($EVLWI_{max}$; T_{24}: 13.9 ± 3.7 vs 11.5 ± 3.2 mL/kg [$P < .001$] and $T_{24\text{-}48}$: 14.4 ± 5.3 vs 12.0 ± 4.4 mL/kg [$P < .001$]) were significantly higher in nonsurvivors than in survivors. In multivariate regression analysis, the DFB (T_{24}: odds ratio [OR] 1.001 [$P = .016$] and $T_{24\text{-}48}$: OR 1.001 [$P = .008$]), $EVLWI_{max}$ (T_{24}: OR 2.158 [$P = .002$] and $T_{24\text{-}48}$: OR 3.277 [$P = .001$]), blood lactate (T_{24}: OR 1.368 [$P = .021$] and $T_{24\text{-}48}$: OR 4.112 [$P < .001$]), and central venous blood oxygen saturation (T_{24}: OR 0.893 [$P = .013$] and $T_{24\text{-}48}$: OR 0.780 [$P = .004$]) were all independently associated with the 28-day mortality. A receiver operating characteristic analysis revealed that area under the curve values of 0.82 (95% confidence interval, 0.74-0.91; $P < .001$) and 0.90 (95% confidence interval, 0.83-0.96; $P < .001$) for $EVLWI_{max} \geq 12.5$ mL/kg (T_{24} and $T_{24\text{-}48}$) predicted a 28-day mortality with sensitivities of 88% (80%-96%) and 95% (90%-100%) and specificities of 60% (46%-74%) and 76% (63%-89%).The $EVLWI_{max}$ was correlated with DFB with Spearman ρ values of 0.497 (T_{24}: $P < .001$) and 0.650 ($T_{24\text{-}48}$: $P < .001$). Cox survival and regression analyses demonstrated that $EVLWI_{max} \geq 12.5$ mL/kg (T_{24} and $T_{24\text{-}48}$) was associated with higher risk and increased mortality, with adjusted ORs of 4.77 ($P < .001$) and 10.86 ($P < .001$).

Conclusions: A higher EVLW in septic shock patients after initial resuscitation was associated with a more positive fluid balance and increased mortality, which is an independent predictor of the 28-day mortality in septic shock patients after initial resuscitation.

1. Introduction

Septic shock is an extremely complex disorder that is characterized by inflammation-induced endothelial dysfunction leading to vascular leakage and vasodilatation [1,2]. Intravenous fluids, along with antibiotics, source control, vasopressors, inotropic agents, and mechanical ventilation, remain the cornerstone of early management of patients with septic shock [3,4]. According to the Surviving Sepsis Campaign guidelines [3], adequate and early goal-directed fluid resuscitation within 6 hours of septic shock presentation targeting a central venous pressure (CVP) of 8 to 12 mm Hg is mandated to increase oxygen delivery and improve organ function and outcome. After initial resuscitation, however, subsequent fluid infusions often fail to augment perfusion and may be harmful. How can we ensure sufficient volume resuscitation of those who will benefit while limiting potential harm in those who will not? How to identify the appropriate fluid management strategies after initial resuscitation in patients with septic shock is becoming a real daily challenge for the intensive caregiver and has been little studied, even in studies of unresuscitated patients in the first 6 hours [5].

Endothelial activation and damage occur early during sepsis. Evidence suggests that the sepsis-induced damage of endothelial cell membranes gives increases capillary permeability, causing an extravagation of protein and fluid leading to interstitial edema, playing an important role in mediating tissue ischemia and organ failure, which titrate fluid therapy. Lungs that are maximally exposed to the proinflammatory cascade, receiving the entire cardiac output, could provide

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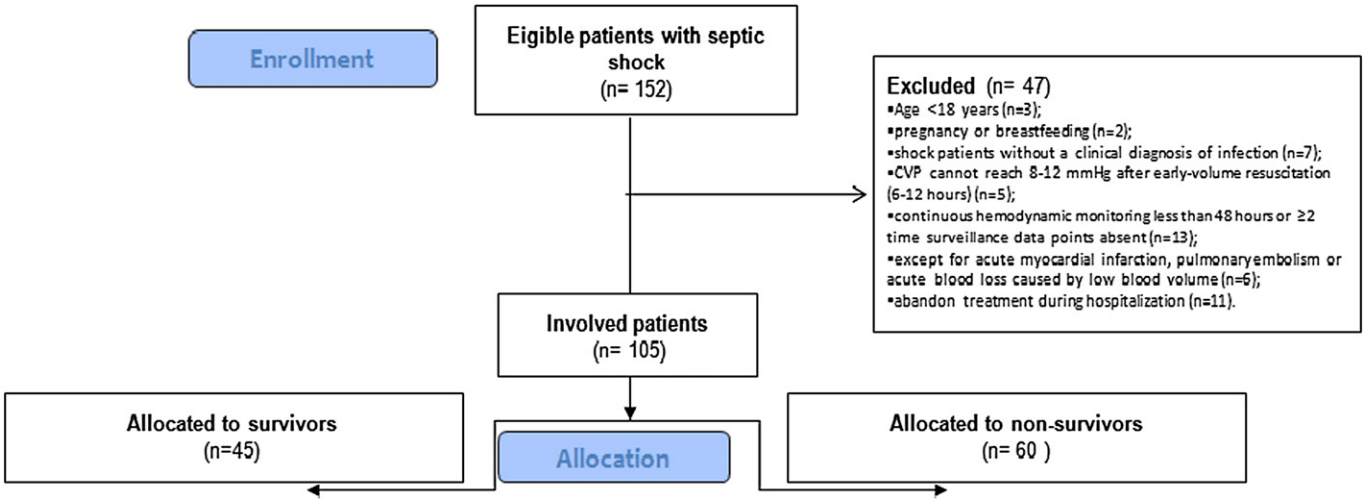

Fig. 1. The flowchart for this study.

valuable insight into dynamic microcirculatory changes during systemic inflammation [6]. Extravascular lung water (EVLW), as the amount of water that is contained in the extravascular space of the lung [7], increases because of elevated pulmonary vascular permeability or hydrostatic pressure. Extravascular lung water, which can be accurately "measured" in critically ill patients by transpulmonary thermodilution, allows for the estimation of the extent of capillary leakage and fluid overload. Extravascular lung water has the advantage of being available at the bedside [8,9]. Indexing EVLW to the predicted body weight has been proposed as a useful marker of quantifying "capillary leakiness," response to treatment, and mortality in patients with acute respiratory distress syndrome (ARDS) [10,11]. In addition, increased EVLW associated with hypoxemia is an independent prognostic factor in various

Table 1
Demographic and baseline characteristics according to survival at day 28

	Survivors (n = 45)	Nonsurvivors (n = 60)	*P*
Demographic data			
Age (y)	66 ± 17	65 ± 18	.634
Sex (male/female)	29:16	38:22	.907
Body mass index (kg/m^2)	22.3 ± 1.4	22.6 ± 1.1	.145
APACHE II score	21.8 ± 7.8	25.5 ± 6.9	.013
Underlying disease, n (%)			
Diabetic mellitus	5 (11.1)	10 (16.7)	.575
COPD	15 (33.3)	31 (51.7)	.075
Chronic cardiovascular disease	24 (53.3)	31 (51.7)	.866
Chronic renal failure	13 (28.9)	17 (28.3)	.950
Source of infection, n (%)			
Pulmonary	25 (55.6)	37 (61.7)	.553
Abdominal	15 (33.3)	16 (26.7)	.520
Other	5 (11.1)	7 (11.7)	.929
Baseline characteristics[a]			
Hemodynamic variables			
MAP (mm Hg)	82 ± 11	85 ± 16	.282
CVP (mm Hg)	10 ± 3	11 ± 3	.113
CI (L/min per m^2)	3.4 ± 1.0	3.3 ± 1.1	.397
SVI (mL/m^2)	30.9 ± 8.6	30.0 ± 11.1	.631
GEDVI (mL/m^2)	703 ± 146	754 ± 153	.092
EVLWI (mL/kg)	11.0 ± 3.6	11.9 ± 4.1	.177
PVPI (mL/kg)	2.1 ± 0.5	2.2 ± 0.7	.161
Lactate (mmol/L)[b]	3.5 ± 1.8	4.4 ± 2.1	.031
$Scvo_2$ (%)[b]	70 ± 10	67 ± 9	.079
Respiratory variables			
Tidal volume (mL/kg)	6.4 ± 0.6	6.3 ± 0.4	.732
PEEP (cm H_2O)	8 (5)	9 ± 4	.134
Compliance (mL/cm H_2O)	41 ± 8	38 ± 7	.077
Pao_2/Fio_2[b]	200 ± 67	187 ± 84	.404
Biological variables			
Hemoglobin (g/L)	9.8 ± 2.0	10.1 ± 2.2	.654
Albumin (g/L)	29.7 ± 4.6	29.6 ± 4.3	.890

Quantitative data are expressed as the mean ± SD or median interquartile (25%-75%).
Qualitative data are expressed as n (%).
COPD indicates chronic obstructive pulmonary disease; PEEP, positive end expiratory pressure.
[a] Variables collected at the end of initial resuscitation.
[b] Variables corresponding to the transpulmonary thermodilution measurements at the end of the initial resuscitation.

Table 2
Process-of-care variables according to survival at day 28

	Survivors (n = 45)	Nonsurvivors (n = 60)	*P*
24 h after initial resuscitation (T_{24})			
Daily fluid balance (mL)	1965 ± 964	2494 ± 1091	.011
MAP (mm Hg)[a]	86 ± 12	85 ± 16	.607
CVP (mm Hg)[a]	11 ± 2	12 ± 3	.079
CI (L/min per m^2)[a]	3.5 ± 1.0	3.4 ± 1.0	.796
SVI (mL/m^2)[a]	33.4 ± 9.6	31.2 ± 10.9	.294
GEDVI (mL/m^2)[a]	724 ± 157	773 ± 137	.089
$EVLWI_{max}$ (mL/kg)[b]	11.5 ± 3.2	13.9 ± 3.7	<.001
PVPI (mL/kg)[a]	2.1 ± 0.6	2.6 ± 0.7	.001
Lactate (mmol/L)[a]	3.2 ± 1.7	4.3 ± 2.1	.002
$Scvo_2$ (%)[a]	71 ± 8	67 ± 8	.003
Pao_2/Fio_2[a]	214 ± 62	168 ± 77	.001
24-48 h after initial resuscitation (T_{24-48})			
Daily fluid balance (mL)	1588 ± 665	2127 ± 783	<.001
MAP (mm Hg)[a]	86 ± 12	84 ± 14	.526
CVP (mm Hg)[a]	12 ± 2	13 ± 2	.135
CI (L/min per m^2)[a]	3.5 ± 1.0	3.4 ± 1.2	.732
SVI (mL/m^2)[a]	35.2 ± 10.4	31.8 ± 12.0	.131
GEDVI (mL/m^2)[a]	763 ± 146	800 ± 144	.194
$EVLWI_{max}$ (mL/kg)[b]	12.0 ± 4.4	14.4 ± 5.3	<.001
PVPI (mL/kg)[a]	2.3 ± 0.5	2.9 ± 0.7	<.001
Lactate (mmol/L)[a]	2.4 ± 0.9	4.2 ± 1.6	<.001
$Scvo_2$ (%)[a]	72 ± 7	66 ± 8	<.001
Pao_2/Fio_2[a]	224 ± 89	155 ± 70	<.001
48 h after initial resuscitation (T_{48})			
Need for MV, n (%)[c]	41 (91.1)	59 (98.3)	.162
Inotropic support, n (%)[c,d]	13 (28.9)	23 (38.3)	.407
Need for RRT, n (%)[c]	10 (22.2)	15 (25.0)	.819
Length of ICU stay (d)	23 (17)	7 (10)	<.001

Quantitative data are expressed as the mean ± SD or median interquartile (25%-75%).
Qualitative data are expressed as n (%).
MV indicates mechanical ventilation; RRT, renal replacement therapy.
[a] Variables corresponding to the transpulmonary thermodilution measurements of daily maximum value of EVLWI.
[b] Daily maximum value of EVLWI.
[c] Life-sustaining treatments needed for at least 12 hours during the 48 hours after initial resuscitation.
[d] Variable defined as a minimum of 50 μg of dobutamine or 5 μg of milrinone per minute.