J Korean Med Sci. 2022 May 9;37(18):e145
https://doi.org/10.3346/jkms.2022.37.e145
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Emergency & Critical Care Medicine

Check for updates

Prognostic Value of Estimated Plasma Volume Status in Patients With Sepsis

Kyung Hoon Kim,[1] **Hyeong Jun Cho**,[2] **Seok Chan Kim**,[2] **and Jongmin Lee** [2]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

OPEN ACCESS

Received: Nov 4, 2021
Accepted: Apr 12, 2022
Published online: May 4, 2022

Address for Correspondence:
Jongmin Lee, MD, PhD
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.
Email: dibs03@gmail.com

ORCID iDs
Kyung Hoon Kim
https://orcid.org/0000-0001-7744-920X
Hyeong Jun Cho
https://orcid.org/0000-0001-6347-245X
Seok Chan Kim
https://orcid.org/0000-0002-1947-9811
Jongmin Lee
https://orcid.org/0000-0002-0165-5856

Funding
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2020R1I1A1A01066003).

Disclosure
Authors have no potential conflicts of interest to disclose.

ABSTRACT

Background: In patients with sepsis, timely risk stratification is important to improve prognosis. Although several clinical scoring systems are currently being used to predict the outcome of sepsis, but they all have certain limitations. The objective of this study was to evaluate the prognostic value of estimated plasma volume status (ePVS) in patients admitted to the intensive care unit (ICU) with sepsis or septic shock.
Methods: This single-center, prospective observational study, included 100 patients admitted to the ICU with sepsis or septic shock. Informed consent, blood samples, and co-morbidity data were obtained from the patients on admission, and the severity of sepsis was recorded. The primary outcome was in-hospital mortality and multivariable logistic regression analysis was used to adjust for confounding factors to determine the significant prognostic factor.
Results: The in-hospital mortality was 47%. The ePVS was correlated with the amount of total fluids administered 24 hours before the ICU admission. The mean ePVS in patients who died was higher than in those who survived (7.7 ± 2.1 dL/g vs. 6.6 ± 1.6 dL/g, $P = 0.003$). To evaluate the utility of ePVS in predicting in-hospital mortality, a receiver operating characteristic curve was produced. Sensitivity and specificity were optimal at a cut-off point of 7.09 dL/g, with an area under the curve of 0.655. In the multivariate analysis, higher ePVS was significantly associated with higher in-hospital mortality (adjusted odds ratio, 1.39; 95% confidence interval, 1.04–1.85, $P = 0.028$). The Kaplan-Meier curve showed that an ePVS value above 7.09 was associated with an increased risk of in-hospital mortality compared with the rest of the population ($P = 0.004$).
Conclusion: The ePVS was correlated with the amount of intravenous fluid resuscitation and may be used as a simple and novel prognostic factor in patients with sepsis or septic shock who are admitted to the ICU.

Keywords: Sepsis; Estimated Plasma Volume Status; Prognostic Value

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Although the prognosis of patients with sepsis has been improved due to advances in critical care management, mortality from sepsis remains high.[2] Sepsis is associated with a deficit in effective blood volume, endothelial cell dysfunction, and fluid leakage

Author Contributions

Conceptualization: Kim KH, Lee J. Data curation: Kim KH, Cho HJ, Lee J. Formal analysis: Kim KH, Lee J. Investigation: Kim KH, Lee J. Methodology: Kim KH, Lee J. Software: Kim KH. Validation: Lee J, Kim SC. Visualization: Kim KH. Writing - original draft: Kim KH. Writing - review & editing: Kim SC, Lee J.

into the interstitial space.[3,4] Therefore, intravenous fluid resuscitation is a mainstay in the treatment of sepsis.[5] However, as reported in previous studies, a positive fluid balance may be associated with worse prognosis.[4,6] Therefore, to manage sepsis, it is important to assess the volume status of patients.

Plasma volume is associated with the regulation between interstitial and intravascular spaces and can be used as a marker for volume overload.[7] Recently, Duarte et al.[8] proposed to use a simple formula based on hemoglobin and hematocrit to estimate the plasma volume in patients with heart failure (HF). Previous studies have reported that a high estimated plasma volume status (ePVS) was related to a poor prognosis of patients with HF.[9,10] Although previous studies have shown that the ePVS value on admission to the emergency department (ED) correlated with the risk of death in patients with fever or dyspnea,[11,12] few studies have evaluated its prognostic power in patients with sepsis or septic shock admitted to the intensive care unit (ICU).

Therefore, we conducted a prospective observational study to assess the prognostic power of ePVS in critically ill patients with sepsis who required admission to the ICU.

METHODS

Study population

This is a monocentric prospective observational study conducted in the ICU of the Seoul St. Mary's Hospital, Korea (460,000 visits per year, 1,369 beds, and 20 medical ICU beds) from March 2019 to June 2020. During the study period, blood samples were collected from patients with sepsis on the day of the ICU admission (day 1). Sepsis was diagnosed according to the third international consensus definitions for sepsis and septic shock (Sepsis-3). Patients with a history of bleeding or transfusion within 3 days prior to the ICU admission were excluded. On day 1, Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score 3 (SAPS3) scores were used as indicators of sepsis severity. We collected comorbidity data of the patients to calculate the Charlson comorbidity score index.[13] The variables shown in **Table 1** were measured and recorded on admission (day 1).

ePVS measurement

Blood samples were collected on admission to the ICU and a complete blood count (CBC) analysis was performed using the Sysmex analyzer (Sysmex XN-9000, Sysmex Co, Kobe, Japan). The ePVS value was calculated using the hematocrit and hemoglobin values from the CBC, using the following formula[8]:

$$\text{ePVS}\left(\frac{\text{dL}}{\text{g}}\right) = \frac{100 - \text{Ht}(\%)}{\text{Hb (g/dl)}}$$

Statistical analyses

All statistical analyses were performed using the R 4.0.2 version (R Foundation, Vienna, Austria). All results are reported as means ± standard deviations for normally distributed continuous variables and as medians and interquartile ranges (IQRs) for non-normally distributed continuous data. Categorical data are described as numbers and percentages. Patient characteristics were compared using the χ^2 test or Fisher's exact test for categorical variables, and independent samples *t*-tests for continuous variables. We performed linear

https://doi.org/10.3346/jkms.2022.37.e145

JKMS

Table 1. Comparison of baseline characteristics of the study population at ICU admission (N = 100)

Variables	Total (N = 100)	Survivor (n = 53)	Non-survivor (n = 47)	*P* value
Age, yr	69 (56.5–80.0)	71.0 (61.0–79.0)	64.0 (51.5–80.0)	0.335
Sex, male, %	54 (54.0)	31 (58.5)	23 (48.9)	0.450
Body weight, kg	58.0 (51.0–66.8)	59.4 (52.0–66.6)	57.0 (50.5–66.0)	0.429
Septic shock	60 (60.0)	30 (56.6)	30 (63.8)	0.595
SAPS3 score	78.3 ± 14.1	72.2 ± 12.0	85.1 ± 13.2	< 0.001
SOFA score	9.0 (7.0–12.0)	8.0 (7.0–11.0)	11.0 (8.0–14.0)	< 0.001
Charlson comorbidity index	5.0 (4.0–7.0)	6.0 (4.0–8.0)	5.0 (4.0–7.0)	0.228
Use of vasopressors at day 1	74 (74.0)	37 (69.8)	37 (78.7)	0.883
Use of inotropics at day 1	2 (2.0)	0 (0.0)	2 (4.3)	0.423
Use of IMV at day 1	44 (44.0)	16 (30.2)	28 (59.6)	0.006
Hemoglobin, g/dL	10.3 ± 2.0	10.5 (9.2–11.7)	9.2 (8.5–10.8)	0.007
Hematocrit, %	29.9 (26.2–35.0)	31.8 (27.6–35.4)	28.0 (25.0–33.1)	0.012
ePVS, dL/g	7.1 ± 1.9	6.6 ± 1.6	7.7 ± 2.1	0.003
Lactic acid at day 1, mmol/L	3.0 (1.5–6.5)	2.4 (1.3–4.0)	4.0 (1.8–7.7)	0.040
Procalcitonin at day 1, ng/mL	10.6 (2.2–52.0)	10.6 (1.5–40.2)	11.3 (2.8–54.1)	0.912
WBC at day 1, 10^9/L	10.1 (3.0–16.8)	10.2 (4.3–17.5)	8.6 (1.1–16.1)	0.334
ANC at day 1, 10^9/L	7.8 (1.7–14.5)	7.9 (2.5–15.2)	6.6 (0.5–13.4)	0.224
Platelets at day 1, 10^9/L	104.0 (35.0–206.0)	168.0 (47.0–234.0)	64.0 (30.0–127.0)	0.004
CRP at day 1, mg/dL	16.3 (9.1–25.9)	16.7 (9.1–24.1)	16.1 (9.3–27.2)	0.617
BUN at day 1, mg/dL	35.6 (24.6–52.5)	35.2 (23.2–51.2)	36.1 (24.7–55.3)	0.377
Creatinine at day 1, mg/dL	1.6 (0.9–2.4)	1.6 (0.9–2.6)	1.6 (0.8–2.4)	0.738
GFR at day 1, mL/min/1.73m^2	38.1 (21.8–71.8)	37.7 (22.4–68.3)	40.9 (22.1–80.8)	0.691
SBP at day 1, mmHg	80.0 (70.0–90.0)	78.0 (70.0–88.0)	81.0 (71.5–90.0)	0.597
DBP at day 1, mmHg	47.5 (40.0–55.5)	47.7 ± 11.3	48.9 ± 13.0	0.602
HR at day 1, beat/min	131.8 ± 26.6	124.4 ± 25.2	140.0 ± 25.9	0.003
RR at day 1, rate/min	31.0 (24.0–35.5)	28.0 (23.0–34.0)	33.0 (26.5–38.5)	0.019
Total fluids administered 24 hr before ICU admission, mL	3,215.0 (2,364.5–4,623.0)	3,008.0 (2,060.0–3,878.0)	3,481.0 (2,811.2–4,941.6)	0.007

Values are presented as number (%) or mean ± standard deviation or median (interquartile range).
ICU = intensive care unit, SAPS3 = Simplified Acute Physiology Score 3, SOFA = sequential organ failure assessment, IMV = invasive mechanical ventilation, ePVS = estimated plasma volume status, WBC = white blood cells, ANC = absolute neutrophil count, CRP = C-reactive protein, BUN = blood urea nitrogen, GFR = glomerular filtration rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rates, RR = respiratory rates.

regression to determine the association of ePVS with the amount of total fluids administered 24 hours before the ICU admission. Logistic regression analyses were performed to investigate associations between patient characteristics and in-hospital mortality. Clinical parameters with a *P* value of 0.05 in the univariate logistic regression were included in the multivariate logistic regression. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were computed. Goodness-of-fit was computed to assess the relevance of the logistic regression model. Receiver operating characteristic (ROC) curves were used to evaluate the ability of ePVS to predict in-hospital mortality. Probabilities of in-hospital survival for each group were estimated using the Kaplan-Meier method and compared using the log rank test. All tests were two-sided, and *P* values < 0.05 were considered statistically significant.

Ethics statement

This study was conducted in accordance with the relevant legislation and approved by the Ethics Committee of Seoul St. Mary's Hospital (KC18DESI0739). The study complied with the Declaration of Helsinki and Good Clinical Practice Guidelines, and all patients provided informed consent for inclusion in the study.

https://doi.org/10.3346/jkms.2022.37.e145

RESULTS

Baseline characteristics

Of the 119 patients with sepsis admitted to our ICU from March 2019 to June 2020, 100 patients (54 men and 46 women), were included in this study and 47 (47.0%) patients died in-hospital (**Fig. 1**). All patients met the criteria for sepsis or septic shock according to the Sepsis-3 criteria. Baseline characteristics of the patients are shown in **Table 1**. The median age of the patients was 69.0 years (IQR, 56.5–80.0), and median body weight was 58.0 kg (IQR, 51.0–66.0). Septic shock was diagnosed in 60 (60.0%) patients. The mean initial SAPS3 and median SOFA score on day 1 were 78.3 ± 14.1 and 9.0 (IQR, 7.0–12.0), respectively, and both scores were significantly higher in non-survivors than those in survivors (both, $P < 0.001$). The median hemoglobin and hematocrit values were significantly lower in non-survivors than in survivors ($P = 0.007$ for hemoglobin; $P = 0.012$ for hematocrit). Among the cases, 74 (74.0%) needed vasopressor support and 44 (44.0%) had hypoxemia-requiring invasive ventilation. The amount of total fluids administered 24 hours before the ICU admission was 3,215.0 mL (2,364.5–4,623.0) and significantly higher in non-survivors than in survivors (3,481.0 [2,811.2–4,941.6] vs. 3,008.0 [2,060.0–3,878.0], $P = 0.007$). The mean value of ePVS was 7.1 ± 1.9 dL/g and significantly higher in non-survivors (7.7 ± 2.1 vs. 6.6 ± 1.6, $P = 0.003$).

Clinical determinants of ePVS

Univariable linear regression analysis showed that the amount of total fluids administered 24 hours before the ICU admission, old age, higher lactic acid and higher SAPS3 score were significantly correlated with higher ePVS (**Table 2**). In multivariate linear regression models, only the amount of total fluids administered 24 hours before the ICU admission and higher lactic acid were significantly correlated with higher ePVS.

In-hospital mortality prediction performance of ePVS

ROC curves were generated to compare the ePVS, SOFA, and SAPS3 for predicting in-hospital mortality in patients with sepsis or septic shock who required admission to the ICU (**Fig. 2**). In all patients, ePVS showed an area under the curve (AUC) of 0.655 (95% CI, 0.553–0.747),

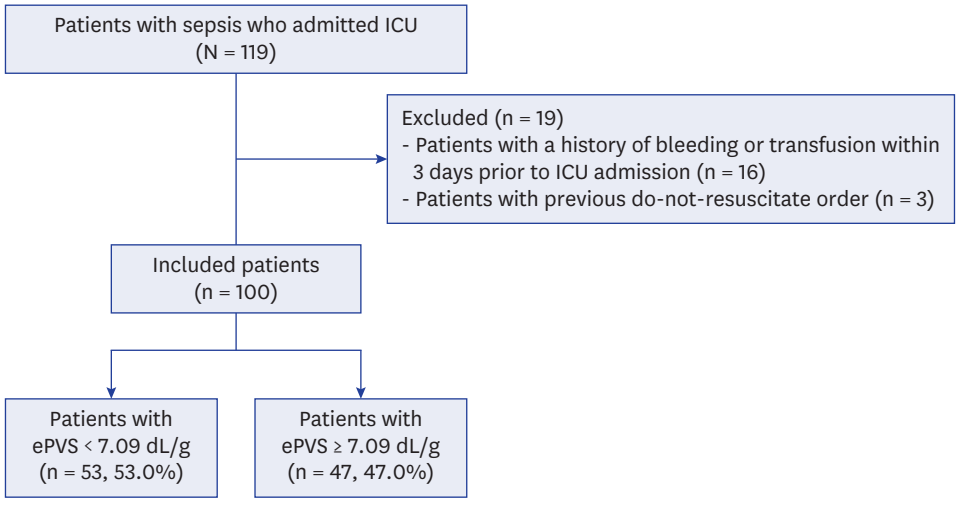

Fig. 1. Study flow diagram.
ICU = intensive care unit, ePVS = estimated plasma volume status.

https://doi.org/10.3346/jkms.2022.37.e145

Table 2. Multivariate model for the association of clinical parameters with estimated plasma volume status

Variables	Univariate analysis		Multivariate analysis[a]	
	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Total fluids administered 24 hr before ICU admission, L	0.561 (0.484 to 0.638)	< 0.001	0.597 (0.497 to 0.697)	< 0.001
Sex, male	−0.461 (−0.844 to −0.078)	0.232		
Age, yr	−0.035 (−0.048 to −0.022)	0.006	−0.003 (−0.015 to 0.009)	0.798
Presence of septic shock	−0.356 (−0.747 to −0.035)	0.364		
Lactic acid at day 1, mmol/L	−0.023 (−0.063 to 0.017)	0.009	−0.101 (−0.134 to −0.068)	0.003
SAPS3 score	0.038 (0.025 to 0.051)	0.005	0.008 (−0.005 to 0.021)	0.524

CI = confidence interval, ICU = intensive care unit, SAPS3 = Simplified Acute Physiology Score 3.
[a]Clinical parameters with a *P* value of 0.05 in the univariate logistic regression were included in the multivariate logistic regression.

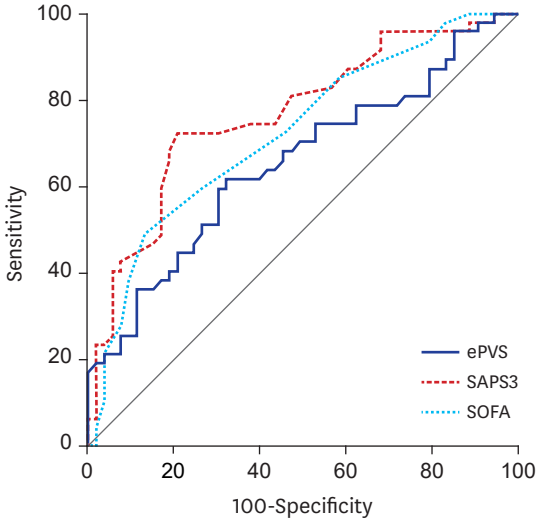

Fig. 2. Comparison of receiver operating characteristics curves of ePVS, SAPS3, and SOFA for predicting in-hospital mortality in critically ill patients with sepsis.
ePVS = estimated plasma volume status, SAPS3 = Simplified Acute Physiology Score 3, SOFA = sequential organ failure assessment.

with 61.7% sensitivity and 67.9% specificity, at a cutoff point ≥ 7.09 dL/g. While SAPS3 showed an AUC of 0.768 (95% CI, 0.673–0.847) with 72.3% sensitivity and 79.3% specificity, and SOFA showed an AUC of 0.724 (95% CI, 0.625–0.809) with 48.9% sensitivity and 72.3% specificity, but the AUC among the three scores was not significantly different ($P = 0.365$).

Table 3 lists the patient outcomes according to ePVS values. Patients with ePVS > 7.09 dL/g had a significantly higher rate of ICU mortality (53.2% vs. 30.2%, $P = 0.033$), and in-hospital mortality (61.7% vs. 34.0%, $P = 0.010$) than those with ePVS < 7.09 dL/g. In adittion, patients with ePVS > 7.09 dL/g had a significantly higher rate of renal replacement therapy (RRT) during the ICU stay (44.7% vs. 20.8%, $P = 0.019$). After adjusting for potential confounding factors, higher ePVS remained significantly associated with RRT during the ICU stay (adjusted OR, 1.41; 95% CI, 1.03 – 1.92; P = 0.030) (**Supplementary Table 1**).

Factors associated with in-hospital mortality in patients with sepsis

Logistic regression analysis of clinical parameters for evaluating the risk factors associated with hospital mortality in patients with sepsis is shown in **Table 4**. The increase of 1 dL/g in ePVS at day 1 was independently associated with in-hospital mortality by univariate analysis (crude OR, 1.40; 95% CI, 1.11–1.77; $P = 0.005$). Other independent risk factors for hospital mortality were higher lactic acid, higher SAPS3 score, higher SOFA score, use of mechanical ventilation

https://doi.org/10.3346/jkms.2022.37.e145

Table 3. Comparison of baseline characteristics and outcomes according to cut-off ePVS value

Variables	ePVS < 7.09 dL/g (N = 53)	ePVS ≥ 7.09 dL/g (N = 47)	*P* value
Age, yr	71.0 (62.0–82.0)	63.0 (51.0–76.5)	0.011
Sex, male, %	33 (62.3)	21 (44.7)	0.119
Septic shock	32 (60.4)	28 (59.6)	1.000
SAPS3 score	74.6 ± 13.7	82.4 ± 13.5	0.005
SOFA score	9.0 (7.0–11.0)	9.0 (8.0–13.0)	0.143
SBP at day 1, mmHg	81.0 (70.0–87.0)	80.0 (70.5–90.0)	0.507
DBP at day 1, mmHg	47.0 (41.0–55.0)	49.0 (40.0–56.0)	0.844
HR at day 1, beat/min	128.9 ± 28.3	135.0 ± 24.4	0.250
RR at day 1, rate/min	28.0 (22.0–35.0)	31.0 (26.5–36.5)	0.126
Lactic acid at day 1, mmol/L	3.2 (1.4–6.9)	3.0 (1.8–5.4)	0.887
Procalcitonin at day 1, ng/mL	9.7 (1.8–40.2)	12.2 (2.9–59.0)	0.342
CRP at day 1, mg/dL	16.7 (7.8–25.5)	16.1 (11.1–25.6)	0.785
BUN at day 1, mg/dL	32.9 (23.2–45.1)	39.0 (26.8–63.9)	0.073
Creatinine at day 1, mg/dL	1.6 (0.9–2.3)	1.6 (0.8–2.8)	0.983
GFR at day 1, mL/min/1.73m^2	42.7 (23.5–71.2)	35.2 (18.7–73.4)	0.777
Use of IMV during ICU stay	30 (56.6)	32 (68.1)	0.330
Use of RRT during ICU stay	11 (20.8)	21 (44.7)	0.019
Use of ECMO during ICU stay	1 (1.9)	1 (2.1)	1.000
ICU mortality	16 (30.2)	25 (53.2)	0.033
In-hospital mortality	18 (34.0)	29 (61.7)	0.010

Values are presented as number (%) or mean ± standard deviation or median (interquartile range).
ePVS = estimated plasma volume status, SAPS3 = Simplified Acute Physiology Score 3, SOFA = sequential organ failure assessment, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, CRP = C-reactive protein, BUN = blood urea nitrogen, GFR = glomerular filtration rate, IMV = invasive mechanical ventilation, RRT = renal replacement therapy, ECMO = extracorporeal membrane oxygenation, ICU = intensive care unit.

(MV), higher heart rate, higher respiratory rate on day 1, and total fluids administered 24 hours before ICU admission (**Table 4**). After adjusting for potential confounding factors, higher ePVS, higher SAPS3 score, and use of MV on day 1 remained independently associated with in-hospital mortality ($P = 0.028$, $P = 0.011$, $P = 0.020$, respectively).

Finally, the Kaplan–Meier survival analysis showed that patients with ePVS > 7.09 dL/g were associated with an increased risk of in-hospital death compared with the rest of the population (log-rank test $P = 0.004$) (**Fig. 3**).

Table 4. Logistic regression analysis for in-hospital mortality

Variables	Univariate analysis			Multivariate analysis[a]		
	Crude OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Lactic acid at day 1	1.10	1.01–1.21	0.038			
SAPS3 score at day 1	1.09	1.04–1.13	< 0.001	1.06	1.01–1.10	0.011
SOFA score at day 1	1.27	1.11–1.45	< 0.001			
Use of IMV at ICU admission	3.41	1.49–7.79	0.004	3.78	1.23–11.61	0.020
Hemoglobin at day 1	0.73	0.58–0.92	0.009			
Hematocrit at day 1	0.91	0.85–0.98	0.014			
ePVS at day 1	1.40	1.11–1.77	0.005	1.39	1.04–1.85	0.028
Heart rate at day 1	1.02	1.01–1.04	0.005			
Respiratory rate at day 1	1.06	1.01–1.12	0.017			
Platelets at day 1	0.99	0.99–1.00	0.004	0.99	0.99–1.00	0.044
Total fluids administered 24 hr before ICU admission, L	1.41	1.10–1.82	0.008			

OR = odds ratio, CI = confidence interval, SAPS3 = Simplified Acute Physiology Score 3, SOFA = sequential organ failure assessment, IMV = invasive mechanical ventilation, ICU = intensive care unit, ePVS = estimated plasma volume status.
[a]Clinical parameters with a *P* value of 0.05 in the univariate logistic regression were included in the multivariate logistic regression.

https://doi.org/10.3346/jkms.2022.37.e145

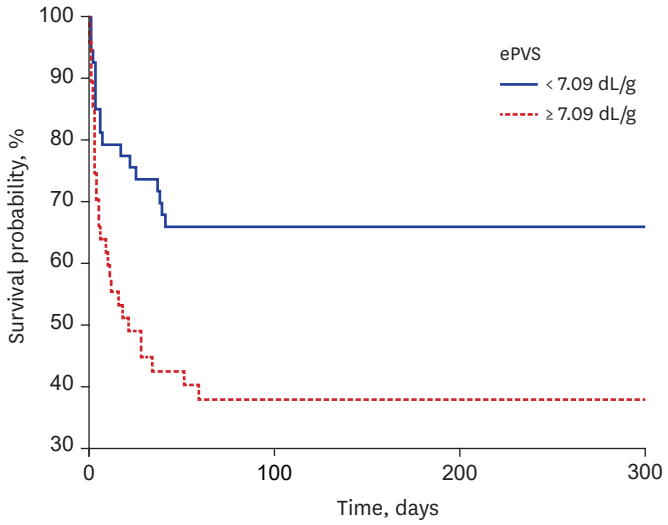

Fig. 3. Kaplan-Meier survival analysis plot for in-hospital mortality divided between above and below cut-off ePVS value (7.09 dL/g).
ePVS = estimated plasma volume status.

DISCUSSION

In this prospective observational study of sepsis patients admitted to the ICU, the ePVS was correlated with the amount of total fluids administered before the ICU admission and independently associated with in-hospital mortality even after multivariate adjustment for other patient clinical and laboratory conditions. To our knowledge, this result is the first attempt to predict the outcome of sepsis patients admitted to the ICU using this new biological surrogate. Our results suggest that ePVS could be a promising tool to predict the prognosis of patients with sepsis.

Key components of treatment in patients with sepsis include intravenous fluid resuscitation to restore tissue perfusion, along with antibiotic therapy, source control, and vasopressors.[5] However, recent studies have shown that positive fluid balance is associated with poor outcome in patients with sepsis.[4,6,14] The mechanisms by which positive fluid balance could cause harm are uncertain, but previous studies suggest that excessive intravenous fluid resuscitation may induce iatrogenic endothelial injury.[15,16] Increased endothelial permeability due to endothelial injury leads to tissue edema and hypoxia, which might eventually lead to organ damage.[16,17] Therefore, a simple and universally available tool for assessing volume status is needed.

In the present study, ePVS was correlated with the amount of total fluids administered 24 hours before the ICU admission. Plasma volume is a marker of volume overload and is linked to the regulation between the interstitial and intravascular spaces.[7] By using a simple formula based on hemoglobin and hematocrit concentrations, the plasma volume of each patient can be calculated; previous studies have shown that the calculated plasma volume measured by this method was well correlated with actual plasma volume, which is measured by radiolabeled albumin techniques.[8,18,19] The ePVS is defined as the percentage difference between ideal plasma volume and actual plasma volume and has emerged as a noninvasive method to assess volume status.[8-10]

https://doi.org/10.3346/jkms.2022.37.e145

Initially, the ePVS was developed to predict the prognosis of patients with HF; after acute myocardial infarction, higher ePVS was significantly associated with hospitalization or cardiovascular death.[8] Furthermore, a decrease in the ePVS was related to decongestion associated with effective treatment and better cardiovascular outcome.[8-10] Recently, Chouihed et al.[12] reported the results of the PARADISE study, which consisted of patients with acute HF and inflammatory diseases. Results showed that high ePVS was significantly associated with in-hospital mortality in patients who visited the ED with acute dyspnea. In patients who visited the ED with fever, ePVS was independently associated with poor prognosis after adjusting for confounding factors.[11]

In this study, higher ePVS was significantly associated with in-hospital mortality and the risk of RRT in critically ill patients with sepsis. A possible explanation for these results may be the side effect of excessive fluid resuscitation. As previously stated, ePVS was correlated with the amount of fluids administered before the ICU admission, and intravenous fluid resuscitation could cause harm in patients with sepsis. Studies have shown that volume overload was associated with poor outcome such as mortality and renal failure.[4,6,20] Increased endothelial permeability due to endothelial injury leads to tissue edema and hypoxia, a key factor in the development of organ dysfunction and death.[21,22]

The SAPS3 and SOFA score are systematic scoring systems for sepsis patients created and verified through large-scale clinical studies.[1,23] In this study, ePVS has a prognostic value similar to SAPS3 or SOFA score in critically ill patients with sepsis. Although the in-hospital mortality AUC for ePVS (0.655) was lower than for SAPS3 (0.768) or SOFA score (0.724), it was not significantly different. Although similar, the SAPS3 and SOFA scores are calculated using distinct, complicated formulas; therefore, ePVS could be a simple tool to predict the prognosis of critically ill patients with sepsis.

To the best of our knowledge, this is the first study to evaluate the value of the ePVS in predicting the prognosis of critically ill patients with sepsis. However, the present study had some limitations. First, the size of this study was relatively small. Second, we did not evaluate the association between a dynamic change in the ePVS value and the prognosis of patients with sepsis. Although previous studies have suggested that a variation of the ePVS is associated with poor prognosis,[9,10] transfusion or bleeding commonly occurred after the ICU admission in this study; therefore, change in the ePVS could not be evaluated. Third, the correlation between the ePVS value and actual plasma volume status was not investigated. Although previous studies have reported that the ePVS reflected plasma volume status, it would have been possible to provide more accurate information if the plasma volume status was measured by other methods. Therefore, additional studies need to be carried out in order to evaluate the correlation between the ePVS and the actual plasma volume value.

In summary, we found that the ePVS, which is simple to perform on admission to the ICU, was correlated with the amount of intravenous fluid resuscitation and significantly associated with mortality in patients with sepsis. Although further research is required to determine these clinical findings, the ePVS may provide the prognostic granularity required for clinical use in critically ill patients with sepsis.

https://doi.org/10.3346/jkms.2022.37.e145

JKMS

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Logistic regression analysis for use of renal replacement therapy inintensive care unit

Click here to view

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315(8):801-10.
PUBMED | CROSSREF
2. Quartin AA, Calonge RO, Schein RM, Crandall LA. Influence of critical illness on physicians' prognoses for underlying disease: a randomized study using simulated cases. *Crit Care Med* 2008;36(2):462-70.
PUBMED | CROSSREF
3. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, Ospina-Tascón GA, et al. The endothelium in sepsis. *Shock* 2016;45(3):259-70.
PUBMED | CROSSREF
4. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care* 2015;19(1):251.
PUBMED | CROSSREF
5. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021;49(11):e1063-143.
PUBMED | CROSSREF
6. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39(2):259-65.
PUBMED | CROSSREF
7. Miller WL. Fluid volume overload and congestion in heart failure: time to reconsider pathophysiology and how volume is assessed. *Circ Heart Fail* 2016;9(8):e002922.
PUBMED | CROSSREF
8. Duarte K, Monnez JM, Albuisson E, Pitt B, Zannad F, Rossignol P. Prognostic value of estimated plasma volume in heart failure. *JACC Heart Fail* 2015;3(11):886-93.
PUBMED | CROSSREF
9. Kobayashi M, Rossignol P, Ferreira JP, Aragão I, Paku Y, Iwasaki Y, et al. Prognostic value of estimated plasma volume in acute heart failure in three cohort studies. *Clin Res Cardiol* 2019;108(5):549-61.
PUBMED | CROSSREF
10. Huang CY, Lin TT, Wu YF, Chiang FT, Wu CK. Long-term prognostic value of estimated plasma volume in heart failure with preserved ejection fraction. *Sci Rep* 2019;9(1):14369.
PUBMED | CROSSREF
11. Turcato G, Zaboli A, Ciccariello L, Pfeifer N. Estimated plasma volume status (ePVS) could be an easy-to-use clinical tool to determine the risk of sepsis or death in patients with fever. *J Crit Care* 2020;58:106-12.
PUBMED | CROSSREF
12. Chouihed T, Rossignol P, Bassand A, Duarte K, Kobayashi M, Jaeger D, et al. Diagnostic and prognostic value of plasma volume status at emergency department admission in dyspneic patients: results from the PARADISE cohort. *Clin Res Cardiol* 2019;108(5):563-73.
PUBMED | CROSSREF
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.
PUBMED | CROSSREF
14. Pittard MG, Huang SJ, McLean AS, Orde SR. Association of positive fluid balance and mortality in sepsis and septic shock in an Australian cohort. *Anaesth Intensive Care* 2017;45(6):737-43.
PUBMED | CROSSREF
15. Hippensteel JA, Uchimido R, Tyler PD, Burke RC, Han X, Zhang F, et al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. *Crit Care* 2019;23(1):259.
PUBMED | CROSSREF

https://doi.org/10.3346/jkms.2022.37.e145

16. Bateman RM, Sharpe MD, Jagger JE, Ellis CG. Sepsis impairs microvascular autoregulation and delays capillary response within hypoxic capillaries. *Crit Care* 2015;19(1):389.
PUBMED | CROSSREF
17. Ince C. The microcirculation is the motor of sepsis. *Crit Care* 2005;9 Suppl 4:S13-9.
PUBMED | CROSSREF
18. Strauss MB, Davis RK, Rosenbaum JD, Rossmeisl EC. Water diuresis produced during recumbency by the intravenous infusion of isotonic saline solution. *J Clin Invest* 1951;30(8):862-8.
PUBMED | CROSSREF
19. Fudim M, Miller WL. Calculated estimates of plasma volume in patients with chronic heart failure-comparison with measured volumes. *J Card Fail* 2018;24(9):553-60.
PUBMED | CROSSREF
20. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009;76(4):422-7.
PUBMED | CROSSREF
21. Koch T, Geiger S, Ragaller MJ. Monitoring of organ dysfunction in sepsis/systemic inflammatory response syndrome: novel strategies. *J Am Soc Nephrol* 2001;12 Suppl 17:S53-9.
PUBMED | CROSSREF
22. Miranda M, Balarini M, Caixeta D, Bouskela E. Microcirculatory dysfunction in sepsis: pathophysiology, clinical monitoring, and potential therapies. *Am J Physiol Heart Circ Physiol* 2016;311(1):H24-35.
PUBMED | CROSSREF
23. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005;31(10):1345-55.
PUBMED | CROSSREF