

Association of estimated Plasma Volume Status (ePVS) and Clinical Outcomes in Septic Patients in the Emergency Room: A Prospective Cohort Study

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Background. Early risk stratification in emergency department sepsis management is essential for improving patient outcomes. Fluid resuscitation is a critical intervention, yet it can be associated with adverse effects if not properly managed. Assessing plasma volume status (ePVS) offers a non-invasive method to guide fluid administration. Previous studies have shown that elevated ePVS correlates with poor outcomes in heart failure and myocardial infarction, but its prognostic value in emergency room sepsis remains underexplored.

Objectives. To determine the prognostic significance of ePVS on in-hospital mortality and its associations with mechanical ventilation, vasopressor use, IV fluid resuscitation, and length hospital stay in septic patients at the emergency room.

Methodology. Single center prospective cohort study included 217 patients presented with Sepsis in the Emergency Room. ePVS was calculated using hematocrit and hemoglobin levels at admission. The primary outcome was in-hospital mortality; secondary outcomes included mechanical ventilation, vasopressor use, 24-hour fluid resuscitation, and length of hospital stay. Descriptive statistics, t-tests, Mann-Whitney U tests, Chi-square tests, receiver operating characteristics, logistic and linear regression analyses were used to identify significant associations and adjust confounding factors.

Results. Higher ePVS values were significantly associated with increased in-hospital mortality (OR 1.5, 95% CI 1.15-1.95, $p = 0.002$) along with increased 24-hour IV fluid resuscitation (OR 1.0004, 95% CI 1.0000-1.0008, $p = 0.03$). Violin and box plot analyses demonstrated that patients with $ePVS \geq 5.37$ had nearly three times the risk of in-hospital mortality compared to those with lower values (HR 2.84, $p = 0.0069$). ROC analysis revealed moderate predictive accuracy for ePVS (AUC 0.63, $p < 0.001$). The length of hospital stay was independently correlated with high ePVS (OR 0.97, 95% CI 0.96-0.99, $p = 0.002$); however, this association lost significance when adjusted for additional variables ($p > 0.05$). Higher ePVS did not correlate with the use of mechanical ventilation or vasopressor/inotrope use ($p > 0.05$).

Conclusion. Elevated estimated plasma volume status (ePVS) and increased 24-hour fluid resuscitation are significantly associated with a higher risk of in-hospital mortality, with patients exhibiting elevated ePVS having a threefold increase in mortality risk. ePVS demonstrates moderate predictive accuracy when compared to established risk assessment tools such as APACHE and MSOFA in predicting in-hospital mortality.

Keywords. Sepsis, estimated Plasma Volume Status(ePVS), Fluid Resuscitation, in-hospital mortality, length of hospital stay, use of vasopressors/inotropes

Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis is associated with severe endothelial cell dysfunction leading to dysregulation of hemostasis and vascular reactivity, as well as tissue edema.[2] The true incidence of sepsis in low- and middle-income countries is uncertain due to limited data and underreporting, with infectious diseases contributing significantly to higher

mortality.[3], [4] Even with prompt identification and suitable early management within hours of sepsis onset, existing epidemiological data indicate that sepsis remains a sub

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stantial burden in all economic region. The early administration of fluid therapy may offer benefits during the initial stages of sepsis but when administered at a later stage, it may not be effective in resolving microcirculatory abnormalities induced by sepsis and certain studies have indicated that a positive fluid balance could be linked to a less favorable prognosis.[5], [6], [7] Therefore, assessing the volume status of patients is crucial for the management of sepsis

There are various tools for assessing a patient's volume status, but many rely on invasive or non-invasive techniques that may not be easily accessible in emergency rooms, particularly in developing countries.[5], [8] Therapeutic interventions for suspected hypovolemia in the emergency department are often performed without an accurate assessment of the patient's plasma volume.[9], [10], [11], [12] Since the balance between microcirculatory endothelial function and interstitial hydration is tightly regulated, measuring these parameters could help detect disruptions, indicating potential volume overload or an inability to adequately respond to fluid administration.[13], [14]

In recent times, Duarte et al. introduced a method for estimating plasma volume using a straightforward formula based on hematocrit and hemoglobin levels, aimed at evaluating congestion in patients with heart failure.[15] Prior research findings have indicated an association between an elevated estimated plasma volume status (ePVS) and an unfavorable outcome for patients with heart failure (HF) and myocardial infarction.[16] ePVS remains underutilized, as indicated by the scarcity of studies investigating its use in assessing septic patients in the emergency room setting, particularly in developing countries where no studies have been conducted.[17], [18], [19] Therefore, a prospective cohort study was conducted to evaluate the predictive potential of ePVS in patients with sepsis at the time of their initial admission to the emergency room.

Significance of the Study

A crucial principle in the management of septic patients is the requirement for a comprehensive initial assessment. Patients with sepsis would require prompt antibiotic therapy, use of vasopressors, control of infection and fluid resuscitation. However, it is essential to strike a balance between providing fluids and the potential dangers of fluid accumulation, previous studies have suggested fluid overload has increased mortality among patients with sepsis. Therefore, assessing volume status prior to initial resuscitation is crucial. This study aims to offer an objective method for evaluating patient volume status, which aims to streamline fluid resuscitation according to patient's volume status.

Research Question

What is the prognostic significance of estimated plasma volume status (ePVS) concerning the in-hospital mortality in septic adult patients at the Emergency Room?

Objectives

General Objectives

To determine the prognostic significance of ePVS on in-hospital mortality in patients with sepsis in the emergency room.

Specific Objectives

1. To describe and compare the baseline clinical characteristics of the survivor and non-survivor population and as to:
 - a. Demographics
 - i. Age
 - ii. Sex
 - b. Comorbidities
 - i. Hypertension
 - ii. Diabetes Mellitus
 - iii. Chronic Kidney Disease
 - iv. Chronic Heart Failure
 - v. Stroke
 - vi. Active Tumors
 - vii. Charlson Comorbidity Index
 - c. Vital Signs
 - i. Systolic Blood Pressure
 - ii. Diastolic Blood Pressure
 - iii. Respiratory Rate
 - iv. Heart Rate
 - v. Oxygen Saturation
 - vi. Temperature
 - vii. Septic Shock
 - d. Predictive Ability Scoring
 - i. Modified Sequential Organ Failure Assessment (SOFA)
 - ii. National Early Warning Score (NEWS)
 - iii. Acute Physiology and Chronic Health Evaluation II (APACHE II)
2. To describe and compare the laboratory results of the survivor and non-survivor population.
 - a. Hemoglobin

- b. Hematocrit
 - c. estimated plasma volume status (ePVS) (dl/g)
 - d. White Blood Cell (WBC)
 - e. Absolute Neutrophil Count (ANC)
 - f. Platelets
 - g. Creatinine
 - h. estimated Glomerular Filtration Rate (eGFR)
- 3. To compare and describe the survivor versus non-survivor population as to treatment.
 - a. Need for Mechanical Ventilation
 - b. Need for Vasopressors and/or Inotropic drugs.
- 4. To determine the in-hospital mortality of the patients admitted with sepsis and septic shock.
- 5. To determine factors associated with in-hospital mortality in patients with sepsis and septic shock.
- 6. To compare the performance of ePVS in predicting in-hospital mortality versus that of the following scoring:
 - i. Modified Sequential Organ Failure Assessment (MSOFA)
 - ii. National Early Warning Score (NEWS)
 - iii. Acute Physiology and Chronic Health Evaluation II (APACHE II)
- 7. To determine if estimated plasma volume status is associated with the following parameters:
 - a. Demographics
 - i. Age
 - ii. Sex
 - b. Vital Signs
 - i. Systolic Blood Pressure
 - ii. Diastolic Blood Pressure
 - iii. Respiratory Rate
 - iv. Heart Rate
 - v. Oxygen Saturation
 - vi. Temperature
 - c. Blood Test
 - i. Hemoglobin
 - ii. Hematocrit
 - iii. estimated plasma volume status (ePVS) (dl/g)
 - iv. White Blood Cell (WBC)
 - v. Absolute Neutrophil Count (ANC)
 - vi. Platelets
 - vii. Creatinine
 - viii. estimated Glomerular Filtration Rate (eGFR)
 - d. Septic Shock
 - e. Effect of Intravenous Fluid Resuscitation for 24 hours
 - f. Need for mechanical ventilation
 - g. Need for vasopressors or inotropic agents
 - h. Length of Hospital Admission

C. Prespecified Hypothesis

1. We hypothesized that higher estimated plasma volume status (ePVS) on emergency department admission is independently associated with increased in-hospital mortality among septic patients.

We further hypothesized that ePVS has comparable or superior predictive performance for in-hospital mortality compared with established severity scoring systems, including MSOFA, NEWS, and APACHE II

Review of Related Literature

Sepsis is a common condition that is associated with unacceptably high mortality and, for many of those who survive, long-term morbidity.[20] In most developed countries, severe sepsis and septic shock account for disproportionate mortality and resource utilization. There are no population-level estimates of sepsis incidence from lower-income countries, leading to an inadequate understanding of the true burden of the disease in these regions[3], [4]

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[21] Fluid resuscitation is a vital aspect of early sepsis management, aimed at restoring hemodynamic stability and improving tissue perfusion in patients with septic shock or severe sepsis. However, finding the right balance in fluid administration is challenging, and the approach has evolved over time with new evidence and insights.[7], [22], [23]

Plasma volume represents the fluid within the intravascular compartment and serves as an indicator of fluid volume overload.[24] There are several methods to appraise volume status but none without limitations.[25] Accurate methods require sophisticated test and are expensive.[26] Duarte et al have recently proposed a

method to gauge plasma volume using a simple formula based on hematocrit and hemoglobin levels, allowing for an estimation of congestion severity in heart failure patients. This estimation, known as estimated plasma volume status (ePVS), can be easily determined during the initial complete blood count (CBC). Notably, their research revealed an independent association between ePVS and cardiovascular outcomes, rehospitalization, as well as mortality in individuals with heart failure (HF).[15]

In a separate investigation conducted by Jun Chen and colleagues, which encompassed 1,534 eligible participants (1,004 males and 530 females) with an average age of 67.36 ± 0.36 years who had experienced acute myocardial infarction (AMI), it was observed that elevated ePVS values, determined through the straightforward calculation using Duarte's formula (based on hemoglobin and hematocrit), were correlated with unfavorable outcomes among AMI patients. This indicates that ePVS can serve as a predictive factor for in-hospital mortality in AMI cases, potentially enhancing the precision of risk stratification[16]

In a retrospective analysis conducted by Turcato et al, encompassing 1,502 patients who presented with fever at the Emergency Department (ED), ePVS, derived from the initial blood count's hemoglobin and hematocrit measurements, was found to be independently linked to in-hospital mortality. This association persisted even after accounting for various patient history, clinical, and laboratory factors through multivariate adjustment.[27]

Recent research, including a study from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, found a J-shaped relationship between ePVS and mortality in patients with septic shock. In this retrospective cohort study, patients with an ePVS value exceeding 6.52 dL/g had a significantly increased risk of 28-day and 90-day mortality. The study highlighted the potential of ePVS as an independent predictor of mortality, even after adjusting for variables such as severity scores, age, and comorbidities[19].

Several studies have shown that elevated ePVS is associated with higher mortality in sepsis patients. For instance, Kim et al. (2022) conducted a study on 100 sepsis patients admitted to the ICU and found that ePVS was significantly associated with in-hospital mortality. The study reported that patients with higher ePVS (>7.09 dL/g) had a mortality rate of 61.7%, compared to 34.0% in patients with lower ePVS values. [17] Similarly, Turcato et al. (2023) demonstrated that ePVS was an independent risk factor for in-hospital mortality in septic patients in the emergency department using the mean cut off (5.28 g/dL). ePVS can have prognostic value also in patients at lower apparent risk (APACHE < 12). Their findings suggest that ePVS can be particularly valuable for risk stratification in patients with less severe clinical presentations where traditional tools may fall short.[18] Nevertheless, elevated estimated plasma volume status (ePVS) is consistently correlated with increased mortality and poor prognosis on every studies.

Operational Definition of Terms

1. Estimated Plasma Volume Status: is a clinical measurement used to estimate the volume of plasma, the liquid component of blood, in an individual's circulatory system. It is typically determined based on hematocrit and hemoglobin levels, which are components of a complete blood count (CBC) or blood test.

$$\text{Duarte Formula: } ePVS \left(\frac{dL}{g} \right) = \frac{100 - Hct (\%)}{Hgb (g/dL)}$$

2. Sepsis: we define sepsis on a specific criteria in which there is an evidence of infection (Infiltrates/Abscess on Chest X-Ray/CT Scan/MRI/Ultrasound, Urine Culture positive or positive culture from any site) and met two or more systemic inflammatory response syndrome (SIRS) criteria as recommended by Surviving Sepsis guidelines 2021; core temperature $< 36.0^{\circ}\text{C}$ or $> 38.0^{\circ}\text{C}$, heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute or partial pressure of arterial carbon dioxide < 32 mm Hg or the requirement for invasive mechanical ventilation for an acute process, white cell count $> 12.0 \times 10^9 /\text{L}$ or $< 4.0 \times 10^9 /\text{L}$ or $> 10\%$ immature band forms.
3. Hemodynamic Instability: inability to maintain stable blood pressure (MAP > 65), heart rate (< 60 bpm or > 100 bpm), and organ perfusion (decreased urine output $< 0.5\text{cc/kg/hr.}$, decreased sensorium and cold and clammy extremities).
4. Septic shock: a severe form of sepsis in which there is hemodynamic instability requiring vasopressor or inotropic support to maintain stable blood pressure (MAP > 65).
5. Total 24-hour fluids: cumulative fluid resuscitation during the first 24 hours of hospital admission including oral and IV fluid resuscitation.
6. Vasopressors: Characterized by the administration of norepinephrine or vasopressin via intravenous route with computation of actual doses to maintain hemodynamic stability.
7. Inotropes: Characterized by the administration of dobutamine via intravenous route with computation of actual doses to maintain hemodynamic stability.
8. MSOFA (Modified Sequential Organ Failure Assessment) - is an adapted version of the original SOFA score, used to assess the extent of organ dysfunction in critically ill patients, particularly those with sepsis. The MSOFA score evaluates the function of multiple organ systems (such as respiratory, cardiovascular, liver, coagulation, renal, and neurological systems) to provide a quantifiable measure of a patient's condition. The modification often involves simplifying or adjusting criteria to enhance its applicability in specific clinical settings, such as in emergency departments or resource-limited environments, while maintaining its core function of predicting patient outcomes. [28], [29]

9. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score - is a severity-of-disease classification system widely used in intensive care units (ICUs). It assesses the severity of illness in critically ill patients by combining acute physiological measurements (such as body temperature, blood pressure, and respiratory function), age, and the presence of chronic health conditions.
10. The National Early Warning Score (NEWS) - is a clinical tool used to assess the severity of illness in patients by monitoring key vital signs. It is widely used in emergency departments and hospital wards to detect patients at risk of deterioration.
11. Charlson Comorbidity Index - a weighted index to predict risk of death within 1 year of hospitalization for patients with specific comorbid conditions. Nineteen conditions were included in the index.
12. In-hospital Mortality - a death occurring within 30 days of hospitalization due to sepsis or septic shock and its complications.
13. Length of Hospital Stay - total number of days of admission in the hospital.

Methodology

Research Design and Locale

Prospective, single center cohort study examining the association between estimated plasma volume and in-hospital mortality in patients admitted with sepsis. It was conducted in Perpetual Succour Hospital - Emergency Room, covering a period of 5 months, from March 1, 2024 to July 31, 2024.

Study Setting

Perpetual Succour Hospital, Cebu City, Philippines

Research Subjects

This study included patients aged 18 years and above who presented at the Emergency Room with sepsis. Sepsis screening utilized suspected or documented infection along with ≥ 2 systemic inflammatory response syndrome (SIRS) criteria, as recommended by the Surviving Sepsis Guidelines 2021 for the use of a single screening tool.

Inclusion Criteria

Patients aged 18 years and above who initially presented with a known or presumed infection and met two or more of the systemic inflammatory response syndrome (SIRS) criteria:

- i. Core temperature $< 36.0^{\circ}\text{C}$ or $> 38.0^{\circ}\text{C}$
- ii. Heart rate > 90 beats per minute
- iii. Respiratory rate > 20 breaths per minute, partial pressure of arterial carbon dioxide < 32 mm Hg, or the requirement for invasive mechanical ventilation for an acute process

- iv) White cell count $> 12.0 \times 10^9/\text{L}$ or $< 4.0 \times 10^9/\text{L}$, or $> 10\%$ immature band forms

Exclusion Criteria

Hemodynamic instability due to active bleeding, as assessed by the emergency physician.

- i. Death deemed imminent and inevitable within < 24 hours. Defined by the presence of any of the following: (a) documented comfort-care or do-not-resuscitate (DNR) status on admission; (b) refractory shock despite maximal vasopressor support.
- ii. In-patient transfer from or to another acute health care facility.
- iii. Confirmed or suspected pregnancy.
- iv. Infection resulting from recent surgery or trauma.
- v. Patient who left against medical advice, preventing determination of outcomes.
- vi. Lack of evidence of infection upon review of laboratory results taken at the ER during the hospital stay, including no radiologic evidence of infection (e.g., no infiltrates on chest X-ray or abscess on CT scan, MRI or Ultrasound), and no positive culture from any site.

Data Collection Procedures

A request for approval was sent to both the Hospital's Institutional Ethics and Review Board (IERB) and the head of the emergency department before the study was initiated. Patients who met the inclusion criteria were asked to provide their consent after a comprehensive verbal explanation of the informed consent form, which was presented in easily understandable language to the patient and/or their legal guardian. Once informed consent was obtained, the data collection process commenced.

Upon admission, each patient with suspected infection underwent a detailed clinical evaluation, during which demographic data such as age, sex, medical history, systolic and diastolic blood pressure, respiratory rate, heart rate, oxygen saturation, and cognitive status were recorded.

Patients were included if they had relevant lab results available, specifically a complete blood count (CBC), arterial blood gas (ABG), serum sodium (Na), potassium (K), and creatinine (Crea). In addition, other laboratory tests aimed at identifying the source of infection, including blood cultures, urine analysis, imaging studies (e.g., chest X-ray, ultrasound), and cultures from other relevant sites, were performed as part of the diagnostic workup.

The estimated plasma volume status (ePVS) was determined using hematocrit (Ht) and hemoglobin (Hb) values obtained from the complete blood count performed when the patient arrived in the ER. The ePVS value was calculated using the following formula.

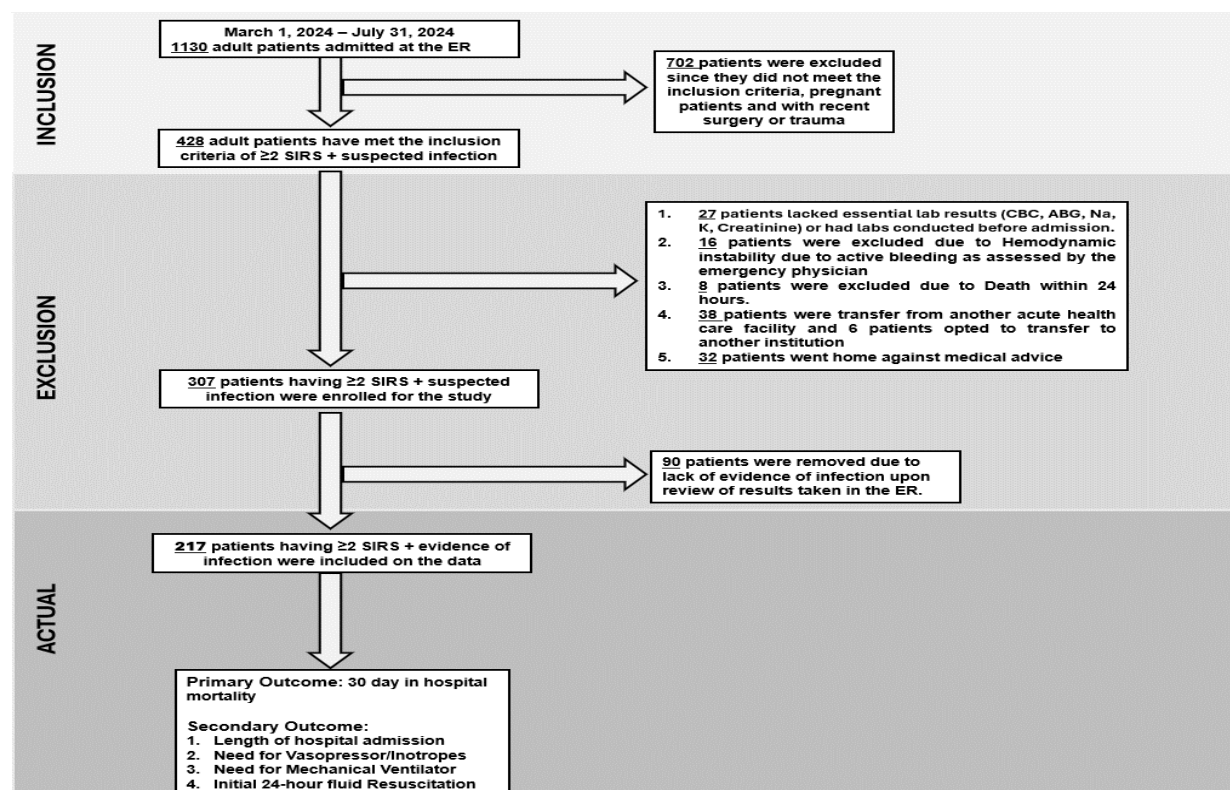
$$\text{Formula: } ePVS \left(\frac{dL}{g} \right) = \frac{100 - Hct (\%)}{Hgb (g/dL)}$$

Complete blood counts were processed using the Cell-Dyn Ruby Hematology Analyzer (Abbott U.S.)

To further assess the severity of sepsis and overall patient condition, the Charlson Comorbidity Index (CCI), Modified Sequential Organ Failure Assessment (MSOFA), National Early Warning Score (NEWS), and Acute Physiology and Chronic Health Evaluation II (APACHE II) were recorded. By the conclusion of the emergency room visit, sepsis was confirmed based on

documented evidence, including laboratory findings (e.g., blood cultures, urinalysis), imaging studies such as chest X-ray or ultrasound, and other diagnostic criteria indicative of infection, ensuring patient eligibility for enrollment in the study. A thorough review of official laboratory results and cultures obtained in the ER was conducted throughout the patient's admission to verify evidence of infection.

Flow Chart of Data Collection



Data Processing and Statistical Analysis

Sample Size Determination

The sample size for this study was calculated to ensure adequate statistical power for multivariate regression analysis. Since the study involves two multivariate models, the calculation was based on the model with the largest number of predictors to ensure that both models were sufficiently powered. The formula used was:

$$N = \frac{L}{f^2} + k + 1$$

N: is the total sample size,

L: is the critical value for the desired statistical power and significance level,

f^2 : is the effect size, and

k: is the number of predictors in the model.

For this study, the critical value (L) was set at 13.81, corresponding to 95% statistical power and a significance level of 0.01. A medium effect size ($f^2=0.15$) was chosen based on Cohen's guidelines, reflecting a moderate relationship between predictors and the outcome variable. The total number of predictor variables (k) included in the multivariate regression model was 13. Substituting these values into the formula:

$$N = \frac{13.81}{0.15} + 13 + 1$$

Thus, the minimum required sample size was calculated to be 107 patients. The actual sample size of 217 patients exceeded this requirement, providing robust statistical power to detect medium-sized effects in the analysis.

Statistical analysis

Data were analyzed using both descriptive and inferential statistics. Continuous variables such as age, systolic and

diastolic blood pressures, respiratory rate, heart rate, hemoglobin, and estimated plasma volume status (ePVS) values were summarized as means with standard deviations (SD) for normally distributed data or medians with interquartile ranges (IQR) for non-normally distributed data. Dichotomization was performed using an optimal cutoff value derived in a data-driven manner from receiver operating characteristic analysis. The cutoff of 5.37 dL/g was selected using Youden's J index to maximize the combined sensitivity and specificity for in-hospital mortality. Categorical variables, including comorbidities, presence of septic shock, and mechanical ventilation or vasopressor use, were presented as frequencies and percentages.

Comparisons between survivors and non-survivors were conducted using the independent t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. The Chi-square test or Fisher's exact test was used for comparing categorical variables.

Receiver operating characteristic (ROC) curves were generated to assess the predictive accuracy of ePVS, MSOFA, NEWS, and APACHE II scores for in-hospital mortality. The area under the curve (AUC) was calculated for each scoring system, with statistical significance set at $p < 0.05$. Cut off values sensitivity and specificity were taken using Youden's J Statistics

Univariate logistic and linear regression analysis was performed to identify potential risk factors for in-hospital mortality, including ePVS, age, presence of septic shock, comorbidities, and the use of mechanical ventilation or vasopressors. Variables found to be significant in univariate analysis were further evaluated in a multivariate logistic regression model to identify independent predictors of mortality. Odds ratios (OR) with 95% confidence intervals (CI) were reported for both univariate and multivariate analyses. Violin plots with box plot overlays were employed to visualize the distribution of ePVS values and their association with clinical outcomes, specifically comparing survivors and non-survivors.

The primary exposure was estimated plasma volume status (ePVS), and the primary outcome was in-hospital mortality. Potential confounders included age, sex, comorbidities (hypertension, diabetes mellitus, chronic kidney disease), source of infection, presence of septic shock, and severity scores (MSOFA, NEWS, and APACHE II).

These variables were selected a priori based on clinical relevance and prior literature demonstrating their association with sepsis-related mortality. No subgroup or interaction analyses were performed. Some laboratory variables required for severity score computation, including arterial blood gas parameters, serum sodium, and potassium, were missing for a subset of patients. Analyses involving severity scores were therefore performed using complete-case analysis.

Sensitivity analyses were not performed and represent an area for future validation.

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY), and statistical significance was defined as $p < 0.05$.

Ethical Considerations

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and the National Ethical Guidelines for Health and Health-related Research (2017). Prior to the initiation of the study, the protocol was reviewed and approved by the Research Ethics Committee (REC) of Perpetual Succour Hospital. Permission to conduct the research was also obtained from the hospital's CEO and the Head of the Emergency Room.

Informed consent, both written and verbal, was obtained from all patients, ensuring the use of a language they could clearly understand. The researcher ensured that all information about the participants was treated with strict confidentiality, and no patient names or identifiable information were included in the data collection. Excel sheets used for data processing did not contain any personal identifiers, and only the researcher and the biostatistician had sole access to the collected data.

Utmost confidentiality was maintained throughout the study, and all data were securely deleted upon completion of the research. This paper is self-funded and not supported by any drug company or individual with a vested interest in the results of the study. The study was conducted as part of the residency compliance requirements of the hospital.

Results

Baseline Characteristics (Table 1)

A total of 307 patients with suspected sepsis were admitted to the Emergency Room from March to July 2024. Among them, 217 met the inclusion criteria and were enrolled in the study. Patients were excluded due to lack of evidence of infection on evaluation or leaving against medical advice prior to completion of assessment. All patients fulfilled the SIRS criteria as recommended by surviving sepsis guidelines 2021 with evidence of infection. Patients were followed up weekly for in-hospital outcomes for up to 30 days from admission. Table 1 presents the baseline characteristics of survivors and non-survivors. Laboratory variables required for severity score computation, including arterial blood gas parameters, serum sodium, and potassium levels, were missing for a subset of patients; all other baseline variables were complete.

The mean age of the study population was 62.35 (SD 18.64), with slightly more men 118 (54.38%) than women 99 (45.62%). There were no significant differences in age or sex between survivors and non-survivors ($p = 0.368$ and $p = 0.454$, respectively). The most common comorbidities were hypertension 155 (71.43%) and Diabetes Mellitus 95 (43.78%) with similar distributions

between survivors and non-survivors. However, non-survivors had significantly higher Charlson Comorbidity Index scores than survivors (6.38 ± 2.39 vs. 4.03 ± 2.57 , $p < 0.001$), indicating a greater burden of chronic illness. Septic Shock was diagnosed in 44 (20.28) patients and was significantly higher in non-survivor (55.88%, $p < 0.001$).

The mean severity scores, including MSOFA, NEWS, and APACHE II, were significantly higher in non-survivors compared to survivors ($p < 0.001$ for all three in the emergency room, while 54 patients (24.88%) required vasopressors or inotropic support. These interventions were significantly more common among non-survivors than survivors ($p < 0.001$ for both mechanical ventilation and vasopressors/inotropes).

Laboratory findings showed that non-survivors had significantly lower hemoglobin levels (11.20 ± 2.74 g/dL $p = 0.014$) and hematocrit levels ($34.14 \pm 8.39\%$ $p = 0.013$) compared to survivors. The estimated plasma volume status (ePVS) was also significantly higher in non-survivors (6.47 ± 2.5 dL/g) compared to survivors (5.17 ± 1.46 dL/g, $p = 0.007$). Mortality was higher among patients with elevated ePVS compared with those with lower ePVS, corresponding to an absolute risk difference in in-hospital mortality between groups. Elevated ePVS indicates increased plasma volume, suggesting a correlation with worse outcomes.

Table 1. Baseline Characteristics, Clinical Parameters, and Outcomes of Patients According to Survival Status

Variable	Total (N=217)	Survivor (n=183)	Non-Survivor (n=34)	p-value
Age, years, mean (SD)	62.35 (18.64)	61.88 (18.89)	64.85 (17.25)	0.368
Sex, n (%)				0.454
Male	118 (54.38)	96 (52.46)	21 (61.76)	
Female	99 (45.62)	86 (46.99)	13 (38.24)	
Baseline characteristics, n (%)				
Hypertension	155 (71.43)	131 (71.58)	24 (70.59)	0.898
Diabetes Mellitus	95 (43.78)	81 (44.26)	14 (41.18)	0.851
Chronic kidney failure	34 (15.67)	30 (16.39)	4 (11.76)	0.614
Chronic heart failure	38 (17.51)	32 (17.49)	6 (17.65)	1.000
Stroke or transient ischemic attack	27 (12.44)	21 (11.48)	6 (17.65)	0.393
Active tumor	42 (19.35)	24 (13.11)	18 (52.94)	1.21*
Charlson Comorbidity Index, mean (SD)	4.40 (2.68)	4.03 (2.57)	6.38 (2.39)	<0.001
Viral parameters				
Systolic blood pressure, mean (SD)	113.96 (26.72)	116.89 (24.51)	98.24 (32.52)	0.003

Diastolic blood pressure, mean (SD)	69.03 (17.89)	71.31 (14.58)	56.76 (27.16)	0.004
Respiratory rate, mean (SD)	24.98 (5.06)	24.41 (4.79)	28.06 (5.42)	0.001
Heart rate, median (IQR)	103 (91.0–115.0)	102 (90.0–114.0)	105 (93.75–116.5)	0.202
Peripheral oxygen saturation, median (IQR)	97 (94.0–98.0)	97 (95.0–99.0)	94.5 (89.5–97.0)	0.013
Temperature, median (IQR)	36.9 (36.5–38.1)	36.9 (36.5–38.1)	36.7 (36.32–38.1)	0.200
Septic shock, n (%)	44 (20.28)	25 (13.66)	19 (55.88)	<0.001
Blood tests				
Hemoglobin, g/dL, mean (SD)	12.34 (2.28)	12.56 (2.13)	11.20 (2.74)	0.014
Hematocrit, %, mean (SD)	37.47 (6.93)	38.09 (6.46)	34.14 (8.39)	0.013
EPVS dL/g, mean (SD)	5.37 (1.74)	5.17 (1.46)	6.47 (2.57)	0.007
White blood cell count, median (IQR)	13.71 (9.02–18.26)	13.7 (9.16–18.04)	14.68 (8.74–19.06)	0.279
ANC, mean (SD)	12.38 (7.86)	12.23 (7.23)	13.21 (10.74)	0.613
Platelets, median (IQR)	215 (156.0 – 302.0)	221 (157.5 – 310.5)	188 (120.25 – 272.75)	0.254
Creatinine, mean (SD)	1.77 (1.44)	1.76 (1.45)	1.86 (1.40)	0.714
eGFR, mean (SD)	57.21 (33.13)	56.78 (32.70)	59.5 (35.76)	0.682
Vasopressor/inotrope use at ER, n (%)	54 (24.88)	33 (18.03)	21 (61.76)	<0.001
Mechanical ventilator use at ER, n (%)	20 (9.22)	10 (5.46)	10 (29.41)	<0.001

SD = Standard Deviation, IQR = interquartile range, MSOFA = Modified Sequential Organ Failure Assessment, NEWS = National Early Warning Score, APACHE = Acute Physiology and Chronic Health Evaluation II, EPVS = estimated plasma volume status, EGFR = estimated glomerular filtration rate, ER = emergency room

Predictive Accuracy of ePVS. (Figure 1)

Receiver operating characteristic (ROC) curves were generated to compare the predictive accuracy of ePVS with other scoring systems, including the Modified Sequential Organ Failure Assessment (MSOFA), National Early Warning Score (NEWS), and Acute Physiology and Chronic Health Evaluation II (APACHE II). Figure 1 shows that MSOFA and APACHE II had the highest predictive accuracy for in-hospital mortality, with areas under the curve (AUC) of 0.78 (95% CI 0.69–0.86) and 0.79 (95% CI 0.72–0.85), respectively. NEWS had moderate predictive accuracy, with an AUC of 0.75 (95% CI 0.65–0.84).

ePVS had an AUC of 0.63 (95% CI 0.51-0.74), with a sensitivity of 58.82% and specificity of 64.48% at a cut-off value of 5.37 dL/g. While ePVS had lower predictive accuracy compared to MSOFA and APACHE II, it remains a significant predictor ($p < 0.001$) and could serve as an easily accessible tool in settings where more complex scoring systems may not be available.

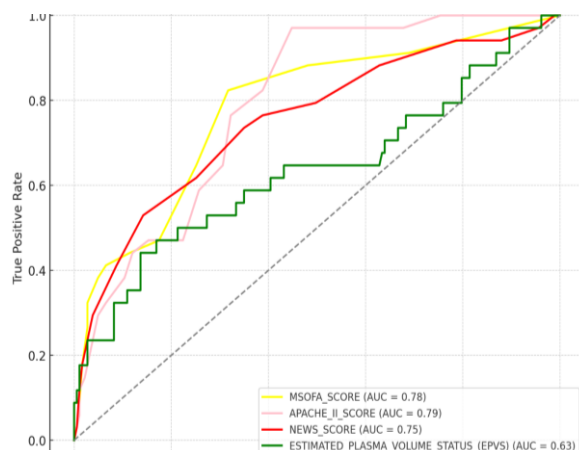


Figure 1. Comparison of receiver operating characteristics curves of ePVS, MSOFA, NEWS and APACHE II for predicting in-hospital mortality in patients with sepsis at Emergency Room. ePVS = estimated plasma volume status, MSOFA = Modified Sequential Organ Failure Assessment, NEWS = National Early Warning Score, APACHE II = Acute Physiology and Chronic Health Evaluation

Table 2. Baseline Characteristics and Clinical Outcomes According to ePVS Category

Variable	ePVS < 5.37	ePVS ≥ 5.37	p-value
Age, years, mean (SD)	61.52 (20.14)	63.62 (16.07)	0.396
Sex, n (%)			0.299
Male	76 (57.58)	42 (49.41)	
Female	56 (42.42)	43 (50.59)	
Vital parameters			
Systolic blood pressure, mean (SD)	116.82 (26.62)	109.53 (26.41)	0.049
Diastolic blood pressure, mean (SD)	71.21 (18.33)	65.65 (16.72)	0.022
Respiratory rate, mean (SD)	25.23 (5.11)	24.59 (4.99)	0.357
Heart rate, mean (SD)	101.58 (18.61)	103.53 (18.13)	0.446
Peripheral oxygen saturation, median (IQR)	97 (94.75-99.0)	97 (94.0-98.0)	0.912
Temperature, median (IQR)	36.8 (36.4-38.1)	37.0 (36.6-38.2)	0.236
MSOFA score, mean (SD)	2.48 (3.03)	3.38 (3.47)	0.052
NEWS score, mean (SD)	6.42 (3.36)	6.84 (3.67)	0.407
APACHE score, mean (SD)	10.93 (6.00)	14.35 (5.91)	<0.001
Blood tests			
Hemoglobin, g/dL, mean (SD)	13.79 (1.45)	10.10 (1.32)	<0.001
Hematocrit, %, mean (SD)	41.86 (4.32)	30.64 (4.09)	<0.001

Leukocytes, median (IQR)	13.71 (9.60-18.55)	14.0 (8.24-18.07)	0.433
ANC, mean (SD)	12.56 (7.44)	12.11 (8.51)	0.691
Platelets, median (IQR)	218.5 (155.75-295.25)	206 (157.0-326.0)	0.500
Creatinine, mean (SD)	1.54 (1.02)	2.66 (3.71)	0.007
EGFR, mean (SD)	61.28 (30.66)	50.48 (36.36)	0.025
Septic shock, n (%)	20 (15.15)	24 (28.24)	0.056
Vasopressor use at ER, n (%)	18 (13.64)	20 (23.53)	0.091
Inotropes use at ER, n (%)	6 (4.55)	2 (2.35)	0.640
Length of hospital stay, median (IQR)	7 (5.0-11.0)	8 (5.0-12.0)	0.033
In-hospital mortality, n (%)	10.61 (30.91)	23.53 (42.67)	0.010

SD = Standard Deviation, IQR = interquartile range, MSOFA = Modified Sequential Organ Failure Assessment, NEWS = National Early Warning Score, APACHE = Acute Physiology and Chronic Health Evaluation II, EPVS = estimated plasma volume status, EGFR = estimated glomerular filtration rate, ANC = Absolute neutrophil count, ER = Emergency Room

Clinical determinants and performance of ePVS (Table 2 and Table 3)

Table 2 shows patient outcomes according to the cut-off ePVS values. Patients with ePVS >5.37 dL/g had a significantly prolonged hospital stay, with a median length of stay of 8 days (IQR, 5.0-12.0, $p = 0.033$). These patients also had a higher in-hospital mortality rate of 23.53% (SD, 42.67%) compared to 10.61% (SD, 30.91%) in patients with ePVS <5.37 dL/g. APACHE score was significantly correlated with higher ePVS values ($p < 0.001$). Creatinine levels were significantly higher in patients with high ePVS, with a mean value of 2.77 dL/g (SD, 3.71, $p = 0.007$). Linear Multivariate

Regression shown in Table 3 demonstrated a significant clinical correlation with APACHE II score (OR 1.02, 95% CI: 1.00-1.03, $p = 0.017$), indicating that higher ePVS is associated with patients at higher risk, as reflected by their APACHE II scores. Creatinine levels were also significantly correlated (OR 1.60, 95% CI: 1.02-2.50, $p = 0.041$), suggesting that elevated plasma volume may be linked to renal impairment. However, the length of hospital stay lost its significance when adjusted for other variables, indicating that its effect is likely influenced by the presence of other clinical factors.

Risk Factors associated with in-hospital mortality (Table 4)

Logistic regression analysis of clinical parameters and fluid resuscitation for evaluating the risk factors associated with in-hospital mortality in patients with sepsis shown in Table 4. The increase in total fluids resuscitation within 24 hours and higher ePVS at the emergency room was independently associated with in-hospital mortality by univariate analysis (crude OR, 1.0003; 95% CI, 1.0001-1.005; $p = 0.017$ and crude OR,

1.45, 95% CI, 1.19-1.77; $p = <0.001$, respectively). Other independent risk factors for in-hospital mortality includes presence of septic shock, Higher Charlson Comorbidity Index, low systolic and diastolic blood pressure, higher respiratory rate, lower peripheral O₂ saturation, high MSOFA, NEWS and APACHE score, use of vasopressors/inotropes and use of mechanical ventilator.

After adjusting for potential confounding factors, higher ePVS, increased fluid resuscitation within 24 hours, higher comorbidity index and higher respiratory rate remained independently associated with in-hospital mortality ($p = 0.002$, $p = 0.017$, $p <0.001$ and $p <0.001$, respectively) suggesting these factors are important in predicting mortality in septic patients.

Table 3. Linear regression analysis for clinical determinants of ePVS

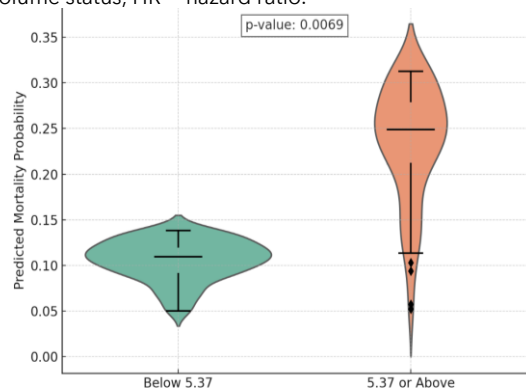
Variables	Univariate Analysis				Multivariate Analysis			
	Crude OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Systolic Blood Pressure	0.99	0.98	1.00	0.033	–	–	–	–
Diastolic Blood Pressure	0.9825	0.9671	0.9982	0.022	–	–	–	–
APACHE II Score	1.0998	1.0466	1.1556	<0.001	1.02	1.00	1.03	0.017
Hematocrit Day 1	0.105	0.0367	0.300	<0.001	0.06	0.013	0.272	0.001
MSOFA Score	1.3661	1.1146	1.6741	0.020	–	–	–	–
Creatinine	1.3616	1.0828	1.7127	0.008	1.596	1.019	2.500	0.041
Length of Hospital Stay	0.97	0.96	0.99	0.006	–	–	–	–
Presence of Septic Shock	1.03	0.95	1.12	0.527	–	–	–	–

CI = Confidence Interval, OR = odds ratio, BP = Blood Pressure MSOFA = Modified Sequential Organ Failure Assessment, APACHE = Acute Physiology and Chronic Health Evaluation II, ePVS = estimated plasma volume status

Table 4. Logistic regression analysis for in-hospital mortality

Variables	Univariate Analysis				Multivariate Analysis			
	Crude OR	Lower 95% CI	Upper 95% CI	p-value	Adjusted OR	Lower 95% CI	Upper 95% CI	p-value
Septic Shock	8.01	3.61	17.77	<0.001	1.88	0.16	22.31	0.619
Charlson Comorbidity Index	1.45	1.23	1.71	<0.001	1.58	1.23	2.02	0.0003
Systolic BP	0.97	0.96	0.99	<0.001	1.01	0.97	1.04	0.683
Diastolic BP	0.96	0.94	0.98	<0.001	0.97	0.93	1.02	0.259
Respiratory Rate	1.13	1.06	1.22	<0.001	1.14	1.01	1.29	0.036
Peripheral O ₂ Saturation	0.94	0.90	0.98	0.003	1.00	0.94	1.06	0.923
MSOFA Score	1.36	1.21	1.52	<0.001	0.99	0.78	1.25	0.934
ePVS	1.45	1.19	1.77	<0.001	1.50	1.15	1.95	0.002
APACHE II Score	1.17	1.10	1.24	<0.001	0.93	0.83	1.07	0.243
Vasopressor/Inotropes	7.71	3.43	17.37	<0.001	2.00	0.15	25.75	0.597
Mechanical Ventilator Use	7.21	2.72	19.11	<0.001	4.11	0.78	21.77	0.097
Total Fluids (24 Hours)	1.0003	1.0001	1.0005	0.017	1.0004	1.0000	1.0008	0.030

Figure 2. Overlay of Box Plot and Violin Plot Showing Predicted In-Hospital Mortality Probability divided between above and below cut-off ePVS value (5.37 dL/g). ePVS = estimated plasma volume status, HR = hazard ratio.



Predicted Mortality and Hazard Ratio (Figure 2)

The violin and box plot overlay in Figure 2 shows a significant difference in predicted in-hospital mortality between patients with ePVS values below and above 5.37 dL/g. Patients with ePVS < 5.37 dL/g had a median predicted mortality of 0.11 (IQR 0.091-0.120), while those with ePVS ≥ 5.37 dL/g had a higher median predicted mortality of 0.25 (IQR 0.212-0.280).

The hazard ratio of 2.84 and a p-value of 0.0069 indicate that patients with ePVS ≥ 5.37 dL/g are nearly three times more likely to experience in-hospital mortality compared to those with lower ePVS values. This demonstrates the significant impact of elevated ePVS on patient outcomes.

Discussion

The study assessed the predictive value of estimated Plasma Volume Status (ePVS) in septic patients, correlating it with in-hospital mortality, association with 24 hours fluid resuscitation and other critical outcomes such as the need for mechanical ventilation, vasopressor use, and length of stay in the hospital. The results demonstrated that higher ePVS values were significantly associated with worse outcomes, including higher mortality rates and it is independently correlated with increased length of hospital stay.

Sepsis remains a significant healthcare burden globally, especially in low- and middle-income countries where its true incidence may be underreported due to limited data and resource constraints.[3],[4] Fluid resuscitation is a cornerstone of sepsis management aimed at restoring hemodynamic stability; however, recent studies have shown that fluid overload, particularly in the later stages of sepsis, can worsen outcomes, making accurate plasma volume assessment critical for treatment.[5],[7],[8]

Plasma volume represents the fluid within the intravascular compartment and serves as an indicator of fluid volume overload.[24] There are several methods to appraise volume status but none without limitations.[25] Accurate methods require sophisticated test and are expensive.[26]

Previous research has demonstrated the prognostic significance of ePVS in conditions such as heart failure and acute myocardial infarction, where elevated ePVS values were associated with higher mortality and adverse outcomes.[15],[16] However, its use in the context of sepsis, especially in emergency room settings, remains underexplored. This study sought to address this gap by examining the association between ePVS and outcomes in septic patients in the emergency room.

The study found that non-survivors had significantly higher ePVS values compared to survivors, with values of 6.47 ± 2.5 dL/g versus 5.17 ± 1.46 dL/g, respectively ($p = 0.007$). A cut-off value of 5.37 dL/g was established. There is currently no universally established cutoff for ePVS, as different studies have used various thresholds. For instance, some studies have utilized thresholds like 6.52 dL/g and 7.09 dL/g to assess the risk of mortality and adverse outcomes in different patient populations, including those with acute myocardial infarction and sepsis in intensive care units.[16],[17] The choice of this balanced threshold emphasizes the importance of clinical utility in the ER setting. An ePVS cutoff of 5.37 (sensitivity 58.82%, specificity 65.03%) provides a practical compromise, it identifies a fair proportion of at-risk patients while maintaining a reasonable rate of false positives. Such a balanced approach is essential when the clinical goal is to initiate prompt management in patients likely to deteriorate while avoiding the potential harm of overtreatment in patients who are unlikely to require aggressive measures.

Elevated ePVS and increased fluid resuscitation within the first 24 hours were independently linked to higher

mortality ($p < 0.001$), reinforcing the concept that careful fluid management is crucial in sepsis care.[12] These findings align with existing literature, which suggests that a positive fluid balance and hypervolemia can adversely impact outcomes in septic patients.[6], [12] Interestingly, even after adjusting for confounders using multivariate logistic analysis, ePVS remained a significant predictor of mortality ($p < 0.002$). This underscores its value as a practical tool, particularly in emergency settings where rapid assessments are necessary ensuring that each patient receives an appropriate amount of fluid based on their individual plasma volume status.[6],[7],[8],[12]

In evaluating the predictive accuracy of ePVS, the study observed that while ePVS demonstrated promise as a prognostic marker, it had lower accuracy compared to established scoring systems such as the Modified Sequential Organ Failure Assessment (MSOFA) and the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores.[1],[26] The area under the curve (AUC) for ePVS was 0.63, indicating moderate predictive power. In contrast, MSOFA and APACHE II had higher AUCs of 0.78 and 0.79, respectively, showing that they remain more reliable tools for assessing mortality risk in septic patients. However, the ease of computing the ePVS especially in resource limited setting makes it a valuable addition to our armamentarium. Unlike APACHE II and MSOFA, which need more tests and detailed clinical information.

Although patients with elevated ePVS values initially appeared to have a significantly longer median hospital stay compared to those with lower values (median 8 days, IQR 5.0–12.0 vs. shorter stays for lower ePVS values, $p = 0.033$), this association did not remain significant ($p > 0.05$) after adjusting for other variables in the multivariate analysis. This suggests that the relationship between ePVS and length of hospital stay may be influenced by other factors, such as illness severity and renal function, rather than an independent effect of plasma volume status alone. Additionally, mechanical ventilation and vasopressor use were not significantly associated with elevated ePVS levels ($p > 0.05$), indicating that ePVS may not directly correlate with the need for these intensive interventions.

Several potential sources of bias should be considered. Selection bias may be present due to the single-center design and emergency department-based recruitment, which may limit external validity. Measurement bias is possible because estimated plasma volume status is derived from hemoglobin and hematocrit values, which may be influenced by pre-hospital fluid administration and individual hematologic variability. Residual confounding is inherent in observational studies despite adjustment for clinically relevant covariates. However, the prospective design, standardized data collection, and use of multivariable analyses helped mitigate these potential sources of bias.

Conclusion

Elevated estimated plasma volume status (ePVS) and increased 24-hour fluid resuscitation are significantly associated with a higher risk of in-hospital mortality, with patients exhibiting elevated ePVS having a threefold increase in mortality risk. ePVS demonstrates moderate predictive accuracy when compared to established risk assessment tools such as APACHE and MSOFA in predicting in-hospital mortality. The length of hospital stay was significantly correlated with elevated ePVS, but this significance was lost when adjusted for confounders. ePVS may not directly correlate with the need for mechanical ventilation and vasopressor/inotropes use.

Limitations of the Study

The study has several limitations that may affect the generalizability and robustness of its findings. It was conducted in a single center, which limits its applicability to broader populations, and the relatively small sample size may weaken the statistical power. Potential confounding variables, such as variations in clinical practices and unmeasured factors, could influence outcomes. The focus on in-hospital mortality without long-term follow-up misses the impact of sepsis on long-term patient outcomes. Additionally, the lack of external validation means that the identified ePVS thresholds may not be applicable in other settings. The study also does not thoroughly explore how the timing, type, or amount of fluid resuscitation affects ePVS and outcomes. Finally, relying solely on hematologic parameters for ePVS calculation may introduce variability, especially in patients with conditions like anemia or dehydration. Further research is needed to validate these findings and address these limitations.

Recommendations

Given the prognostic value of estimated plasma volume status (ePVS) in septic patients, incorporating ePVS as a routine assessment tool in acute clinical settings should be considered. Its ease of calculation using standard hematologic parameters makes it a practical addition to the clinical armamentarium, especially in emergency and resource-limited environments. Further multicenter studies are needed to validate ePVS thresholds, refine its application, and establish standardized protocols for its use in guiding fluid management and risk stratification. Additionally, integrating ePVS into existing clinical algorithms could enhance the precision of early interventions, ultimately improving patient outcomes in sepsis care.

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