Estimated plasma volume status can help identify patients with sepsis at risk of death within 30 days in the emergency department

Gianni Turcato,[1] Arian Zaboli,[4] Serena Sibilio,[3,4] Michael Mian,[2,4,5] Francesco Brigo[4]

[1]Department of Internal Medicine, Intermediate Care Unit, Hospital Alto Vicentino (AULSS-7), Santorso; [2]Innovation, Research and Teaching Service (SABES-ASDAA), Teaching Hospital of the Paracelsus Medical Private University (PMU), Bolzano; [3]Department of Emergency Medicine, Hospital of Merano-Meran (SABES-ASDAA), Merano-Meran, Italy; [4]Teaching hospital of Paracelsus Medical Private University, Salzburg, Austria; [5]College of Health Care-Professions Claudiana, Bozen, Italy

Correspondence: Gianni Turcato, Department of Internal Medicine, Intermediate Care Unit, Hospital Alto Vicentino (AULSS-7), via Garziere, 43, 36014, Santorso, Italy.
E-mail: gianni.turcato@yahoo.it

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Abstract

For patients with sepsis in the Emergency Department (ED), early risk stratification is important to improve prognosis. The study aimed to evaluate the predictive role of estimated plasma volume (ePVS) on admission to the ED. All sepsis patients who were admitted to our ED in 2021, were included in this prospective study. Multivariate models adjusted for patients' clinical characteristics were used to assess the contribution of ePVS to the independent prediction of death at 30 days. A total of 455 septic patients were enrolled and 16.9% of patients died. Patients who survived to 30 days had a mean ePVS of 5.19, while those who died at 30 days had a value of 5.74 (p=0.004). ePVS was an independent risk factor for 30-day mortality with an adjusted OR of 1.211 (95% CI 1.004–1.460, p=0.045). The AUROC of ePVS was 0.619 (95% CI 0.545–0.689). Decision tree analysis showed a predictive role for ePVS in less severe patients. In septic patients, ePVS is an independent predictor of 30-day mortality and may improve risk prediction in less severe patients.

Introduction

Sepsis is a serious organ dysfunction caused by a dysregulated response to infection.[1] Despite advancements in diagnosis and therapeutic therapy, it is associated with high mortality rates and accounts for 30% of in-hospital deaths.[1,2] One of the central pathophysiological changes in sepsis is systemic volume dysregulation caused by inflammation-induced endothelial dysfunction and the consequent increase in interstitial permeability; consequently, volume resuscitation with intravenous crystalloids remains the mainstay of acute treatment.[1,3,4] However, recent studies suggest that replacement when the microcirculatory system is unable to respond to fluids may worsen prognosis and that new approaches for measuring volume status should be implemented to improve short- and medium-term outcomes.[1,5,6] Moreover, as indicated in recent guidelines, the use of vasoactive drugs is crucial in the event of reduced tissue inflow following volemic therapy to improve the patient's prognosis by ensuring minimal vital organ flow.[1]

Despite the availability of various tools, designed and applied in ICUs, for assessing tissue and patient perfusion status, the therapeutic interventions in ED for suspected hypovolaemia are carried out without a precise evaluation of the patient's plasma volume.[1,7-10] Since the relationship between microcirculatory endothelial function and interstitial hydration status is finely regulated, such measurements could reveal disruption of this balance and indicate potential states of volume overload or the incapacity to respond to a fluid load.[11,12]

Recently, Duarte et al. suggested estimating plasma volume in patients with heart failure using a simple formula based on hemoglobin and hematocrit. High estimated plasma volume status (ePVS) has been associated with a poor prognosis in patients with heart failure, according to earlier research.[13,14] Although studies have demonstrated the prognostic value of ePVS in patients with fever or sepsis in the Intensive Care Unit (ICU), no studies have yet evaluated its prognostic utility in patients with sepsis or septic shock at initial evaluation in the Emergency Department (ED).[12,15] Therefore, a prospective observational study was conducted to assess the predictive potential of ePVS in patients with sepsis upon their first admission to the ED.

Materials and Methods

Design and setting

A prospective, observational, single-center study was performed in the ED at the Hospital of Merano, Italy (53,000 visits in 2021). The study was conducted between January 1 and December 31, 2021.

Patients

All patients aged ≥ 18 years were considered for enrolment in the study.

This real-world study was performed in the ED during daily clinical activities. Therefore, all patients with suspected infection were initially considered as potentially eligible; in these patients, the study protocol was applied and specific blood tests for suspected infection were carried out. Subsequently, following the recent Surviving Sepsis Campaign Guidelines 2021, after determining the Sequential Organ Failure Assessment (SOFA) score, patients with a suspected or confirmed infection and a SOFA ≥ 2 were enrolled and considered as affected by sepsis.[1,16]

Other exclusion criteria included: i) vasopressor therapy or invasive ventilation administered before arrival in the ED by healthcare professionals working in the territorial emergency system; ii) the presence of concomitant major bleeding as assessed by the ED physician; iii) known or suspected pregnancy; iv) fluid infusion ≥ 500 mL before the admission to the ED; v) sepsis or infection due to recent surgery or trauma; vi) predicted survival time of < 24 h after initial ED assessment; vii) tourists or non-residents were excluded due to an inability to determine outcomes; viii) transfer from another ED or healthcare facility; ix) study protocol initiated > 3 h after patient arrival in the ED.

Data collection and study protocol

Each patient with a suspected infection underwent a battery of blood tests as part of their initial evaluation. Complete blood count with differential leucocyte counts, serum electrolytes, renal and hepatic function, serum albumin, C-reactive protein, total bilirubin, coagulation status, and arterial blood gas were among the analyses performed. By the end of the ED visit, definitive confirmation of sepsis based on previously established criteria was required for patient enrolment. At the initial examination, the ED physician also collected demographic and clinical information, such as sex, age, medical history, systolic and diastolic blood pressure, respiration rate, heart rate, capillary oxygen saturation, and cognitive status. In addition, the Charlson Comorbidity Index (CCI), the National Early Warning Score (NEWS), and the Acute Physiology and Chronic Health Evaluation (APACHE) and SOFA scores were recorded.

The ePVS value was determined using hematocrit (Ht) and hemoglobin (Hb) values from the complete blood count performed when the patient arrived in the ED and was calculated using the formula below.

Complete blood counts were obtained using a Sysmez analyzer (Sysmex XN-2000, Sysmex Inc. Kobe, Japan).

Outcome

The primary outcome of the study was death within 30 days after the first evaluation in the ED. Mortality was derived from information provided by the registry office.

Statistical analysis

Categorical variables were expressed as percentages and number of events relative to the total and univariate comparisons were performed with Fisher's exact and chi-square tests. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the underlying distribution. Comparisons were performed with Student's t-tests, and Mann-Whitney or Kruskal-Wallis tests where appropriate.

To assess the discriminatory ability of ePVS, we calculated the area under the receiver operating characteristic (AUROC) curve against 30-day mortality. To evaluate the prognostic ability of ePVS and validate its effect on 30-day mortality, logistic regression models were developed using the CCI (a surrogate of medical history and severity of comorbidities), NEWS (a surrogate of immediate urgency), and SOFA and APACHE scores (surrogates of prognostic severity) as possible clinical confounders. The results of possible independent associations with PVS with 30-day mortality were reported as adjusted odds ratio (OR) with a 95% confidence interval (95% CI). The variables reported in the univariate analysis were not included in the multivariate analysis, as the aim of the study was to understand the role of ePVS in predicting the risk of death at 30 days in patients with sepsis and not to create a prognostic model.

A decision tree analysis was also performed with the same variables to assess the prognostic ability of ePVS on 30-day mortality. Decision tree analyses are powerful data-mining analyses that create a non-parametric supervised learning algorithm.[17] The decision tree was developed using the chi-square automatic interaction detection technique. This consists of a hierarchical tree structure comprising a root node, branches, internal nodes, and leaf nodes. At each classification level along the tree, the model identifies the most significant predictor using the chi-square test to split the data interactively.[17] The root node is at the top of the hierarchy and the data begin to subdivide from this point. Subsequent levels include the parent nodes, which are further subdivided into other nodes at lower levels. Leaf nodes, where further subdivision is not possible, identify subgroups of patients sharing the same risk.[17] A 10-fold cross-validation was used to resolve any overfitting. The predictive performance of the decision tree for 30-day mortality was calculated by reporting the estimated correct classifications.[17]

All results were considered statistically significant for $p<0.05$. The statistical software packages STATA 16.0 and R were used for the analyses.

Ethical statement

The study was conducted by the Declaration of Helsinki and approved by the local ethics committee (approval number 94-2020).

Results

There were 455 patients with sepsis included in the study (Figure 1). The mean ePVS value in the study cohort was 5.28 (1.53). Patient characteristics for the cohort are listed in Table 1.

The mortality rate was 16.9% (77 out of 455 patients died within 30 days). The mean ePVS was 5.19 (1.49) in survivors and 5.74 (1.63; p=0.004) in non-survivors. The characteristics of the non-survivors are reported in Table 2.

In the multivariate model adjusted for age, comorbidity (CCI), urgency (NEWS score), and severity (SOFA and APACHE scores), ePVS was an independent risk factor for 30-day mortality, with an adjusted OR of 1.211 (95% CI 1.004–1.460, p=0.045). An ePVS value above the mean (> 5.28) was associated with an adjusted OR of 1.831 (95% CI 1.021–3.286, p=0.042).

The discriminatory ability of ePVS for 30-day mortality is shown in Figure 1. The AUROC of ePVS was 0.619 (95% CI 0.545–0.689).

According to the Kaplan-Meier analysis, patients with an above-average ePVS had shorter survival (p=0.004, log-rank test) (Figure 2). The decision tree analysis showed that ePVS was effective in predicting 30-day mortality in patients with a low APACHE score (Figure 3), suggesting its prognostic utility in patients with a low apparent risk of mortality. As shown in Figure 3, the APACHE score is unable to correctly identify 15.6% (12/77) of the patients who achieved the study outcome among those with sepsis. In this category of patients, ePVS played an important role, being able to discriminate high-risk patients from low-risk patients. As shown by the decision tree for high-risk patients, the currently available tools (APACHE and NEWS) can accurately identify patients at risk of death at 30 days, whereas ePVS represents a relevant parameter to identify low-risk patients.

Discussion

In this prospective observational study conducted on patients with sepsis admitted to the ED, ePVS was an independent risk factor for 30-day mortality. To the best of our knowledge, this is the first study to assess a possible predictive role for ePVS obtained

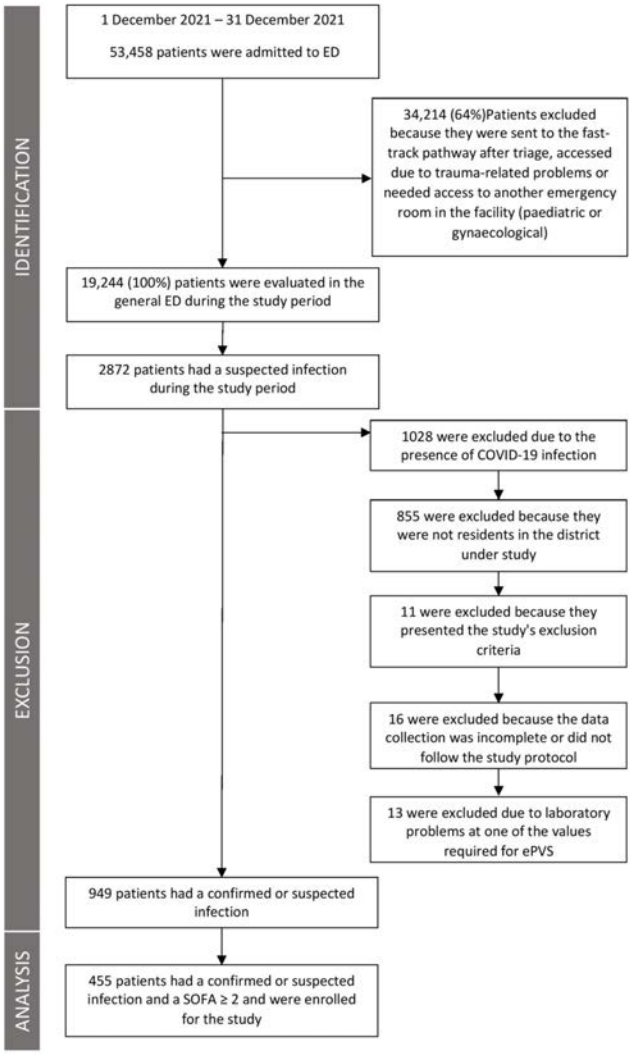

Figure 1. Flowchart of patients enrolled in the study.

Table 1. Clinical characteristics of patients enrolled in the study, divided by mean ePVS value.

Variable	ePVS < 5.28	ePVS ≥ 5.28	p
Patients, n (%)	268 (58.9)	187 (41.1)	
Age, years, mean (SD)	74.2 (16.7)	79.4 (13.2)	<0.001
Sex, n (%)			0.051
Male	93 (34.7)	82 (43.9)	
Female	175 (65.3)	105 (56.1)	
Baseline characteristics, n (%)			
Ischaemic heart disease	53 (19.8)	45 (24.1)	0.298
Hypertension	175 (65.3)	149 (79.7)	0.001
Diabetes	45 (16.8)	40 (21.4)	0.224
Chronic kidney failure	40 (14.9)	51 (27.3)	0.002
Chronic heart failure	57 (21.3)	57 (30.5)	0.028
Stroke or transient ischemic attack	30 (11.2)	17 (9.1)	0.533
Active tumor	16 (6)	32 (17.1)	<0.001
Vital parameters			
Systolic blood pressure, mean (SD)	123.8 (26.3)	116.3 (25.8)	0.004
Respiratory rate, mean (SD)	22.8 (7.3)	22.9 (7.1)	0.943
Heart rate, median (IQR)	100 (85-113)	96 (80-108)	0.013
Peripheral oxygen saturation, median (IQR)	94 (90-96)	95 (92-97)	0.509
Temperature, median (IQR)	38 (37.2-38.6)	37.9 (37.1-38.5)	0.335

Table 2. Clinical and laboratory characteristics of patients enrolled in the study were divided between dead and undead patients at 30 days.

Variable	Alive at 30 days	Dead at 30 days	p
Patients, n (%)	378 (83.1)	77 (16.9)	
Age, years, mean (SD)	74.6 (16.1)	84.9 (8.5)	<0.001
Sex, n (%)			0.123
Male	139 (36.8)	36 (46.8)	
Female	239 (63.2)	41 (53.2)	
Baseline characteristics, n (%)			
Ischaemic heart disease	77 (20.1)	22 (28.6)	0.127
Hypertension	258 (68.3)	66 (85.7)	0.001
Diabetes	64 (16.9)	21 (27.3)	0.038
Chronic kidney failure	66 (17.5)	25 (32.5)	0.005
Chronic heart failure	93 (24.6)	21 (27.3)	0.665
Stroke or transient ischemic attack	38 (10.1)	9 (11.7)	0.682
Active tumor	35 (9.3)	13 (16.9)	0.065
Charlson Comorbidity Index, media (SD)	4.7 (2.3)	6.5 (2.1)	<0.001
Vital parameters			
Systolic blood pressure, mean (SD)	123.4 (25.3)	107.6 (27.2)	<0.001
Respiratory rate, mean (SD)	22.1 (6.6)	26.5 (8.9)	<0.001
Heart rate, median (IQR)	98 (82-110)	102 (84-120)	0.011
Peripheral oxygen saturation, median (IQR)	94 (92-97)	93 (90-96)	0.001
Temperature, median (IQR)	38 (37.3-38.6)	37.6 (36.6-38.3)	0.013
NEWS score, mean (SD)	4.8 (3.4)	8.1 (4.6)	<0.001
Blood tests			
Haemoglobin, g/dL, mean (SD)	12.5 (2.1)	11.7 (2.3)	0.003
Haematocrit, %, mean (SD)	37.9 (6.1)	36.2 (7.1)	0.032
Leukocytes, median (IQR)	11.2 (7.6-14.5)	13.4 (9.6-18.5)	0.003
Platelets, median (IQR)	184 (140-249)	268 (169-369)	<0.001
Lactate, median (IQR)	1.5 (1-2.2)	2.3 (1.5-3.4)	<0.001
C-reactive protein, median (IQR)	7.2 (2.1-15.3)	13.2 (6.1-20.1)	<0.001
Creatinine, median (IQR)	1.24 (0.92-1.66)	1.51 (1.01-2.48)	0.006
Bilirubin, median (IQR)	1.03 (0.66-1.75)	0.86 (0.59-1.27)	0.031
APACHE score, mean (SD)	11.7 (4.6)	16.4 (4.5)	<0.001

from blood counts in patients who arrived in the ED with a suspicion of sepsis. Furthermore, the decision tree analysis showed that ePVS can have prognostic value also in patients at lower apparent risk (APACHE < 12). Overall, these findings suggest that ePVS could be a promising tool for predicting the prognosis of patients with sepsis in the ED. Furthermore, ePVS has proven to be useful in a comprehensive patient assessment using other laboratory tests and clinical evaluations, making it an excellent tool to support clinical decisions.

Key aspects of sepsis management include resuscitation with intravenous fluids to restore tissue perfusion, antibiotic therapy, infection control, and the use of vasopressors.[1] However, recent studies have shown that a positive fluid balance is associated with a negative outcome in patients with sepsis.[6,11,12] Although the exact mechanisms are unknown, previous studies suggest that excessive intravenous fluid resuscitation may result in iatrogenic endothelial damage.[18] Increased tissue edema and hypoxia are the results of increased endothelial permeability, which may ultimately cause organ damage.[18-20] The treatment and prognostic assessment of patients with sepsis are currently complicated by the lack of a gold-standard method to determine if endothelial damage is present and the capacity for capillary filtration.[1] Targeted and individualized therapy is still a long way off due to a lack of diagnostic or clinical tools capable of rapid and non-invasive determination of volume status and response to fluid load.[1] Therefore, given the importance of determining volume status, any available additional indication of the patient's blood volume is likely to be clinically relevant.

In previous studies using radiolabelled albumin techniques, ePVS derived from hemoglobin and hematocrit correlated well with plasma volume measured with radioisotopes.[13] ePVS is defined as the percentage difference between ideal and actual plasma volume; it has been recently proposed as a non-invasive, rapid, and simple method to assess volume status, particularly in patients with acute conditions.[12-15] Chen *et al.* initially proposed a clinical role for ePVS in the prognostic evaluation of patients with heart failure after acute myocardial infarction, reporting that higher

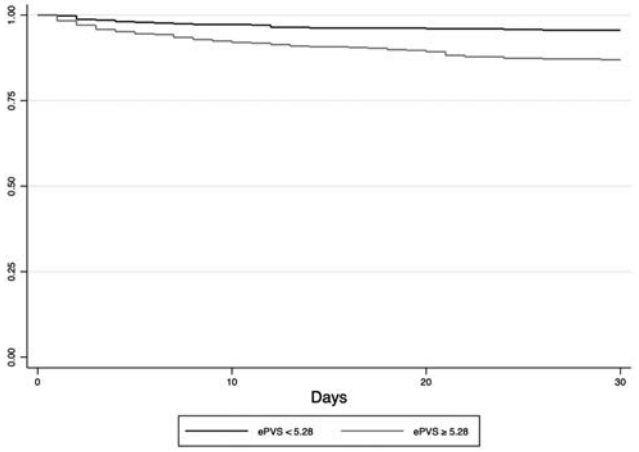

Figure 2. Kaplan-Meier for 30-day mortality comparing patients who had an ePVS value above or below the mean.

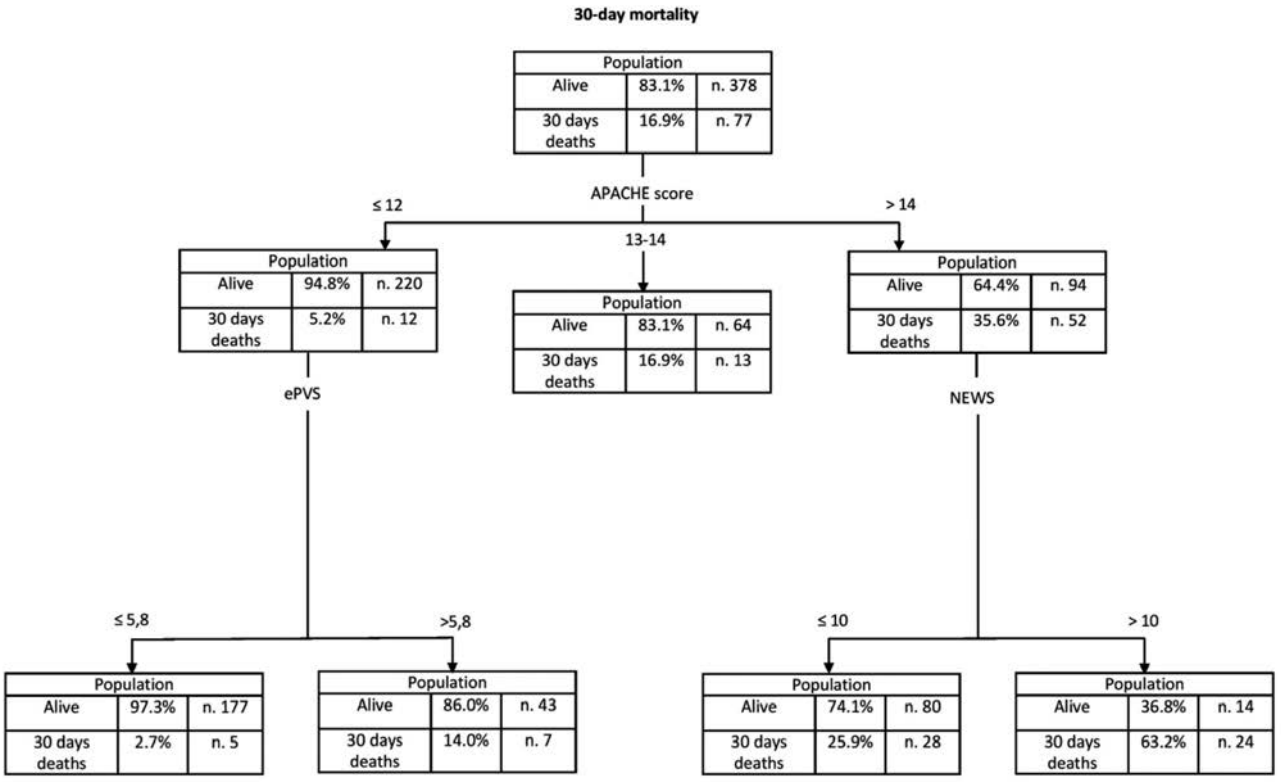

Figure 3. Decision tree for 30-day mortality in patients with sepsis.

ePVS was significantly associated with hospitalization or death from cardiovascular causes.[21] Furthermore, a decrease in ePVS was correlated with decongestion following effective treatment and with a better cardiovascular outcome.[21] High ePVS was recently found to be strongly associated with in-hospital mortality in patients who arrived at the ED with acute dyspnea and acute heart failure.[22] Furthermore, among patients admitted to the ED with fever, ePVS was associated with 30-day mortality with an adjusted OR of 2.717 (95% CI 1.103–6.692, p=0.020) and with sepsis or septic shock with an OR of 1.824 (95% CI 1.055–3.154, p=0.030).[11] In a subsequent study, Kim et al. found that ePVS was an independent risk factor for in-hospital mortality among sepsis patients admitted to the ICU, with a multivariate OR of 1.39 (95% CI 1.04-1.85, p=0.028), suggesting that ePVS may aid in predicting the risk of death.[12] An important innovation of the present study is the use of decision tree analysis, a potent statistical technique that overcomes the inherent difficulties of traditional multivariate analyses. High APACHE scores may be sufficient to categorize patients with a poor prognosis. However, among patients with lower APACHE scores which may appear to be less severe cases, ePVS may improve prognostic prediction by providing additional clinical data. Patients with lower APACHE scores who appear clinically stable when they enter the ED may already have microcirculatory changes that, if untreated, could worsen the prognosis. In these patients, the ePVS may thus represent a useful early prognostic marker that correlates with initial endothelial dysfunction.

Overall, we established that ePVS, a rapid and easy test to administer at the time of ED admission, was independently associated with mortality in sepsis patients and that it plays a role in identifying mortality risk in patients with initially less severe sepsis. Although more studies are required to corroborate these clinical findings, ePVS may eventually be used as a clinical tool in the complex prognostic assessment of sepsis patients.

Overall, ePVS, recorded on the patient's immediate arrival in the ED, was an independent risk factor for 30-day mortality in septic patients. Given its simplicity rapid availability and immediacy, ePVS may be one of the indices that can assist the ED physician in the intricate and sensitive multidimensional assessment to estimate the prognosis and severity of the septic patient in the ED, despite its suboptimal discriminatory ability. The analysis of decision trees further supports this conclusion. Hence, in clinical conditions and patient groups where prognosis and assessment cannot be accomplished very effectively using the tools that are currently available, ePVS can provide useful additional predictive information.

This study has a few limitations. It was conducted in a single center, which could have limited the generalisability of the findings. We initially considered all patients with suspicion of infection, as the definition of sepsis is currently linked to the SOFA score; this facilitated the rapid identification of patients who had sepsis. In addition, we excluded patients who were admitted to the Shock Room directly with invasive ventilation or who were administered amines out-of-hospital. This decision was made in agreement with the local committee because it was believed that the study design could not be applied to these patients, even though it may have resulted in the exclusion of patients with sepsis and septic shock. Patients with sepsis and infection caused by a recent surgical procedure or trauma were also excluded. Consequently, only patients with a community infection were considered and recruited in the study, which may have resulted in the exclusion of several sepsis cases.

Finally, we did not include COVID-19 patients as they underwent a separate healthcare pathway with specific management during the study period.[23]

Conclusions

In this preliminary study, the simple and rapid calculation of ePVS based on the first blood count performed on patient arrival in the ED predicts 30-day mortality in patients with sepsis. It also has a useful predictive role in patients with low APACHE scores; if these results are confirmed in further studies, ePVS could prove to be a simple and manageable clinical tool that can facilitate the complex prognostic assessment of patients with sepsis immediately upon arrival in the ED.

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