BPR MCS Bulletin of Pioneering Researches of Medical and Clinical Science

Bulletin of Pioneering Researches of Medical and Clinical Science

Available online: https://bprmcs.com
2021 | Volume 1 | Issue 1 | Page: 7-15

Early Mortality Prediction in Adult Sepsis Patients Using the Vasoactive-Inotropic Score

Qin-Zhe Sun[1*], Si-Chen Li[2], Jing Zhao[1]

[1] Department of Pediatrics intensive care unit, The Affiliated Hospital of Putian University, Putian, Fujian, PR China.
[2] Department of General practice, The Affiliated Hospital of Putian University, Putian, Fujian, PR China.

Abstract

Vasoactive and inotropic agents are vital in sepsis treatment, but the link between the peak Vasoactive-Inotropic Score (VISmax) and patient outcomes in adults is not well understood. This study examined whether VISmax could serve as an early indicator of mortality in adult sepsis patients admitted to the emergency department (ED) and compared its predictive ability with the Sequential Organ Failure Assessment (SOFA) score. We conducted a single-center retrospective analysis of 910 sepsis patients between January 2016 and March 2020. VISmax was determined using the highest doses of administered vasopressors and inotropes within the first six hours of ED admission and classified into five categories: 0–5, 6–15, 16–30, 31–45, and >45. The main outcome measured was 30-day mortality. Mortality rates increased with higher VISmax: 17.2 percent, 20.8 percent, 33.3 percent, 54.6 percent, and 70.0 percent across the respective groups. A VISmax threshold of 31 points was identified as optimal for predicting mortality. VISmax outperformed the cardiovascular component of SOFA and initial lactate levels in prognostic accuracy and showed similar predictive value to the APACHE II score. Multivariable analysis confirmed that VISmax ranges of 16–30, 31–45, and >45 independently predicted 30-day mortality. Early VISmax assessment in the ED may therefore provide clinicians with a valuable tool to identify sepsis patients at higher risk of death.

Keywords: Vasopressors, Inotropes, Septic Shock, Sepsis

Corresponding author: Qin-Zhe Sun
E-mail: Sunzheqin@gmail.com

How to Cite This Article: Sun QZ, Li SC, Zhao J. Early Mortality Prediction in Adult Sepsis Patients Using the Vasoactive-Inotropic Score. Bull Pioneer Res Med Clin Sci. 2021;1(1):7-15. https://doi.org/10.51847/oMr5or5VzG

Introduction

Sepsis is a major contributor to death and severe illness in critically ill adults [1–4], and mortality remains alarmingly high despite advances in treatment strategies [5, 6]. Timely recognition and early intervention during the first hours of hospital admission are crucial for improving outcomes. Current Surviving Sepsis Campaign (SSC) recommendations suggest maintaining a mean arterial pressure (MAP) of at least 65 mmHg in patients with septic shock who require vasopressors [7]. Vasopressors are indicated when hypotension persists after initial fluid resuscitation, and dobutamine may be administered if tissue perfusion remains inadequate despite fluids and vasopressor therapy [7].

Originally developed by Gaies *et al.*, the Vasoactive-Inotropic Score (VIS) was designed to quantify cardiovascular support in infants following cardiopulmonary bypass and to help predict clinical outcomes [8]. This scoring system incorporates commonly used agents including dopamine, dobutamine, epinephrine, milrinone, vasopressin, and norepinephrine. In pediatric cardiac surgery and sepsis populations, higher

This work is licensed under the Creative Commons Attribution 4.0 International License.

VIS values have been linked to poorer outcomes [8–13]. However, there is a gap in knowledge regarding the application of VIS, particularly the maximum VIS (VISmax) measured in the emergency department, for predicting outcomes in adult sepsis and septic shock.

This study aimed to explore whether VISmax measured during the early ED stay could serve as a predictor of short-term mortality in adults meeting Sepsis-3 criteria. Its predictive performance was compared against established markers including the total SOFA score, the cardiovascular component of SOFA, and initial lactate levels.

Materials and Methods

Study design and population

We conducted a retrospective cohort study at a single tertiary hospital (Korea University Ansan Hospital) including adult patients (≥18 years) who presented to the ED with sepsis between January 2016 and March 2020. Inclusion required suspected or confirmed infection accompanied by an increase of ≥2 points in the SOFA score. For patients with a known baseline SOFA score, the increase was calculated relative to baseline; for those without prior scores, two infectious disease specialists reviewed clinical and laboratory data to confirm that sepsis accounted for the organ dysfunction. Management adhered to the 2016 SSC guidelines [7].

Exclusion criteria included: age under 18 years, ED stay shorter than six hours, incomplete compliance with SSC guidelines, missing clinical or outcome data, or prior use of extracorporeal membrane oxygenation (ECMO) before initiation of vasopressors or inotropes. Patients were stratified into five groups according to VISmax quintiles inspired by Koponen *et al.*'s methodology for post-cardiac surgery patients [14]: 0–5 (group 1), 6–15 (group 2), 16–30 (group 3), 31–45 (group 4), and >45 (group 5) **(Figure 1)**.

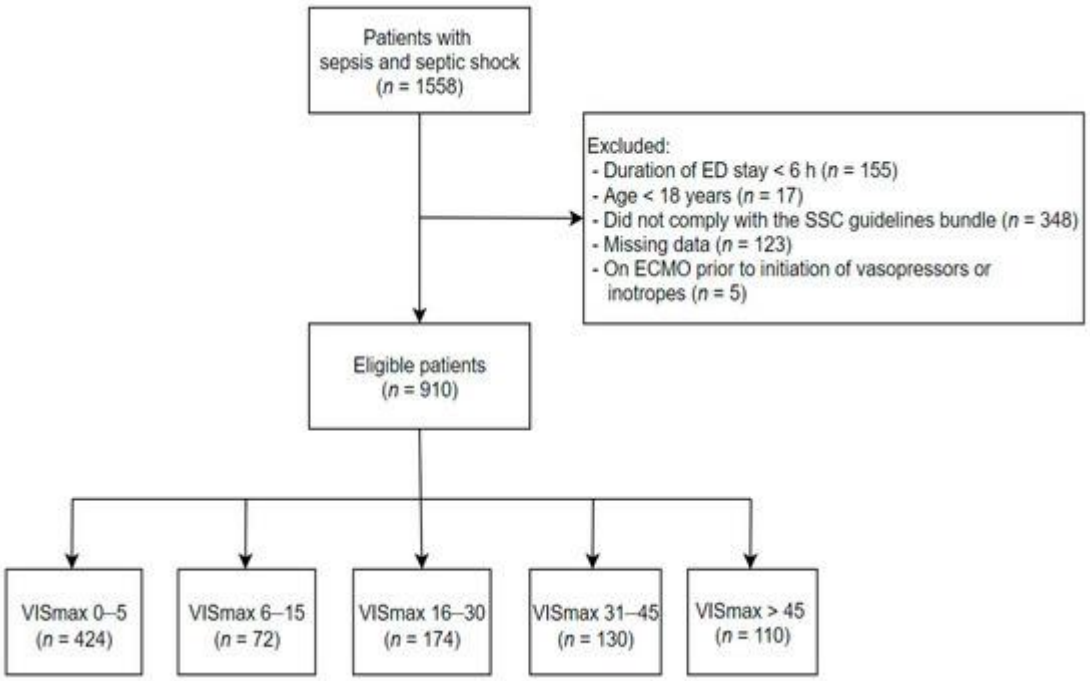

Figure 1. Flow diagram of study enrollment. Abbreviations: ED= emergency department; SSC= Surviving Sepsis Campaign; ECMO= extracorporeal membrane oxygenation; VIS= Vasoactive-Inotropic Score

Data collection

Patient information was obtained retrospectively from the hospital's intelligent sepsis management registry [15]. Collected variables included demographic data, laboratory measurements, infection sites, disease severity (sepsis versus septic shock), and details of early management, including fluid resuscitation, intravenous antibiotics, and administration of vasopressors or inotropes within the first six hours following ED admission. Outcome data were also recorded.

Definitions

Sepsis is defined as organ dysfunction resulting from an abnormal and dysregulated response to infection [1], whereas septic shock represents a more severe condition in which circulatory and metabolic disturbances significantly increase the risk of death compared with sepsis alone [1, 2]. The Sepsis-3 guidelines recommend the quick SOFA (qSOFA) score as a rapid tool to identify patients at higher risk of poor outcomes outside the ICU [1]. The qSOFA uses three criteria: systolic blood pressure ≤100 mmHg, respiratory rate ≥22 breaths/min, and altered

mental status (Glasgow Coma Scale <15), assigning one point per criterion; scores range from 0 to 3. For this study, a qSOFA score of ≥2 at the time of infection onset was required for inclusion.

Per Sepsis-3 definitions, sepsis is diagnosed when there is an increase of ≥2 points in the SOFA score associated with infection, and septic shock is characterized by persistent hypotension requiring vasopressors to maintain a MAP of ≥65 mmHg and serum lactate >2 mmol/L despite adequate fluid therapy [1,2].

VISmax was determined by summing the maximum doses of all vasopressors and inotropes administered during the first six hours of ED stay, as documented in the electronic ED records:

VISmax = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (units/kg/min) + 100 × norepinephrine dose (μg/kg/min)

Outcomes

This study focused primarily on 30-day mortality, with additional attention to deaths occurring at 7 and 14 days. Sepsis mortality is known to follow a biphasic pattern: an early phase, typically within the first few days, often results from inadequate resuscitation causing cardiac and pulmonary failure, while a later phase, occurring weeks afterward, is associated with persistent organ dysfunction. In this analysis, 7- and 14-day mortality served as markers for early-phase deaths, whereas 30-day mortality reflected late-phase deaths linked to ongoing organ injury. Patient outcomes were obtained from electronic health records.

Statistical analysis

Based on prior studies, the expected 30-day mortality in this cohort was approximately 35%. Previous research demonstrated that vasopressor-based mortality prediction models can outperform SOFA scores (AUC 0.73 vs. 0.65) [3, 16], and we anticipated similar predictive performance in our cohort. With 95% statistical power and a two-sided alpha of 0.05, a minimum sample size of 521 patients was required (339 survivors and 182 non-survivors).

Continuous variables were summarized as means ± standard deviation or medians with interquartile ranges (IQR), depending on distribution, which was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons between survivors and non-survivors employed Student's t-test or Mann–Whitney U test, while categorical variables (number and percentage) were analyzed using chi-square or Fisher's exact test. Differences across the five VIS groups were evaluated using ANOVA or Kruskal–Wallis tests for continuous variables and chi-square or Fisher's exact test for categorical variables, with post hoc pairwise comparisons adjusted using the Bonferroni method.

The relationship between potential predictors and mortality was examined using Cox proportional hazards models. Variables with a univariate p-value <0.2 were entered into a multivariate model, and stepwise backward elimination was applied to identify independent predictors of 30-day mortality. Hazard ratios and 95 percent confidence intervals (CIs) were reported. Predictive performance of VISmax, SOFA score, APACHE II score, the cardiovascular component of SOFA, and initial lactate levels was assessed through AUCs, with pairwise ROC comparisons conducted using the nonparametric Delong method [17]. Survival curves for each VIS group were generated with the Kaplan–Meier method and compared using the log-rank test.

All statistical analyses were performed using MedCalc version 19.1.6 (MedCalc Software, Mariakerke, Belgium) and SPSS version 23.0 (IBM, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

Results

During the study period, 1,558 patients with sepsis were initially screened. After excluding 648 patients, 910 were included in the final analysis **(Figure 1)**. Of these, 488 (53.6 percent) received vasopressors or inotropes within six hours of ED admission. VISmax scores were categorized into five groups: 0–5 (n = 424), 6–15 (n = 72), 16–30 (n = 174), 31–45 (n = 130), and >45 (n = 110) **(Figure 1)**.

The median age of participants was 76 years (IQR 65–82), with 518 (56.9%) male. The median VISmax for the cohort was 9.0 (IQR 0.0–36.0). Non-survivors had significantly higher VISmax values than survivors (36.0 [IQR 5.8–54.0] vs. 0.0 [IQR 0.0–18.0]; p <0.001). In addition, non-survivors were older, more frequently developed septic shock, and exhibited higher SOFA scores, lactate, procalcitonin, and CRP levels compared with survivors.

Table 1. Baseline patient characteristics according to 30-day mortality.

Variables	All Patients (n = 910)	30-Day Mortality		p-Value
		Non-Survivors (n = 294)	Survivors (n = 616)	
Median age, years (IQR)	76 (65–82)	78 (69–84)	74 (63–81)	<0.001
Male, n (%)	518 (56.9)	168 (57.1)	350 (56.8)	0.926
Median CCI (IQR)	4 (3–5)	5 (4–6)	4 (3–5)	0.158

Septic shock, n (%)	410 (45.1)	201 (68.4)	209 (33.9)	<0.001
VISmax, median (IQR)	9.0 (0.0–36.0)	36.0 (5.8–54.0)	0.0 (0.0–18.0)	<0.001
NEmax, median (IQR), μg/kg/min	0.1 (0.0–0.3)	0.3 (0.1–0.4)	0.0 (0.0–0.2)	<0.001
Infection sites, n (%)				
Respiratory	573 (63)	183 (62)	390 (63)	0.691
Genitourinary	215 (24)	73 (25)	142 (23)	0.348
Gastrointestinal	93 (10)	31 (11)	62 (10)	
Others	87 (10)	28 (10)	59 (10)	
Median time to first antibiotics, min (IQR)	120 (71–196)	122 (70–203)	123 (72–205)	0.427
Median fluid volume, mL (IQR)				
within 3 h	1800 (1275–2200)	1600 (1300–2000)	1800 (1200–2400)	0.044
within 6 h	2600 (2000–3300)	2800 (2300–3225)	2600 (1800–3300)	0.045
SOFA score, median (IQR)	8 (6–11)	10 (8–12)	7 (5–9)	<0.001
APACHE II score, median (IQR)	20 (15–25)	23 (18–29)	18 (14–23)	<0.001
Lactate, mmol/L	2.9 (1.8–5.4)	4.3 (2.3–7.8)	2.5 (1.6–4.5)	<0.001
Procalcitonin, ng/mL	1.6 (0.4–11.7)	2.4 (0.6–12.1)	1.3 (0.3–11.5)	0.002
CRP, mg/dL	10.2 (4.6–18.5)	11.9 (6.0–20.2)	9.4 (4.0–18.0)	0.003

IQR= interquartile range; CCI= Charlson comorbidity index; VISmax= maximum Vasoactive-Inotropic score; NEmax= maxium dose of norepinephrine; SOFA= sequential organ failure assessment; APACHE= acute physiology and chronic health evaluation; CRP= C-reactive protein.

Table 2 summarizes patient characteristics across the different VIS categories. Demographic factors, including age and sex, as well as clinical indicators such as Charlson comorbidity index, presence of septic shock, sites of infection, and timing of initial antibiotic therapy, were similar across all five VIS groups. In contrast, patients with higher VIS scores received greater volumes of fluids during the first 3 and 6 hours, showed elevated baseline lactate levels, and had higher SOFA scores compared with those in lower VIS categories.

Table 2. Clinical characteristics according to each VIS group

Variables	VIS 0–5 (n = 424)	VIS 6–15 (n = 72)	VIS 16–30 (n = 174)	VIS 31–45 (n = 130)	VIS > 45 (n = 110)	p-Value
Median age, years (IQR)	76 (66–82)	77 (67–81)	73 (61–82)	76 (65–83)	77 (66–84)	0.336
Male, n (%)	234 (55.2)	36 (50.0)	98 (56.3)	84 (64.6)	66 (60.0)	0.238
Median CCI (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	5 (4–6)	5 (4–6)	0.147
Septic shock, n (%)	2 (0.5)	59 (81.9)	132 (75.9)	110 (84.6)	107 (97.3)	<0.001
Infection sites, n (%)						
Respiratory	267 (63)	46 (64)	108 (62)	82 (63)	70 (64)	0.687
Genitourinary	98 (23)	17 (24)	42 (24)	30 (23)	28 (25)	0.592
Gastrointestinal	42 (10)	8 (11)	17 (10)	14 (11)	12 (11)	
Others	40 (9)	8 (11)	16 (9)	13 (10)	10 (9)	
Median time to first antibiotics, min (IQR)	119 (70–194)	125 (75–205)	123 (72–200)	121 (71–202)	120 (72–199)	0.397
Median fluid volume, mL (IQR)						
within 3 h	1500 (900–1800)	1800 (1500–2200)	2000 (1500–2500)	2000 (1500–2500)	2400 (1800–2500)	<0.001
within 6 h	2200 (1800–2600)	3000 (2300–3300)	3100 (2600–3600)	3200 (2600–3600)	3350 (3000–3800)	<0.001
SOFA score, median (IQR)	6 (4–7)	9 (8–11)	10 (8–12)	10 (9–12)	11 (9–13)	<0.001
APACHE II score, median (IQR)	17 (13–21)	20 (16–24)	22 (17–28)	22 (18–27)	24 (19–29)	<0.001
Lactate, mmol/L	2.2 (1.5–3.9)	2.9 (2.0–4.6)	3.0 (2.0–5.3)	4.3 (2.5–6.4)	7.8 (4.1–11.3)	<0.001
Procalcitonin, ng/mL	0.7 (0.2–4.3)	2.5 (0.5–18.0)	2.8 (0.8–17.5)	5.6 (0.9–26.7)	3.9 (0.6–21.6)	<0.001
CRP, mg/dL	9.1 (3.5–16.8)	12.6 (5.2–20.9)	11.4 (5.2–20.7)	11.6 (6.2–20.4)	9.4 (4.3–16.6)	0.003

IQR= interquartile range; CCI= Charlson comorbidity index; SOFA= sequential organ failure assessment; APACHE= acute physiology and chronic health Evaluation CRP= C-reactive protein; VIS= Vasoactive-Inotropic score.

Within thirty days of presentation to the emergency department, 294 patients, accounting for 32.3% of the cohort, had died. Shorter-term mortality was 179 (19.7 percent) at 7 days and 237 (26.0%) at 14 days **(Table 3)**. Mortality risk increased progressively with higher VIS scores. Statistical analysis using the chi-square test confirmed a significant difference in 30-day mortality among the five VIS categories ($p < 0.001$). When comparing groups pairwise, significant differences were observed in most comparisons, except for group 1 versus group 2 ($p = 0.458$), and borderline significance for group 2 versus group 3 ($p = 0.05$). After adjusting for multiple comparisons using the Bonferroni method (threshold $p < 0.005$), seven out of ten pairwise comparisons remained

statistically significant, highlighting that higher VIS levels were strongly associated with increased 30-day mortality.

Table 3. Clinical outcomes (short-term mortality) according to each VIS group

Outcomes	VIS 0–5 (n = 424)	VIS 6–15 (n = 72)	VIS 16–30 (n = 174)	VIS 31–45 (n = 130)	VIS > 45 (n = 110)	p-Value
7-day mortality	42 (9.9)	10 (13.9)	25 (14.4)	40 (30.8)	62 (56.4)	<0.001
14-day mortality	63 (14.9)	12 (16.7)	37 (21.3)	55 (42.3)	70 (63.6)	<0.001
30-day mortality	73 (17.2)	15 (20.8)	58 (33.3)	71 (54.6)	77 (70.0)	<0.001

VIS= Vasoactive-Inotropic score.

In univariate Cox proportional hazards analysis, several factors showed potential associations with 30-day mortality ($p < 0.2$), including VIS categories 16–30, 31–45, and >45, age, SOFA scores, presence of septic shock, initial lactate, CRP, and procalcitonin levels, as well as fluid administration at 3 and 6 hours **(Table 4)**. When these variables were entered into a multivariable Cox model, VIS levels of 16–30, 31–45, and >45 emerged as independent predictors of 30-day mortality, with VIS 0–5 serving as the reference. In contrast, there was no significant difference in mortality between the VIS 0–5 and 6–15 groups. Other factors independently associated with 30-day mortality in the multivariable model included age, SOFA score, initial lactate levels, and fluid volumes administered at 3 and 6 hours.

Table 4. Predictors of 30-day mortality using the Cox proportional hazards model

	Univariable HR (95% CI)	p-Value	Multivariable HR (95% CI)	p-Value
VIS group				
VIS 0–5	1 (Reference group)		1 (Reference group)	
VIS 6–15	1.236 (0.709–2.155)	0.454	1.028 (0.525–2.015)	0.936
VIS 16–30	2.060 (1.459–2.908)	<0.001	1.884 (1.159–3.063)	0.011
VIS 31–45	3.975 (2.866–5.514)	<0.001	3.717 (2.305–5.994)	<0.001
VIS > 45	6.934 (5.025–9.567)	<0.001	6.266 (3.624–10.834)	<0.001
Age, years	1.018 (1.009–1.028)	<0.001	1.014 (1.004–1.025)	0.005
Sex				
Male	1 (Reference group)			
Female	0.989 (0.785–1.246)	0.926		
SOFA score	1.221 (1.181–1.263)	<0.001	1.132 (1.075–1.191)	<0.001
APACHE II score	1.187 (1.148–1.229)	<0.001	1.093 (1.036–1.152)	<0.001
Septic shock				
Sepsis	1 (Reference group)			
Septic shock	3.236 (2.530–4.139)	<0.001		
Lactate	1.103 (1.080–1.128)	<0.001	1.069 (1.034–1.106)	<0.001
CRP	1.013 (1.002–1.024)	0.019	1.003 (0.990–1.016)	0.692
Procalcitonin	1.004 (1.000–1.008)	0.065	0.999 (0.995–1.003)	0.684
Fluid in 3 h	0.9999 (0.9997–1.0000)	0.164	0.998 (0.998–0.999)	<0.001
Fluid in 6 h	1.0001 (1.0000–1.0002)	0.119	1.001 (1.000–1.001)	0.001

HR= hazard ratio; VIS= Vasoactive-Inotropic score; SOFA= sequential organ failure assessment; APACHE= acute physiology and chronic health evaluation; CRP= C-reactive protein.

Figure 2 depicts survival over time for each VIS group using Kaplan–Meier analysis. There was no statistically significant difference between the lowest two VIS groups (group 1 vs. group 2; $p = 0.437$). However, patients in groups 4 and 5 not only differed markedly from each other ($p < 0.001$) but also experienced higher mortality compared with groups 1 through 3 (all $p < 0.001$). The highest VISmax categories showed a steep increase in mortality risk within the first two weeks, which continued to climb steadily over the full 30-day observation period.

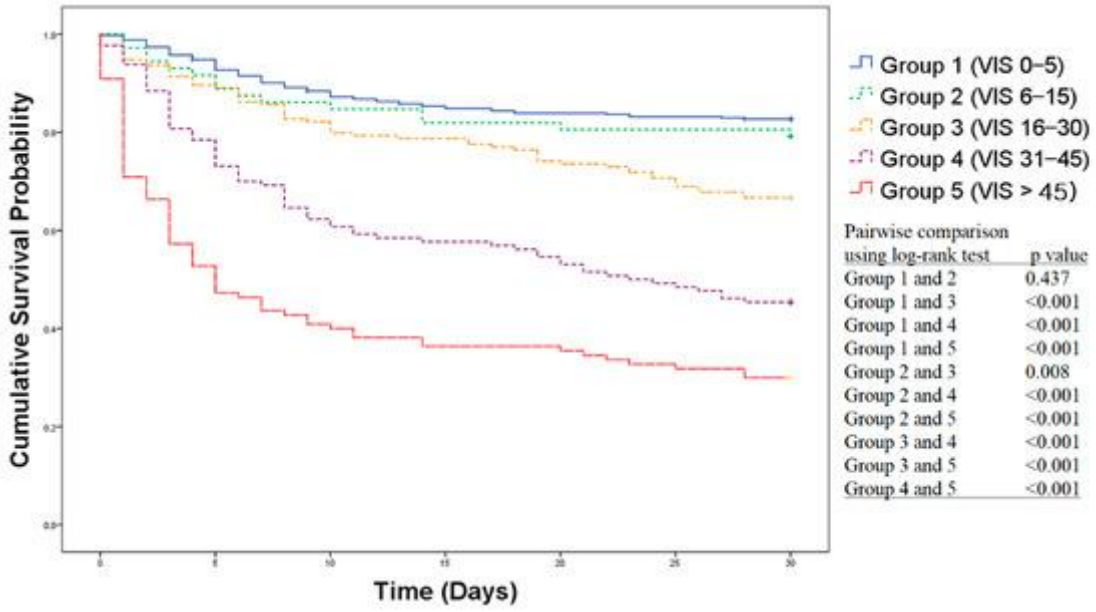

Figure 2. Kaplan–Meier survival curves for each VIS group. VIS: Vasoactive-Inotropic Score

Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the predictive performance of VISmax, APACHE II score, SOFA score, the cardiovascular component of SOFA, and initial lactate levels for 30-day mortality, with pairwise comparisons performed among these measures. VISmax demonstrated a similar ability to predict 30-day mortality compared with the SOFA score (AUC = 0.724; 95 percent CI: 0.694–0.753 vs. AUC = 0.734; 95% CI: 0.704–0.736; p = 0.518) and the APACHE II score (AUC = 0.721; 95% CI: 0.690–0.748; p = 0.632). In contrast, VISmax outperformed both the cardiovascular component of the SOFA score (AUC = 0.659; 95% CI: 0.628–0.690; p < 0.001) and initial lactate levels (AUC = 0.655; 95% CI: 0.623–0.686; p = 0.001) in discriminating 30-day mortality. The optimal VISmax threshold for predicting 30-day mortality was 31, corresponding to a sensitivity of 52.7% and a specificity of 83.1%. Furthermore, 30-day mortality across six subgroups, defined by combining two VISmax categories with three lactate level groups, is summarized in **Table 5**.

Table 5. Thirty-day mortality for the six different groups generated by the two VISmax categories and the three lactate groups

VISmax Category	Lactate Group (mmol/L) Lactate ≤ 2 Total, n (Died n/%)	Lactate > 2 to ≤4 Total, n (Died n/%)	Lactate > 4 Total, n (Died n/%)
VISmax < 31	262 (43/16.4)	226 (46/20.4)	182 (57/31.3)
VISmax ≥ 31	28 (15/53.6)	57 (34/59.6)	155 (99/63.9)

A subgroup analysis was conducted focusing exclusively on patients with septic shock (n = 410). In this cohort, ROC curve analysis was performed to compare the predictive performance of VISmax, APACHE II score, SOFA score, the cardiovascular component of the SOFA score, and initial lactate levels for 30-day mortality, with pairwise comparisons across these variables. VISmax showed similar discriminative ability to both the SOFA score (AUC = 0.703; 95 percent CI: 0.655–0.748 vs. AUC = 0.702; 95 percent CI: 0.654–0.747; p = 0.974) and the APACHE II score (AUC = 0.675; 95 percent CI: 0.627–0.721; p = 0.420). In contrast, VISmax outperformed the cardiovascular component of SOFA (AUC = 0.532; 95 percent CI: 0.483–0.582; p < 0.001) and initial lactate levels (AUC = 0.630; 95 percent CI: 0.581–0.677; p = 0.019) in predicting 30-day mortality. The optimal VISmax cut-off for septic shock patients was determined to be 27, yielding a sensitivity of 67.7% and specificity of 65.2%. Multivariable Cox proportional hazards modeling restricted to this subgroup mirrored the findings in the overall sepsis population, with VIS categories 16–30, 31–45, and >45 emerging as independent predictors of 30-day mortality relative to VIS 0–5 (all p < 0.001).

Discussion

To our knowledge, this study is the first to evaluate the prognostic utility of VISmax calculated in the ED among adult sepsis patients defined according to Sepsis-3 criteria. While VISmax demonstrated predictive performance comparable to the SOFA and APACHE II scores, its use in isolation offered limited accuracy for forecasting 30-day mortality.

The Sepsis-3 criteria rely on the SOFA score to assess organ dysfunction [1]. However, modern critical care practices—including the use of multiple vasoactive and inotropic agents—have diminished the ability of the cardiovascular component of SOFA to fully capture current clinical scenarios [3]. Previous work has shown that a modified cardiovascular SOFA, incorporating serum lactate, shock index, and total vasopressor load, predicts ICU mortality more accurately than the original score in critically ill adults [16]. This underscores the central role of cardiovascular function in prognostication. High-dose vasoactive therapy has been linked to poorer outcomes in sepsis-associated cardiovascular dysfunction [18-20], a finding consistent with our results showing higher VIS scores correlated with worse survival. Furthermore, VIS outperformed the cardiovascular SOFA component and matched the SOFA score in predicting short-term mortality.

Prior studies examining VIS in pediatric sepsis have demonstrated associations with adverse outcomes [12,13]. These investigations, conducted in both resource-limited and resource-rich ICU settings, suggested that post-ICU vasoactive support correlates with poor prognosis. Our study differs by evaluating adult sepsis patients in the ED, thereby capturing early cardiovascular status at presentation, which may better reflect initial disease severity.

The VIS has also been extensively validated in pediatric cardiac surgery populations [8–11], with higher scores linked to increased morbidity and mortality. More recently, VIS has been associated with in-hospital mortality in adults with cardiogenic shock requiring intensive cardiac care [23]. These findings, stratified by VISmax quintiles, consistently show that elevated VIS correlates with poorer outcomes, aligning with the trends observed in our cohort.

Vasoactive and inotropic medications remain essential in managing septic shock, yet they carry risks including arrhythmias, ischemia, and hemodynamic instability, which may contribute to adverse outcomes. Our study demonstrated a strong association between elevated VIS and worse clinical outcomes. While it is unclear whether this effect stems primarily from the severity of refractory septic shock or from the medications themselves, we hypothesize that the underlying shock is the predominant driver. All patients were managed according to SSC guidelines, with careful titration of vasopressors and inotropes to minimize potential adverse effects.

A recent investigation focusing exclusively on patients with septic shock compared three methods for quantifying peak vasoactive medication use: norepinephrine equivalents, the Vasoactive-Inotropic Score (VIS), and the cumulative vasopressor index [3]. The authors developed a predictive model incorporating mechanical ventilation, APACHE-III, vasopressors, inotropes, and the Charlson comorbidity index. Including quantitative measures of vasopressor usage improved the model's ability to predict 28-day mortality compared with APACHE-III and SOFA scores. However, the model's discriminative ability remained moderate (AUC = 0.73), closely aligning with the predictive performance of VISmax in our cohort (AUC = 0.724).

Norepinephrine remains the recommended first-line vasopressor for patients with sepsis-induced hypotension unresponsive to fluid resuscitation [7,24–26], offering lower mortality and fewer adverse events than dopamine [25,26]. Dopamine is no longer advised as a primary agent for sepsis or septic shock with hypotension [7], and in our practice, it was reserved for patients with bradycardia or low risk of tachyarrhythmia. Consistent with SSC guidelines and contemporary studies, norepinephrine was administered as the initial vasopressor in patients with fluid-refractory hypotension, while dobutamine was rarely used and only in cases of sepsis-related myocardial dysfunction [24,26].

Post-cardiac arrest syndrome (PCAS) exhibits a "sepsis-like" immunologic profile [27]. Recent evidence suggests that the 24-hour peak VIS can predict in-hospital mortality in out-of-hospital cardiac arrest patients admitted to the ICU, with an AUC of 0.762 (95% CI: 0.690–0.852) [28]. In a manner analogous to PCAS, our findings indicate that VIS can serve as a useful tool for predicting 30-day mortality in adult patients with sepsis and septic shock.

To our knowledge, this is the first study evaluating the relationship between ED-measured VISmax and mortality in adult sepsis patients. The association between early VISmax and poor outcomes suggests that elevated VIS values in the ED may prompt clinicians to monitor patients more closely, expedite ICU admission, and consider more aggressive interventions, including corticosteroids or emerging therapies. Future prospective trials are warranted to further validate the clinical utility of VISmax in this population.

This study has several limitations. Its retrospective design introduces potential selection bias and confounding. Despite adherence to SSC guidelines, the choice of vasoactive or inotropic therapy, fluid resuscitation strategy, and arterial pressure targets were determined by individual ED physicians, which may have influenced both VISmax and outcomes. Additionally, our analysis focused on early VISmax measured in the ED, potentially overlooking the prognostic relevance of later VIS values. The study also did not differentiate the effects of individual vasoactive agents on outcomes. VISmax alone demonstrated only modest predictive accuracy (AUC <0.8). Finally, as a single-center study in a tertiary care hospital, the generalizability of our findings is limited.

Conclusions

VISmax measured during the first six hours after ED admission was associated with higher 30-day mortality in adult patients with sepsis defined by Sepsis-3 criteria. Notably, VISmax outperformed the cardiovascular component of the SOFA score and initial lactate levels and demonstrated similar predictive ability to the APACHE II score. Early assessment of VISmax in the ED may assist clinicians in identifying sepsis patients at higher risk of adverse outcomes.

Acknowledgments: None.

Conflict of interest: None.

Financial support: None.

Ethics statement: None.

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;315:801–10.
2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:775–87.
3. Vallabhajosyula S, Jentzer JC, Kotecha AA, Murphree DH Jr, Barreto EF, Khanna AK, et al. Development and performance of a novel vasopressor-driven mortality prediction model in septic shock. Ann Intensive Care. 2018;8:112.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–10.
5. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013;41:1167–74.
6. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of septic shock: The CUB-Réa Network. Am J Respir Crit Care Med. 2003;168:165–72.
7. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486–552.
8. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med. 2010;11:234–8.
9. Butts RJ, Scheurer MA, Atz AM, Zyblewski SC, Hulsey TC, Bradley SM, et al. Comparison of maximum vasoactive inotropic score and low cardiac output syndrome as markers of early postoperative outcomes after neonatal cardiac surgery. Pediatr Cardiol. 2012;33:633–8.
10. Davidson J, Tong S, Hancock H, Hauck A, da Cruz E, Kaufman J. Prospective validation of the vasoactive-inotropic score and correlation to short-term outcomes in neonates and infants after cardiothoracic surgery. Intensive Care Med. 2012;38:1184–90.
11. Gaies MG, Jeffries HE, Niebler RA, Pasquali SK, Donohue JE, Yu S, et al. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: An analysis from the Pediatric Cardiac Critical Care Consortium and Virtual PICU System registries. Pediatr Crit Care Med. 2014;15:529–37.
12. Haque A, Siddiqui NR, Munir O, Saleem S, Mian A. Association between vasoactive-inotropic score and mortality in pediatric septic shock. Indian Pediatr. 2015;52:311–3.
13. McIntosh AM, Tong S, Deakyne SJ, Davidson JA, Scott HF. Validation of the vasoactive-inotropic score in pediatric sepsis. Pediatr Crit Care Med. 2017;18:750–7.
14. Koponen T, Karttunen J, Musialowicz T, Pietiläinen L, Uusaro A, Lahtinen P. Vasoactive-inotropic score and the prediction of morbidity and mortality after cardiac surgery. Br J Anaesth. 2019;122:428–36.
15. Song J, Cho H, Park DW, Ahn S, Kim JY, Seok H, et al. Effect of the intelligent sepsis management system on outcomes among patients with sepsis and septic shock diagnosed according to the Sepsis-3 definition in the emergency department. J Clin Med. 2019;8:1800.
16. Yadav H, Harrison AM, Hanson AC, Gajic O, Kor DJ, Cartin-Ceba R. Improving the accuracy of the cardiovascular component of the sequential organ failure assessment score. Crit Care Med. 2015;43:1449–57.
17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics. 1988;44:837–45.
18. Vallabhajosyula S, Sakhuja A, Geske JB, Kumar M, Poterucha JT, Kashyap R, et al. Role of admission troponin-T and serial troponin-T testing in predicting

outcomes in severe sepsis and septic shock. J Am Heart Assoc. 2017;6:e005930.
19. Vallabhajosyula S, Kumar M, Pandompatam G, Sakhuja A, Kashyap R, Kashani K, et al. Prognostic impact of isolated right ventricular dysfunction in sepsis and septic shock: An 8-year historical cohort study. Ann Intensive Care. 2017;7:94.
20. Vallabhajosyula S, Jentzer JC, Geske JB, Kumar M, Sakhuja A, Singhal A, et al. New-onset heart failure and mortality in hospital survivors of sepsis-related left ventricular dysfunction. Shock. 2018;49:144–9.
21. Kumar M, Sharma R, Sethi SK, Bazaz S, Sharma P, Bhan A, et al. Vasoactive inotrope score as a tool for clinical care in children post cardiac surgery. Indian J Crit Care Med. 2014;18:653–8.
22. Garcia RU, Walters HL III, Delius RE, Aggarwal S. Vasoactive inotropic score (VIS) as biomarker of short-term outcomes in adolescents after cardiothoracic surgery. Pediatr Cardiol. 2016;37:271–7.
23. Na SJ, Chung CR, Cho YH, Jeon K, Suh GY, Ahn JH, et al. Vasoactive inotropic score as a predictor of mortality in adult patients with cardiogenic shock: Medical therapy versus ECMO. Rev Esp Cardiol (Engl Ed). 2019;72:40–7.
24. Stratton L, Berlin DA, Arbo JE. Vasopressors and inotropes in sepsis. Emerg Med Clin North Am. 2017;35:75–91.
25. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the treatment of septic shock: Systematic review and meta-analysis. PLoS One. 2015;10:e0129305.
26. Colling KP, Banton KL, Beilman GJ. Vasopressors in sepsis. Surg Infect (Larchmt). 2018;19:202–7.
27. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation. 2002;106:562–8.
28. Oh YT, Oh J, Park SM, Kim YJ, Jo YH, Yang HC, et al. Vasoactive-inotropic score as a predictor of in-hospital mortality in out-of-hospital cardiac arrest. Signa Vitae. 2019;15:40–4.