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The use of Vasoactive-Inotropic Score in Adult Patients with Septic Shock in Intensive Care

Yoğun Bakımda Septik Şoklu Erişkin Hastalarda Vazoaktif İnotropik Skor Kullanımı

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ABSTRACT

Objective: Sepsis and septic shock are significant causes of mortality and morbidity. In septic shock, vasopressors and inotropic support are given for the treatment of hypotension. This study was designed to investigate the relationship between the vasoactive-inotropic score (VIS) and the results of sepsis patients in ICU.

Methods: The data of 392 patients who were followed up with the diagnosis of septic shock in adult ICU were recorded retrospectively. Vasopressors and inotropic support of the patients during the first 48 hours after the diagnosis of septic shock were recorded. Mean and peak VIS values were calculated according to these values. The patients were divided into groups according to the mean VIS≥10, peak VIS≥10 and intensive care results and statistical analysis was performed.

Results: The median ages of the patients were 68 (54.25-79) years and 239 (61%) were male. Dopamine 188 (47.9%), noradrenaline 365 (93.1%), adrenaline 53 (13.5%) and dobutamine 15 (3.8%) were used in the patients. The mean VIS was 9 (4-15), while the number of mean VIS≥10 patients were 192 (49%). Peak VIS values were 11 (5-20), and the number of peak VIS ≥10 patients were 220 (56.1%). The mortality rate of the patients included in the study was 42.1%. The mean VIS score(13 vs 6, p=0.000), mean VIS≥10 patient ratio (71.5% vs 32.6%, p=0.000), peak VIS score (16 vs 8, p=0.000), and peak VIS ≥10 patient ratio (73.3% vs 43.6%, p=0.000) were higher in non-survivors. The parameters such as mean VIS [OR 1.123, 95% CI 1.027-1.229, p=0.011], mean VIS≥10 [OR 3.455, 95% CI 1.625-7.345, p=0.001] and peak VIS score [OR 0.917, 95% CI 0.851-0.989, p=0.024] were determined as independent risk factors for mortality.

Conclusion: We conclude that vasoactive-inotropic score may be useful in predicting the outcome of septic shock patients in intensive care units.

Key words: Sepsis, septic shock, mortality, morbidity

ÖZ

Amaç: Sepsis ve septik şok önemli bir mortalite ve morbidite nedenidir. Septik şokta hipotansiyonun düzeltilmesinde vazopressör ve inotrop destekleri verilir. Çalışmamızda yoğun bakımda takip edilen septik şoklu hastaların sonuçları ile vazoaktif inotropik skor (VİS) arasındaki ilişkinin incelenmesi amaçlandı.

Yöntemler: Erişkin yoğun bakım ünitesinde septik şok tanısı ile takip edilen 392 hastanın verileri retrospektif olarak kaydedildi. Hastaların septik şok tanısı aldıktan sonraki ilk 48 saate aldığı vazopressör ve inotrop destekleri kaydedildi. Bu değerlere göre mean ve peak VIS değerleri hesaplandı. Hastalar mean VIS≥10, peak VIS≥10 ve mortalite sonucuna göre gruplara ayrılarak istatistiksel analiz yapıldı.

Bulgular: Hastaların median yaşları 68(54,25-79) yıl ve 239(%61) oranında erkek idi. Hastalarda dopamin 188(%47.9), noradrenalin 365(%93.1), adrenalin 53(%13.5) ve dobutamin 15(%3.8) kullanılmaktaydı. Ortalama VIS 9(4-15) olurken mean VIS≥10 hasta sayısı 192(%49) idi. Peak VIS değerleri 11(5-20) olurken peak VIS ≥10 hasta sayısı 220 (%56,1) olarak tespit edildi. Çalışmaya alınan hastaların mortalite oranı %42.1 idi. Ölen hasta grubunda ortalama VIS skoru (13 vs 6, p=0.000), ortalama VIS≥10 olan hasta oranı (%71.5 vs 32.6, p=0.000), peak VIS skoru (16 vs 8, p=0.000) ve peak VIS ≥10 olan hasta oranı (%73.3 vs 43.6, p=0.000) daha yüksek tespit edildi. Mean VIS [OR 1.123, 95% CI 1.027-1.229, p=0.011], mean VIS≥10 [OR 3.455, 95% CI 1.625-7.345, p=0.001] ve peak VIS skoru [OR 0.917, 95% CI 0.851-0.989, p=0.024] gibi parametreler mortalite için bağımsız risk faktörü olarak tespit edildi.

Sonuç: VIS skorunun yoğun bakımlardaki septik şok hastalarının sonuçlarının tahmininde faydalı olabileceği kanaatindeyiz.

Anahtar kelimeler: Vazoaktif inotropik skor, sepsis, septik şok, mortalite

Introduction

Sepsis is an important cause of mortality and morbidity affecting millions of people around the world every year. According to The Third International Consensus, sepsis is defined as life-threatening organ dysfunction resulting from an irregular response to the host's infection. Septic shock is a condition where vasopressor support is required to maintain a mean arterial pressure of 65 mmHg and above. This condition contains deep circulatory, cellular and metabolic disorders (1). According to the Surviving Sepsis Campaign guideline, when there is hypotension not responding to fluid therapy, various vasopressors and inotropic agents are used, first choice noradrenaline (2). Thus, tissue perfusion is continued and the process of organ dysfunction is prevented (1).

Measuring the amounts of supports used in these patients could help in estimating the outcome. The vasoactive inotropic score (VIS), developed to measure vasopressor support, is mostly used in pediatric patients and cardiac surgery patients (3-6). Also, two studies have used VIS in pediatric sepsis patient groups (7,8). To our best knowledge, there is no present study using VIS in adult septic shock. In our study, we aimed to determine the relationship between VIS which we use to determine the amount of vasopressor and inotropic support and some patient results, especially mortality, in patients with septic shock in our adult intensive care unit (ICU).

Material Method

Consent was obtained from the ethics committee of our hospital (Date: 04.07.2018, number: 2018/269). The data of 18 years old and older patients who were admitted to the Intensive Care Unit of Anesthesiology and Reanimation Department between January 2013 and July 2018 were analyzed retrospectively. Surviving Sepsis Campaign 2012 Guideline and Sepsis-3 Definition were regarded in diagnosis and treatment selection of sepsis and septic shock (1,2). The demographic characteristics of patients diagnosed with sepsis / septic shock, intensive care scores, some laboratory values, sepsis foci, some treatments and intensive care results were recorded. Vasopressor values in the first 48 hours after diagnosis of septic shock were recorded. Only the first septic shock attack was recorded in long-term hospitalized patients. Mean VIS and peak VIS scores were calculated according to these values. The patients were divided into two as survivors and non-survivors, and the relationship between mortality and VIS were examined. Then the data were grouped as mean VIS≥10 and peak VIS≥10 and statistical analysis was performed.

VIS calculation method

Vasopressor and inotropic support doses were recorded during the first 48 hours after the diagnosis of septic shock in intensive care. The initiation of vasopressor was 0 hours. Then, at 6^{th}, 12^{th}, 24^{th} and 48^{th} hours, doses of vasopressors were recorded. The averages and peak values of the five values recorded during the two-day period were taken. The calculated values for each drug were collected and the total mean VIS and peak VIS values were found. The following formula was used for VIS.

Vasoactive-Inotropic Score = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x adrenaline dose (μg/ kg/ min) + 100 x noradrenaline dose (μg/kg/min) + 10 x milrinone dose (μg/kg/min) + 10.000 x vasopressin dose (U/kg/min)

Statistical analysis

Data were statistically analyzed using SPSS Version 22.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Data were tested for normality with Kolmogorov–Smirnov (with Lilliefors correction) and Shapiro–Wilk tests. Descriptive statistics were performed in all the patient groups; numerical data were expressed as median (quarter intervals) while categorical data were given as percentages. Patients were classified according to mean VIS (VIS<10 or VIS≥10), peak VIS (VIS<10 or VIS≥10), and ICU outcomes (dead or survive). Patient features were compared using Chi-Square or Fisher's Exact Test for categorical variables and Mann-Whitney U Test for numerical variables. $p<0.05$ value was accepted as statistically significant. To identify any independent risk factor associated with mortality, among the significant parameters of univariate analysis, the ones which were not associated with each other were entered into the multivariate linear regression analysis. ROC analysis was performed.

Results

General characteristics of patients with sepsis / septic shock

In the study period, 1734 patients were followed in the intensive care unit. The diagnosis of septic shock was 22.6% (392 patients) in these patients. The median ages of the patients were 68 (54.2-79) years, and 239 (61%) were male. Median Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) values were 24.5 (18-27) and 11 (9-12), respectively. While the duration of ICU stay was 10(4-22) days, the rates of patients with invasive mechanical ventilation, blood and blood products transfusion and acute kidney injury were 96.9% (380 patients), 58.9% (231 patients) and 26.3% (103 patients), respectively. Mortality was 42.1% (165 patients) (Table 1).

Platelet, hemoglobin, white blood cell, procalcitonin and lactate levels were 107 (94-140) (x 10^3/μL), 9.8(9.1-10.0) (g/dL), 9.5(8.2-13) (x10^3 /L), 7.9 (4-11.1) (ng/ml) ve 4.2 (2.6-6.0) (mEq/L) respectively. The infection foci of septic shock patients were blood-catheter-borne infection 105(%26.8), urinary system infection 143(%36.5), respiratory system infection 182(%46.4) and soft tissue infection 41(%10.5) (Table 1).

Vasopressor and inotropic drugs used in patients with sepsis / septic shock

Dopamine 188 (47.9%), noradrenaline 365 (93.1%), adrenaline 53 (13.5%) and dobutamine 15 (3.8%) were administered to patients. The mean VIS was 9 (4-15), while the number of mean VIS≥10 patients were 192 (49%). Peak VIS values were 11 (5-20) and the number of peak VIS ≥10 patients were 220 (56.1%) (Table 1).

Table 1. General characteristics of patients with sepsis / septic shock

Characteristics	
Age (years)	68(54.2-79)
Gender (male)	239(61%)
ICU admission time (days)	10(4-22)
SOFA score	11(9-12)
APACHE II score	24.5(18-27)
Mechanical ventilation	380(96.9%)
Acute renal failure	103(26.3%)
Blood products transfusion	231(58.9%)
Steroid support	91(23.2%)
Fluid balance (ml)	1600(700-2150)
Outcome (Exitus)	165(42.1%)
Laboratory	
Platelets (x10^3 /µL)	107(94-140)
Hemoglobin (g/dL)	9.8(9.1-10.0)
White blood cell (x10^3 /L)	9.5(8.2-13)
Procalcitonin (ng/ml)	7.9(4-11.1)
Lactate (mEq/L)	4.2(2.6-6.0)
Anatomic localizations of infectious foci	
Blood-catheter borne infection	105(26.8%)
Urinary system infection	143(36.5%)
Respiratory system infection	182(46.4%)
Soft tissue infection	41(10.5%)
Supportive Therapies and Vasoactive Inotropic Score	
Mean dopamine (188 patients)	5(2.5-8)
Mean noradrenaline (365 patients)	7(4-10)
Mean adrenaline (53 patients)	5(3.5-7)
Mean dobutamine (15 patients)	5(4-10)
Mean Vasoactive Inotropic Score (µg/kg/min)	9(4-15)
Mean Vasoactive Inotropic Score ≥10	192(49%)
Peak dopamine (µg/kg/min)	7(5-10)
Peak noradrenaline (µg/kg/min)	8(5-12)
Peak adrenaline (µg/kg/min)	6(5-7)
Peak dobutamine (µg/kg/min)	7(4-10)
Peak Vasoactive Inotropic Score (µg/kg/min)	11(5-20)
Peak Vasoactive Inotropic Score ≥10	220(56.1%)

Data are presented as median (IQR) or n (%). **ICU:** Intensive Care Unit, **SOFA:** Sequential Organ Failure Assessment, **APACHE II:** Acute Physiology and Chronic Health Evaluation 2

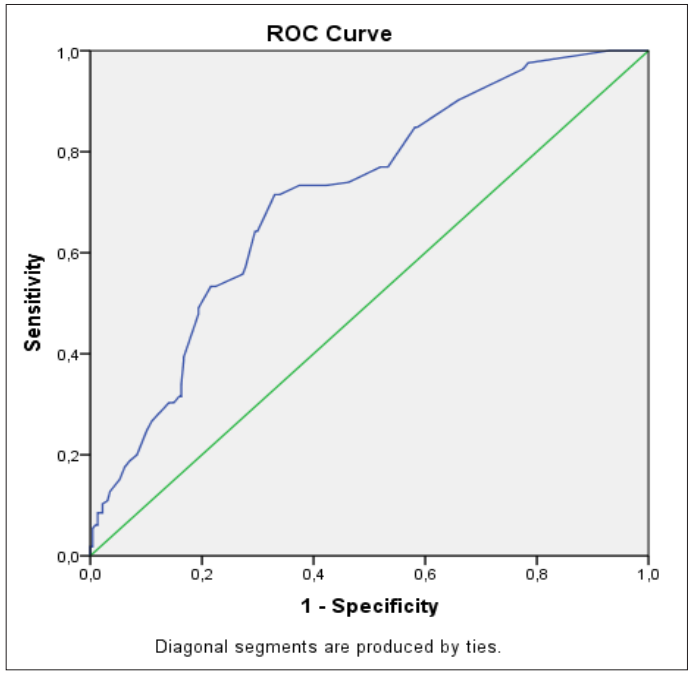

Figure 1. Receiver operating characteristic (ROC) curve for mean Vasoactive-inotropic score

Patient characteristics according to mortality

The age (74 vs 66 years, p = 0.000), SOFA scores (12 vs 10, p = 0.000) and acute renal failure rates (33.3% vs 21.1%, p = 0.008) were higher in non-survivors. In survivors, the duration of hospitalization were longer (13 vs 8 days, p = 0.000) and the fluid balance were more positive (1600 vs 1100 ml, p = 0.018). Procalcitonin (8.6 vs. 7.7, p = 0.000) and lactate levels (4.6 vs 3.8, p = 0.007) were higher in non-survivors. Survivors had higher rates of urinary tract infection (41% vs 30.3%, p=0.034). The mean VIS score (13 vs 6, p = 0.000), mean VIS≥10 (71.5% vs 32.6%, p = 0.000), peak VIS score (16 vs 8, p = 0.000) and peak VIS ≥10 (73.3% vs 43.6%, p = 0.000) were higher in non-survivors (Table 2).

The data with significant results according to univariate analysis were evaluated with multivariate analysis. The parameters such as age [OR 1.034, 95% CI 1.020-1.049, p=0.000], procalcitonin [OR 1.015, 95% CI 1.003-1.028, p=0.014], lactate [OR 1.161, 95% CI 1.039-1.297, p=0.008], mean VIS [OR 1.123, 95% CI 1.027-1.229, p=0.011], mean VIS≥10 [OR 3.455, 95% CI 1.625-7.345, p=0.001] and peak VIS score [OR 0.917, 95% CI 0.851-0.989, p=0.024] were determined as independent risk factors for mortality (Table 2).

Patient characteristics according to mean VIS ≥10

Age (71 vs 67 years, p=0.004), SOFA score (12 vs 9, p=0.000), acute renal failure (33.9% vs 19%, p=0.001) and procalcitonin levels (8.6 vs 6.6, p=0.000) were higher in mean VIS ≥10 patients group, while ICU hospitalization time (8 vs 15.5 days, p=0.000) was shorter (Table 3).

Multivariable logistic regression was performed controlling for patient characteristics. Patients with high mean VIS had significantly greater odds of age [OR 1.018, 95% CI 1.004-

Table 2. Patient characteristics according to mortality

	Univariate Analysis			Multivariate analysis	
Variables	Survivors (n=227)	Non-survivors (n=227)	p value	OR (CI 95% low-upper)	p
Age (years)	66(49-75)	74(63-83)	**0.000**	1.034(1.020-1.049)	**0.000**
Gender (male)	135(59.5%)	104(63%)	0.529		
ICU admission time (days)	13(5-26)	8(2-17)	**0.000**		NS
SOFA score	10(8-12)	12(10-13)	**0.000**		NS
APACHE II score	24(16-27)	25(20-26.5)	0.147		
Mechanical ventilation	222(97.8%)	158(95.8%)	0.374		
Acute renal failure	48(21.1%)	55(33.3%)	**0.008**		NS
Blood products transfusion	130(57.3%)	101(61.2%)	0.467		
Steroid support	50(22.0%)	41(24.8%)	0.340		
Fluid balance (ml)	1600(800-2400)	1100(700-2125)	**0.018**		NS
Laboratory					
Platelets (x 103 /µL)	106(94-138)	108(92-143)	0.416		
Hemoglobin (g/dL)	9.8(9.1-10.1)	9.7(8.9-10)	0.151		
White blood cell (x 103 /L)	9.5(8-12)	10(8.5-14)	0.219		
Procalcitonin (ng/ml)	7,7(3,2-10)	8.6(5.2-14.3)	**0.000**	1.015(1.003-1.028)	**0.014**
Lactate (mEq/L)	3.8(2.4-5.4)	4.6(2.6-6.5)	**0.007**	1.161(1.039-1.297)	**0.008**
Anatomic localizations of infectious foci					
Blood-catheter borne infection	64(28.2%)	41(24.8%)	0.490		
Urinary system infection	93(41%)	50(30.3%)	**0.034**	0.521(0.318-0.852)	**0.009**
Respiratory system infection	110(48.5%)	72(43.6%)	0.358		
Soft tissue infection	25(11%)	16(9.7%)	0.740		
Vasoactive Inotropic Score					
Mean VIS (µg/kg/min)	6(3-12)	13(6-19.5)	**0.000**	1.123(1.027-1.229)	**0.011**
Mean VIS≥10	74(32.6%)	118(71.5%)	**0.000**	3.455(1.625-7.345)	**0.001**
Peak VIS (µg/kg/min)	8(4-15)	16(8.5-22)	**0.000**	0.917(0.851-0.989)	**0.024**
Peak VIS ≥10	99(43.6%)	121(73.3%)	**0.000**		**NS**

Data are presented as median (IQR) or n (%). **ICU:** Intensive Care Unit, **SOFA:** Sequential Organ Failure Assessment, **APACHE II:** Acute Physiology and Chronic Health Evaluation 2, **VIS:** Vasoactive Inotropic Score

1.033, p=0.014], duration of ICU stay [OR 0.961, 95% CI 0.943-0.979, p=0.000], SOFA score [OR 1.823, 95% CI 1.586-2.094, p=0.000], acute renal failure [OR 2.158, 95% CI 1.183-3.937, p=0.012] and procalcitonin [OR 1.018, 95% CI 1.002-1.033, p=0.023] compared to patients with low mean VIS (Table 3).

Patient characteristics according to peak VIS ≥10

Age (70 vs 66 years, p=0.014), SOFA score (12 vs 9, p=0.000), acute renal failure (32.3% vs 18.6%, p=0.003) and procalcitonin levels (8.3 vs 6.4, p=0.000) were higher in peak VIS ≥10 patients group, while ICU hospitalization time (8 vs 16 days, p=0.000) was shorter (Table 4).

Multivariable logistic regression was performed controlling for patient characteristics. Patients with high peak VIS had significantly greater odds of duration of ICU stay [OR 0.958, 95% CI 0.941-0.976, p=0.000], SOFA score [OR 1.785, 95% CI 1.559-2.044, p=0.000] and acute renal failure [OR 2.052, 95% CI 1.112-3.783, p=0.021] compared to patients with low peak VIS (Table 4).

The Correlation Between Mean Cutoff VIS value and Mortality

The cut-off value of mean VIS values according to the receiver operating characteristic (ROC) analysis performed to predict mortality rate was found as 9.75 (Figure 1). The area under the ROC for mean VIS was 0.713 [95% CI 0.662-0.764, p<0.0001], with sensitivity, specificity, and positive and negative predictive values and overall consistency values with 95 % CI of 71.5%, and 66.9 %,61.1%, 76.3% and 68.8%, respectively, at a cutoff ≥9.75 (Table 5).

Discussion

As far as we know, this is the first study that evaluated VIS in septic shock patients followed in the adult intensive care unit. According to our study, high mean and peak VIS values calculated within the first 48 hours in patients with septic shock may predict the increase in mortality. Mean VIS ≥10 is an independent risk factor for mortality.

Sepsis, the most common cause of intensive care admission, is also the most common cause of death in the intensive care unit. Despite all advances in treatment, mortality is around

Table 3. Patient characteristics according to mean VIS ≥10

	Univariate Analysis			Multivariate analysis	
Variables	**Mean VIS <10** n= 200	**Mean VIS ≥10** n=192	**p**	**OR(CI%95)**	**p**
Age (years)	67(49-77.5)	71(59-80)	**0.004**	1.018(1.004-1.033)	**0.014**
Gender (male)	115(57.5%)	124(64.6%)	0.178		
ICU admission time (days)	15.5(6-28.7)	8(2-15)	**0.000**	0.961(0.943-0.979)	**0.000**
SOFA score	9(8-11)	12(12-13)	**0.000**	1.823(1.586-2.094)	**0.000**
APACHE II score	24.5(16-27)	24.5(20-26)	0.636		
Mechanical ventilation	196(98%)	184(95.8%)	0.251		
Acute renal failure	38(19%)	65(33.9%)	**0.001**	2.158(1.183-3.937)	**0.012**
Blood products transfusion	120(60%)	111(57.8%)	0.682		
Steroid support	46(23%)	45(23.4%)	0.830		
Fluid balance (ml)	700(1600-2400)	1600(700-2150)	0.147		
Laboratory					
Platelets (x 103 /µL)	104(95-138)	110(90-141)	0.626		
Hemoglobin (g/dL)	9.8(9.1-10.1)	9.7(9.1-10)	0.235		
White blood cell (x 103 /L)	9.5(8-12.2)	10(8.5-14)	0.199		
Procalcitonin (ng/ml)	6.6(3.2-9.3)	8.6(6.1-17.5)	**0.000**	1.018(1.002-1.033)	**0.023**
Lactate (mEq/L)	4.1(2.4-5.4)	4.3(2.6-6)	0.220		
Anatomic localizations of infectious foci					
Blood-catheter borne infection	55(27.5%)	50(26%)	0.820		
Urinary system infection	76(38%)	67(34.9%)	0.531		
Respiratory system infection	110(55%)	72(37.5%)	**0.001**		**NS**
Soft tissue infection	28(14%)	13(6.8%)	**0.021**		**NS**

Data are presented as median (IQR) or n (%). **ICU:** Intensive Care Unit, **SOFA:** Sequential Organ Failure Assessment, **APACHE II:** Acute Physiology and Chronic Health Evaluation 2, **VIS:** Vasoactive Inotropic Score

Table 4. Patient characteristics according to peak VIS ≥10

	Univariate Analysis			Multivariate analysis	
Variables	**Peak VIS <10** n= 172	**Peak VIS ≥10** n=220	**p**		
Age (years)	66(48.2-78)	70(58-79)	**0.014**		**NS**
Gender (male)	104(60.5%)	135(61.4%)	0.917		
ICU admission time (days)	16(7-30)	8(2-16)	**0.000**	**0.958(0.941-0.976)**	**0.000**
SOFA score	9(8-10)	12(11-13)	**0.000**	**1.785(1.559-2.044)**	**0.000**
APACHE II score	24.5(16-27)	24.5(20-27)	0.550		
Mechanical ventilation	170(98.8%)	210(95.5%)	0.075		
Acute renal failure	32(18.6%)	71(32.3%)	**0.003**	**2.052(1.112-3.783)**	**0.021**
Blood products transfusion	105(61%)	126(57.3%)	0.470		
Steroid support	40(23.2%)	51(23.1%)	1.000		
Fluid balance (ml)	1600(700-2400)	1600(700-2150)	0.388		
Laboratory					
Platelets (x103 /µL)	103(95-139)	109(90-140)	0.776		
Hemoglobin (g/dL)	9.8(9.1-10.1)	9.7(9.1-10)	0.218		
White blood cell (x103 /L)	9.5(8.5-12.8)	9.5(8-13.3)	0.774		
Procalcitonin (ng/ml)	6.45(3.2-9.17)	8.3(5.5-14.3)	**0.000**		**NS**
Lactate (mEq/L)	4.1(2.6-5.4)	4.3(2.6-6)	0.216		
Anatomic localizations of infectious foci					
Blood-catheter borne infection	47(27.3%)	58(26.4%)	0.909		
Urinary system infection	63(36.6%)	80(36.4%)	1.000		
Respiratory system infection	98(57%)	84(38.2%)	**0.000**		**NS**
Soft tissue infection	25(14.5%)	16(7.3%)	**0.030**		**NS**

Data are presented as median (IQR) or n (%). **ICU:** Intensive Care Unit, **SOFA:** Sequential Organ Failure Assessment, **APACHE II:** Acute Physiology and Chronic Health Evaluation 2, **VIS:** Vasoactive Inotropic Score

Table 5. ROC analysis for the prediction of mortality. Cut-off mean VIS value for survivors versus non-survivors based on ROC analysis

		AUC			p value	Asymptotic 95 % confidence intervals lower bound-upper bound	Cut-off value
Mean VIS		0.713			0.000	0.662-0.764	≥9.75
		Exitus				Sensitivity = 118/165= 71.5%	
		Yes	**No**	**Total**		Specificity = 152/227= 66.9%	
Mean	Yes	118	75	193		Positive predictive value = 118/193= 61.1%	
VIS=9,75	No	47	152	199		Negative predictive value = 152/199= 76.3%	
	Total	165	227			Total consistency = 118+152/392= 68.8%	

ROC: Receiver operating characteristic, **AUC:** Area under the curve, **VIS:** Vasoactive-inotropic score.

20-30% (9). According to a meta-analysis, mortality rates in ICU in sepsis can reach 40-60% (10). Mortality was 42.1% in our study group. Hypotension occurs in sepsis as a result of venous and arterial vasoplegia, hypovolemia and myocardial depression. In studies, vasopressor agents such as norepinephrine, epinephrine, vasopressin, dopamine, terlipressin, phenylephrine and inotropic agents such as dobutamine, dopexamine, milrinone and levosimendan were used (11). According to the Surviving Sepsis Campaign guideline, norepinephrine is the first choice for vasopressor support when there is no response to fluid therapy in septic shock (1). Norepinephrine reduces mortality. Dopamine with similar effect has undesirable effects such as tachycardia and arrhythmia. Two other drugs, which are often preferred, are epinephrine and vasopressin, reducing the need for norepinephrine. Inotropes may be added to patients with cardiac dysfunction (12). In our study, 93.1% of patients received norepinephrine in the first 48 hours of septic shock. Other drugs have been dopamine, adrenaline and dobutamine.

It is relatively difficult to evaluate the adequacy of fluid therapy in sepsis and septic shock. Conditions such as acute renal failure, heart failure, pulmonary edema and prolonged mechanical ventilation may occur as the amount of fluid support increases. In our study, we found no significant difference in fluid support between the groups. At the same time, there was no difference between steroid support rates in the case of refractory shock. The aim of using vasopressors in septic shock is to maintain tissue perfusion and to prevent the process of organ dysfunction (1). At the same time, we try to save time for eliminating the potential causes (13). Microcirculatory disorders may continue while blood pressure is increased with the use of vasopressors. Besides, vasoconstriction may cause oxygen diffusion disorder at the cellular level (14). In our study, increased lactate levels were independent risk factors for mortality but not with VIS elevation. However, the levels of procalcitonin in our laboratory were independent risk factors for mortality and were also predictive for mean VIS ≥10.

VIS, which was developed based on the idea that there may be a relationship between the size of these supports given to patients in shock and patient outcomes, has been mostly studied after cardiac surgery and especially in the pediatric patient group. In one study, VIS scores were calculated in infants with cardiopulmonary bypass in congenital heart disease surgery. High maximum VIS values within the first 48 hours postoperatively were associated with poor outcome in terms of cardiac arrest, circulatory support, renal replacement therapy, neurologic injury and death (3). In another study, VIS values calculated in 391 infants who underwent cardiac surgery. The relationship between high VIS values (especially max VIS≥20) and poor clinical outcome was found in the first 48 hours in patients who were followed-up in the ICU postoperatively (6).

To our knowledge, only two studies in septic patients and in a group of pediatric patients underwent VIS (7,8). In a study, pediatric sepsis patients (2 months-18 years) in the intensive care unit were evaluated with VIS. VIS values were calculated at the first 6, 12, 24 and 48 hours after diagnosis. The relationship between VIS and ventilator days and ICU hospitalization periods was evaluated as primary and strong correlation was determined between them. In conclusion, it was reported that use of VIS in pediatric sepsis patients might be beneficial (7). In another study, 71 children with fluid refractory septic shock (1 month-16 year of age) evaluated the relationship between VIS and mortality. Mortality was 44% in patients with VIS <20 and 100% in those with VIS ≥20 (8). A study that reported that only limited data on the use of multiple vasoactive drugs in the ICU revealed that patients who received three or more vasoactive drugs rarely survived (13). In our study, adult septic shock patients were evaluated and both the mean and peak values of VIS were significantly higher in the deceased patient group. Also, mean VIS ≥10 and peak VIS ≥10 were associated with mortality, whereas VIS> 10 was an independent risk factor for mortality.

In a study, patients with low cardiac output syndrome (LCOS) at the early postoperative period were examined in pediatric cardiac surgery. Also calculated maximum VIS. LCOS was not associated with duration of mechanical ventilation, ICU stays, hospitalization time and hospital costs. Increased VIS was moderately related to prolonged mechanical ventilation, longer ICU hospitalization and higher total hospital costs, but was not associated with duration of hospitalization (15). In our study, there was no difference between the groups because almost all patients were in mechanical ventilator. However, the duration of ICU hospitalization was significantly lower in patients with higher VIS and also in deceased patients. In a study, the maximum vasoactive-inotropic score (VIS) and inotrope score (IS) were calculated at 24, 48 and 72 hours postoperatively in infants (in90 days) after cardiovascular surgery. Higher VIS values at 48 hours were strongly associated with increased intubation time and long-term ICU and hospital

stay. Both scores were not associated with time to negative fluid balance, peak lactate, and changes in creatinine (4). However, in our study, increased renal insufficiency and increased VIS were statistically associated. Another study examined the relationship between VIS and morbidity and mortality in adult cardiac surgery. The combination of morbidity and mortality were called as 'bad outcome'. A high VIS were associated with a bad outcome. Secondary results were the duration of ICU stay and time to extubation. Patients with high VIS were required longer ICU hospitalization and longer mechanical ventilation. In conclusion, the amount of cardiovascular support at the end of cardiac surgery has been reported to predict morbidity and mortality in adults (16). In our study, there was a significant relationship between advanced age, mean SOFA and mean and peak VIS ≥10 in both univariate and multivariate analyzes. In another study to determine the relationship between inotropic/vasoactive support and clinical outcomes in children after open heart surgery (208 patients), it was reported that this score could be an excellent tool to measure the severity of the disease, decide on interventions, and provide parental counselling in pediatric cardiac surgery ICUs (17).

In a study, adolescents with congenital heart disease (10-18 years) were examined with VIS postoperatively. Maximum VIS values at 24 and 48 hours were significantly associated with increased hospitalization and prolonged weaning periods. According to cutoff> 4.75, the area under the ROC for the max VIS was 0.76, while the sensitivity, specificity, positive predictive value and negative predictive value were 67%, 74%, 36% and 91%, respectively. It has been proposed that this simple score can be used as a prognostic indicator (18). In our previous study in which the relationship between VIS score and mortality in patients with severe head trauma followed in adult intensive care unit was 72.7%, 74.1%, 68.1% and 78.2% for the cutoff value of mean VIS ≥7.5, respectively (19). In this study, according to the ROC analysis, the cut-off value of VIS 9.75 was taken, and the AUC value was 0.713 when the mortality was estimated. Sensitivity-specificity positive predictive value and negative predictive value were 71.5%, 66.9%, 61.1% and 76.3%, respectively.

Limitations

Our study has some limitations. First, our study was performed in a single-center and single intensive care unit and the data were retrospective. Second, our sepsis patients were heterogeneous and were followed up and treated by different clinicians during the long study period. Thirdly, clinical findings, central venous pressure and passive leg raising have been used to assess fluid status. Very few patients had bedside echocardiography and PICCO. Fourthly, the dose increase of vasopressor drugs was made according to the clinician's decision, accompanied by local protocols for ICU. We also did not have any protocol with maximum drug doses. Finally, there was no vasopressin in our hospital and therefore it was not used for VIS calculation.

Conclusion

We believe that vasoactive-inotropic score which is easy to calculate, does not require any laboratory examination, may be useful in predicting outcome in adult septic shock patients followed in the intensive care unit.

AUTHOR CONTRIBUTIONS:

Concept: IK, MS, YSB, HE, ID, JBC; **Design:** IK, MS, YSB, HE, ID, JBC; **Supervision:** IK, MS, YSB, HE, ID, JBC; BB; **Resources:** IK; **Materials:** IK; **Data Collection and/or Processing:** IK, MS, YSB, HE, ID, JBC; **Analysis and/or Interpretation**: IK, MS, YSB, HE, ID, JBC; **Literature Search:** IK, MS, YSB, HE, ID, JBC; **Writing Manuscript**: IK, MS, YSB: **Critical Review:** IK, JBC

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Fikir: IK, MS, YSB, HE, ID, JBC; **Tasarım:** IK, MS, YSB, HE, ID, JBC; **Denetleme:** IK, MS, YSB, HE, ID, JBC; **Kaynaklar:** IK; **Malzemeler:** IK; **Veri Toplanması ve/veya İşlemesi:** IK, MS, YSB, HE, ID, JBC; **Analiz ve/veya Yorum:** IK, MS, YSB, HE, ID, JBC; **Literatür Taraması:** IK, MS, YSB, HE, ID, JBC; **Yazıyı Yazan:** IK, MS, YSB; **Eleştirel İnceleme:** IK, JBC.

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