Original Article

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The Association of High Dose Vasopressor and Delayed Vasopressor Titration with 28-Day Mortality in Adult Patients with Septic Shock

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Abstract:

Objective: This study aimed to investigate any association between vasopressor dose and mortality, and to identify factors independently associated with 28-day mortality in adult patients with septic shock.

Material and Methods: Adult septic shock patients admitted to internal medicine wards; from May 2018-November 2020, were retrospectively included. Collected data included: patient demographics and clinical characteristics, baseline vital signs, source of infection, vasopressor dose, treatment modalities and patient outcomes. The primary outcome was 28-day mortality.

Results: From 253 patients, 54.9% survived, and 45.1% died. Compared to survivors, non-survivors had a significantly higher median Acute Physiology and Chronic Health Evaluation II score, higher median baseline serum lactate level and required a higher median-maximum dose of vasopressor. Multivariate analysis showed the maximum dose of vasopressor >0.2 mcg/kg/min (odd ratio (OR): 2.91, 95% confidence interval (CI): 1.13-7.47; p-value=0.027), time to maximum dose of vasopressor after 24 hours (OR: 4.98, 95% CI: 2.07-11.99; p-value<0.001), Sequential Organ Failure Assessment score >10 (OR: 2.92, 95% CI: 1.27-6.71; p-value=0.012), pneumonia (OR: 2.16, 95 %CI: 1.01-4.61; p-value=0.047) and receiving fluid resuscitation during the first 24 hours <3,000 mL (OR: 2.27, 95% CI: 1.05-4.89; p-value=0.037) to be independent predictors of 28-day mortality.

Conclusions: A higher intensity of vasopressor and longer time to maximum dose of vasopressor were found to be independent predictors of septic shock mortality.

Keywords: adult patients, factors, mortality, septic shock, Vasopressor dose, 28-day mortality

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Introduction

Septic shock is a serious, critical illness that causes several morbidities. It requires intensive care treatment, and that is associated with high mortality. A recent global study reported an incidence of 49 million cases per year and 11 million sepsis-related deaths in 2017, which accounts for approximately 20% of all annual deaths globally.[1] The reported mortality rate for septic shock ranged from 30% to 60%.[1-5] The outcome of treatment depends on many factors; including, patient comorbidities, the primary site of infection and the treatment given.[5]

Despite continuous advancements in medical knowledge and technology, mortality among patients with septic shock remains high. Local in addition to international guidelines for septic shock management have been developed to improve septic shock outcomes.[6-8] The main treatment for septic shock comprises of hemodynamic resuscitation, appropriate antibiotic administration and organ support. For hemodynamic resuscitation, fluid therapy and vasopressor are given to increase blood pressure and tissue perfusion. Although, fluid therapy and vasopressor administration is not a risk-free treatment option[9], determining the optimal balance between these two treatments can improve septic shock outcomes. Early, low-dose norepinephrine administration is associated with accelerated hemodynamic stabilization and may improve septic shock outcomes; however, there is inadequate information concerning the benefit of higher norepinephrine dose titration during the early phase of septic shock resuscitation.[10] Recent studies reported a relationship between a higher norepinephrine dose and increased septic shock mortality; however, the data reported by Yamamura, et al. did not confirm this association.[11-13] There also was a different in the cutoff value of vasopressor dosage that might be associated with poor outcomes[11-14]; together with the inconsistency of the vasopressors units that varies among the previous studies.[11-14] Hence, the dose limitation of vasopressor in this setting remains unclear. Moreover, we do not know the effect of rapid versus slow vasopressor dose titration on the impact of septic shock treatment. To address this essentially important issue, the aim of this study was to investigate for association between vasopressor dose and mortality, and to identify factors independently associated with 28-day mortality in adult patients with septic shock.

Material and Methods

Study design, location and population

This single-center retrospective observational study, was conducted at the Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; from May 2018 to November 2020. The study included adult (≥18 years) patients who were diagnosed with septic shock according to the Sepsis-3 definition[15], and were admitted to the general medical wards or the medical intensive care unit (ICU). We excluded patients with end-stage malignancy, acute stroke, acute coronary syndrome, acute pulmonary edema, status asthmaticus, active gastrointestinal bleeding, status epilepticus, severe burn, severe trauma, fatal drug overdose, peripheral arterial disease, refusal of vasopressor administration for resuscitation and pregnancy.

Data collection and operational definitions

All information was collected from our center's electronic patient medical record database. The parameters included: age, baseline vital signs, source of infection, dose of vasopressor, timing of vasopressor titration, fluid resuscitation, organ support, and treatment outcomes were recorded. The baseline severity of patient illness was assessed by Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score.[16,17] The primary outcome

of interest was the 28-day mortality rate. For the maximum dose of vasopressor, the summation of all vasopressor dosages were calculated, for which the patient received according to the established formula: norepinephrine dose equivalents [microgram per kilogram per minute (mcg/kg/min)] = [norepinephrine (mcg/kg/min) + epinephrine (mcg/kg/min) + dopamine (mcg/kg/min)/100.[18] The highest norepinephrine dose equivalents of each patient as the maximum vasopressor dose was determined. Time to maximum dose of vasopressor was defined as: the time from the diagnosis of septic shock to the time of administration of the highest dose of vasopressor. It was assumed that septic shock resuscitation could be commenced as of when septic shock was diagnosed. The time point of zero from the first vasopressor initiation to the maximal dose of vasopressor was not used, because it did not represent the delay of vasopressor titration.

Ethical consideration

This study's protocol was approved by the Institutional Review Board (Certification of approval No. Xi 705/2019). The requirement for written informed consent was waived due to the retrospective and anonymity-preserving nature of this study. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.[19]

Statistical analysis

Patient demographic and clinical data were summarized using descriptive statistics. All continuous variables were checked for normal distribution using the Kolmogorov-Smirnov test. Continuous variables with normal distribution are presented as mean ± standard deviation (S.D.), and were compared using Student's t-test. Continuous variables with non-normal distribution are

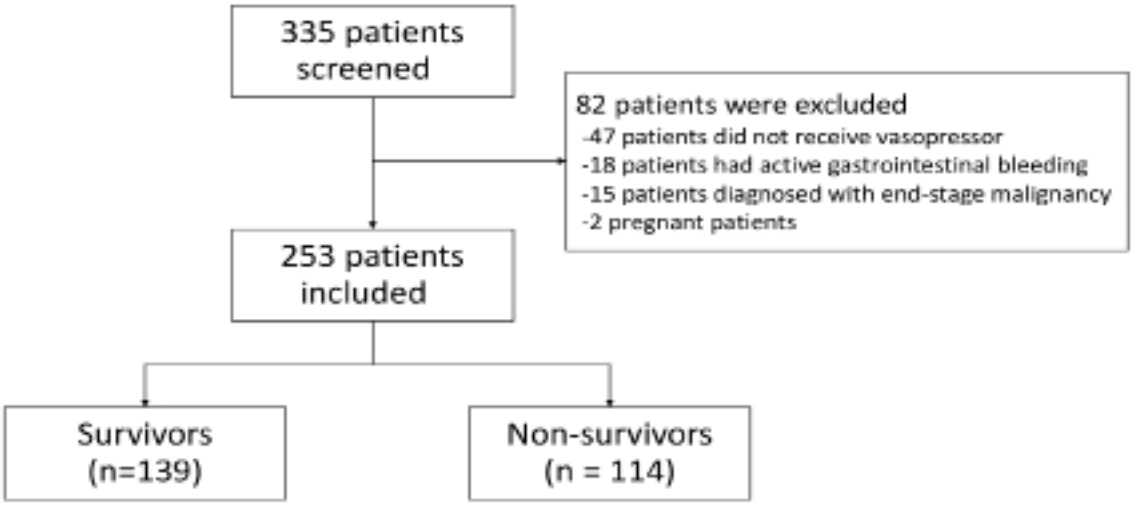

Figure 1 Flow diagram of the patient enrollment protocol

shown as median and interquartile range (IQR), and were compared between survivors and non-survivors by using Mann-Whitney U test. Categorical variables are presented as number and percentage, and were compared between survivors and non-survivors by using chi-square test or Fisher's exact test.

To identify the predictive factors, associated with 28-day mortality, receiver operating characteristic (ROC) curve analysis was performed to identify the cut-off values for the continuous variables that showed significant difference between survivors and non-survivors in each group. The optimal cut-off value, along with its sensitivity and specificity, was determined using Youden's index.[20] Variables were reclassified using the ROC curve identified cut-off values into 2 groups, and then univariate analysis was performed. Variables with a p-value less than or equal to 0.050 in univariate analysis were then entered into the multivariate analysis model. The results of multivariate analysis are shown as adjusted odds ratio (aOR) and 95% confidence interval (CI). A p-value of 0.050 or less was considered to be statistically significant. All statistical analyses were performed using statistical package for the social sciences (SPSS) statistics software version 20 (SPSS, Inc., Chicago, IL, USA).

Results

From the 335 patients with suspected septic shock, who were screened during the study period, 82 were excluded: (Figure 1) the remaining 253 septic shock patients were then included. The 139 patients (54.9%) who survived until 28 days after septic shock diagnosis were classified as the survivor group, with the 114 patients (45.1%) who died before 28 days being included in the non-survivor group.
Characteristics of the study population

Patient characteristics; including, age, gender, body mass index and underlying comorbidities were non-significantly different between groups (Table 1). Compared to survivors, non-survivors had a significantly higher SOFA score (median [IQR] 13 [11-16] vs. 9 [6-12], respectively; p-value<0.001) and APACHE II score (28 [22-33] vs. 20 [15-24], respectively; p-value<0.001). In both the survivor and non-survivor groups, pneumonia was the most common infection, followed by intraabdominal infection and upper urinary tract infection. However, the proportion of pneumonia was significantly higher (48.2% vs. 33.8%, p-value=0.018) and the proportion of upper urinary tract infection was significantly lower (6.1% vs. 14.4%, p-value=0.039) in non-survivors than in survivors. Moreover, non-survivors had a significantly higher median initial serum lactate level (4.9 [3.5-11.1] vs. 4.0 [2.2-7.7] mmol/L, p-value<0.001) and lower median baseline serum albumin level (2.4 [2.1-2.9] vs. 2.9 [2.3-3.3] g/dL, p-value<0.001) compared to survivors.

Comparison of septic shock resuscitation

Concerning septic shock resuscitation, non-survivors received a significantly lower median volume of fluid resuscitation during the first 24 hours of septic shock diagnosis compared to survivors (3,490 [1,825-5,463] vs. 4,320 [2,840-5,840] mL, p-value=0.004), but non-survivors received a significantly higher median-maximum dose of vasopressor (0.73 [0.52-0.73] vs. 0.57 [0.40-0.76] mcg/kg/min, p-value<0.001). Furthermore, non-survivors had a significantly longer median duration from septic shock diagnosis to achieving maximum dose of vasopressor compared to survivors (12 [5-18] vs. 18 [12-36] hours, p-value<0.001) (Table 2). Non-survivors also received significantly more mechanical ventilatory support, renal replacement therapy and hydrocortisone treatment compared to survivors. The median length of hospital stay was significantly shorter among non-survivors than among survivors (10.5 [3-19] vs. 20 [12-41] days, p-value<0.001).

Table 1 Baseline patient characteristics compared between survivors and non-survivors

Patient characteristics	Survivors (n=139)	Non-survivors (n=114)	p-value
Age (years)	66 (55-77)	69.5 (58.8-78)	0.261
Male gender	68 (48.9%)	56 (49.1%)	0.968
Body mass index (kg/m^2)	22.8 (20.3-26.1)	22.6 (19.8-25.0)	0.389
Mean SOFA score[a]	9 (6-12)	13 (11-16)	<0.001
SOFA score >10	46 (33.1%)	84 (73.7%)	<0.001
APACHE II score[b]	20.0 (15-24)	28.0 (22-33)	<0.001
APACHE II >20	56 (40.3%)	83 (72.8%)	<0.001
Underlying conditions			
Hypertension	75 (54.0%)	61 (53.5%)	0.942
Diabetes mellitus	60 (43.2%)	39 (34.2%)	0.148
Chronic kidney disease	42 (30.2%)	30 (26.3%)	0.471
Malignancy	21 (15.1%)	21 (18.4%)	0.479
Coronary artery disease	19 (13.7%)	16 (14.0%)	0.931
Cerebrovascular disease	12 (8.6%)	12 (10.5%)	0.614
Source of infection			
Pneumonia	47 (33.8%)	55 (48.2%)	0.018
Septicemia	30 (21.6%)	32 (28.1%)	0.234
Intraabdominal infection	26 (18.7%)	14 (12.3%)	0.162
Urinary tract infection	20 (14.4%)	7 (6.1%)	0.039
Soft tissue infection	7 (5.0%)	3 (2.6%)	0.334
Other	9 (6.5%)	3 (2.6%)	0.301
Initial vital signs and investigations			
Temperature (°Celsius)	38.6 (37.4-39.6)	38.5 (37.0-39.4)	0.409
Heart rate (beats/min)	110 (98-130)	120 (104-132)	0.100
Respiratory rate (times/min)	28 (24-33)	30 (26-35)	0.024
RR >30/min	46 (33.1%)	52 (45.6%)	0.041
Mean arterial pressure (mmHg)	60 (54-64)	58 (52-63)	0.082
MAP <65 mmHg	80 (57.6%)	67 (58.8%)	0.845
Initial serum lactate (mmol/L)	4 (2.2-7.7)	4.9 (3.5-11.1)	<0.001
Lactate >4 mmol/L	69 (49.6%)	77 (67.5%)	0.003
Serum albumin (g/dL)	2.9 (2.3-3.3)	2.4 (2.1-2.9)	<0.001
Albumin <3 g/dL	90 (64.7%)	92 (80.7%)	0.003

Data presented as median (IQR, interquartile range) or number and percentage

A p-value<0.050 indicates statistical significance

[a]SOFA score ranges from 0 to 24. A higher score represents a greater degree of organ failure.

[b]APACHE II score, which is a severity determination score, ranges from 0 to 71. A higher score indicates more severe disease.

SOFA score=Sequential Organ Failure Assessment score, APACHE II score=Acute Physiology and Chronic Health Evaluation II score, RR=respiratory rate, MAP=mean arterial pressure, kg/m^2=Kilogram per square meter, min=minute, mmHg=millimeter of mercury, mmol/L=millimole per liter, g/dL=gram per deciliter

Table 2 Septic shock resuscitation compared between survivors and non-survivors

Treatments	Survivors (n=139)	Non-survivors (n=114)	p-value
Fluid administered (mL)			
In 1st hour	700 (280-920)	600 (300-1,000)	0.783
In 6 hours	2120 (1,300-3,180)	2000 (808-2,878)	0.032
In 24 hours	4320 (2,840-5,840)	3490 (1,825-5,463)	0.010
<3,000 ml in 24 hours	39 (28.1%)	52 (45.6%)	0.004
Vasopressor			
Norepinephrine	122 (87.8%)	109 (95.6%)	0.031
Dopamine	6 (4.3%)	2 (1.8%)	0.252
Adrenaline	42 (30.2%)	90 (78.9%)	<0.001
Maximum dose of vasopressor (mcg/kg/min)	0.57 (0.40-0.76)	0.73 (0.52-0.93)	<0.001
Maximum dose of vasopressor >0.2 (mcg/kg/min)	54 (38.8%)	97 (85.1%)	<0.001
Time to maximum dose of vasopressor (hours)	12 (5-18)	18 (12-36)	<0.001
>24 hours	27 (19.4%)	38 (33.3%)	<0.001
Inotrope			
Dobutamine	1 (0.7%)	1 (0.9%)	0.887
Hydrocortisone	107 (77.0%)	108 (94.7%)	<0.001
Mechanical ventilation	113 (81.3%)	110 (96.5%)	<0.001
Renal replacement therapy	61 (43.9%)	75 (65.8%)	0.001
Target of treatment			
Mean arterial pressure ≥65 mmHg	53 (38.1%)	29 (25.4%)	0.029
Urine output ≥0.5 mL/kg/hour	40 (28.8%)	10 (8.8%)	<0.001
Lactate clearance ≥10%	31 (22.3%)	16 (14.0%)	0.049
Hospital length of stay (days)	20 (12-41)	10.5 (3-19)	<0.001

Data presented as median (IQR, interquartile range) or number and percentage
A p-value<0.050 indicates statistical significance, mL=milliliter, mcg/kg/min=microgram per kilogram per minute, mmHg= millimeter of mercury

Univariate and multivariate analysis

ROC curve analysis identified a SOFA score >10, APACHE II score >20, respiratory rate >30/min, initial serum lactate >4 mmol/L, baseline serum albumin <3 g/dL, receiving fluid resuscitation volume in the first 24 hours <3,000 mL, receiving maximum dose vasopressor >0.2 mcg/kg/min, and time to achieve maximum dose of vasopressor >24 hours as the cut-off value associated with 28-day mortality. Univariate analysis was performed, using the cut-off value derived from the ROC curve. Variables with a p-value less than or equal to 0.050 in univariate analysis were entered into the multivariate analysis model. Our multivariate analysis revealed the following 5 factors to be independent predictors of 28-day mortality among adult septic shock patients: SOFA score >10 (aOR: 2.92, 95% CI: 1.27-6.71; p-value=0.012), receiving fluid resuscitation in the first 24 hours <3,000 mL (aOR: 2.27, 95% CI: 1.05-4.89; p-value=0.037), receiving maximum dose of vasopressor >0.2 mcg/kg/min (aOR: 4.98, 95%CI: 2.07-11.99; p<0.001), time to achieving maximum dose of vasopressor >24 hours (aOR: 2.91, 95% CI: 1.13-7.47; p-value=0.027) and pneumonia (aOR: 2.16, 95% CI: 1.01-4.61; p-value=0.047) (Table 3).

Table 3 Univariate and multivariate analysis for independent predictors of 28-day mortality

Predictive factors	Univariate		Multivariate	
	OR (95%CI)	p-value	aOR (95%CI)	p-value
SOFA score >10[a]	6.57 (3.72-11.63)	<0.001	2.92 (1.27-6.71)	0.012
APACHE II score >20[b]	5.85 (3.23-10.63)	<0.001	2.08 (0.93-4.67)	0.075
Respiratory rate >30/min	1.70 (1.02-2.83)	0.042	1.51 (0.73-3.15)	0.268
Serum lactate >4 mmol/L	2.17 (1.29-3.64)	0.003	0.93 (0.41-2.12)	0.866
Serum albumin <3 g/dL	2.39 (1.33-4.29)	0.003	2.06 (0.91-4.65)	0.083
Fluid in 24 hours <3,000 ml	2.15 (1.28-3.63)	0.004	2.27 (1.05-4.89)	0.037
Time to maximum dose of vasopressor >24 hours	5.01 (2.34-10.75)	<0.001	2.91 (1.13-7.47)	0.027
Maximum dose vasopressor >0.2 mcg/kg/min	8.98 (4.84-16.66)	<0.001	4.98 (2.07-11.99)	<0.001
Renal replacement therapy	2.46 (1.47-4.10)	0.001	0.73 (0.34-1.58)	0.423
Pneumonia	1.83 (1.10-3.03)	0.020	2.16 (1.01-4.61)	0.047
Urinary tract infection	0.39 (0.16-0.96)	0.035	0.93 (0.28-3.12)	0.901
Mechanical ventilation	6.33 (2.14-18.12)	<0.001	1.45 (0.29-7.32)	0.652
Hydrocortisone	5.38 (2.16-13.40)	<0.001	2.51 (0.43-14.78)	0.308

A p-value<0.050 indicates statistical significance

[a]SOFA score ranges from 0 to 24. A higher score represents a greater degree of organ failure.

[b]APACHE II score, which is a severity determination score, ranges from 0 to 71. A higher score indicates more severe disease.

OR=odds ratio, aOR=adjusted OR, SOFA=Sequential Organ Failure Assessment, APACHE=Acute Physiology and Chronic Health Evaluation, CI=confidence interval, min=minute, mmol/L=millimole per liter, g/dL=gram per deciliter, ml=milliliter, mcg/kg/min=microgram per kilogram per minute

Table 4 Adverse events compared between the lower and higher maximum vasopressor dosage groups

Adverse events	Overall (N=253) %	Maximum vasopressor ≤0.2 mcg/kg/min (n=102) %	Maximum vasopressor >0.2 mcg/kg/min (n=151) %	OR (95%CI)	p-value
Death within 28 days	114 (45.1)	17 (16.7)	97 (64.2)	8.98 (4.84-16.66)	<0.001
Metabolic acidosis	184 (73.0)	76 (74.5)	108 (72.0)	0.88 (0.50-1.56)	0.657
Acute kidney injury	170 (67.5)	63 (61.8)	107 (71.3)	1.54 (0.90-2.63)	0.112
Pulmonary edema	59 (23.3)	36 (35.3)	23 (15.2)	0.33 (0.18-0.60)	<0.001
Cardiac arrhythmia	29 (11.5)	12 (11.8)	17 (11.3)	0.95 (0.43-2.09)	0.901
Acute mesenteric ischemia	4 (1.6)	0 (0.0)	4 (2.6)	Not available	0.151
Acute limb ischemia	4 (1.6)	0 (0.0)	4 (2.6)	Not available	0.151
Skin necrosis	2 (0.8)	1 (1.0)	1 (0.7)	0.67 (0.04-10.89)	0.779

A p-value<0.050 indicates statistical significance

OR=odds ratio, CI=confidence interval, mcg/kg/min=microgram per kilogram per minute

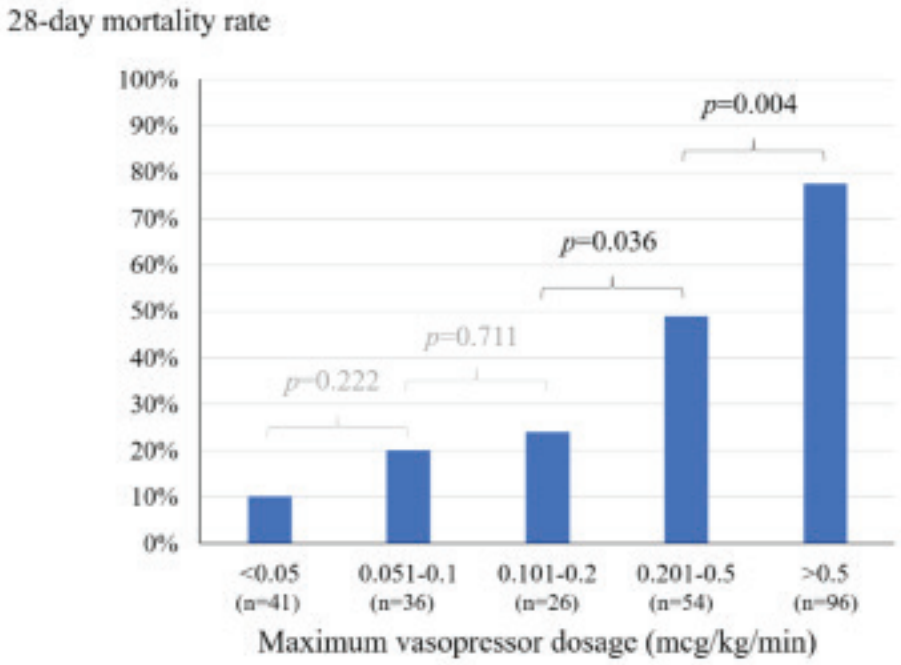

Figure 2A Mortality at 28 days; stratified by maximum vasopressor dosage in mcg/kg/min

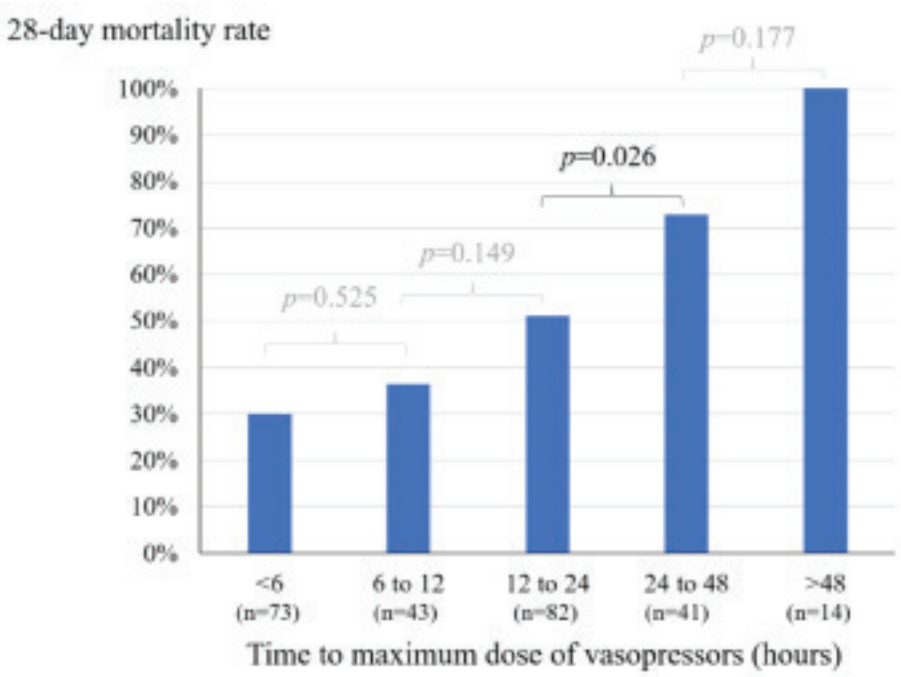

Figure 2B Mortality at 28 days; stratified by time to maximum dose of vasopressor in hours

Analysis for association between maximum vasopressor dosage and mortality, and between time to achieving maximum vasopressor dose and mortality are shown in Figure 2A and Figure 2B, respectively.

Overall adverse events and comparisons between the lower and higher maximum vasopressor dosage groups are shown in Table 4. When patients were stratified, according to the maximum dose of vasopressor using the cut-off value of 0.2 mcg/kg/min, the 28-day mortality rate was significantly higher among patients who received a maximum dose of vasopressor >0.2 mcg/kg/min than among those who received ≤0.2 mcg/kg/min (64.2% vs. 16.7%, respectively; OR: 8.98, 95%CI: 4.84-16.66; p-value<0.001); however, pulmonary edema was significantly lower among patients who received a maximum dose of vasopressor >0.2 mcg/kg/min (15.2% vs. 35.3%, respectively; OR: 0.33, 95% CI: 0.18-0.60; p-value<0.001). Acute mesenteric ischemia [4/151 (2.6%)] and acute limb ischemia [4/151 (2.6%)] were observed exclusively in patients who received maximum vasopressor >0.2 mcg/kg/min. Other adverse events; including, metabolic acidosis, acute kidney injury, cardiac arrhythmia, and skin necrosis, were similar between groups.

Discussion

In this retrospective cohort study, it was found that a higher maximum dose of vasopressor being greater than 0.2 mcg/kg/min, time to achieving maximum dose vasopressor being longer than 24 hours, a baseline SOFA score >10, receiving fluid resuscitation in the first 24 hours <3,000 mL, and pneumonia were independent predictors of 28-day mortality in adult septic shock patients. Of these 5 independent predictors, 3 are modifiable, which indicates that their adjustment or optimization may improve patient outcomes in septic shock management. Also, the results of this study could be interpreted in that, the major factor associated with septic shock mortality were severity of the patients, delayed resuscitation and a delay in goal achievement.

The use of catecholamine vasoactive agents; especially, norepinephrine, adrenaline, and dopamine is recommended to increase arterial blood pressure in septic shock patients who do not respond to fluid resuscitation; however; the uptitration of these agents is not risk-free. Several serious complications; including, intestinal ischemia, limb ischemia, myocardial infarction, and life-threatening arrhythmia have been reported during vasopressor administration.[21,22] Furthermore, the use of norepinephrine at 0.08 mcg/kg/min or more was identified as an independent predictor of impaired left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <50%) among sepsis and septic shock patients.[23] The result from this study were consistent with those from previous studies. Recently, Roberts, et al. reported that in septic shock patients, the elevation of every 10 mcg/min of norepinephrine equivalent dose over an entire 24 hours was associated with an increased risk of 30-day mortality (aOR: 1.33, 95% CI: 1.16-1.53), and that this association did not depend on the amount of fluid administration.[11] However, the dose of norepinephrine was not adjusted according to the patient's baseline body weight, so their findings cannot be compared to those from studies; such as this one, that adjusted the dose of vasopressor according to patient body weight. A multicenter retrospective observational study that enrolled 730 adult septic shock patients, having been admitted to 8 European ICUs, found the use of norepinephrine 0.3 mcg/kg/min or more was associated with higher ICU mortality.[12] This level is slightly higher than this study's findings, which was norepinephrine equivalent to greater than 0.2 mcg/kg/min.

The use of vasopressor during septic shock resuscitation may be influenced by the rate and volume of fluid resuscitation. Some recent studies have reported the

benefits of early administration of norepinephrine for septic shock resuscitation, which could reduce the volume of fluid resuscitation required to increase patient blood pressure.[10,24] However, septic shock patients who receive inadequate fluid resuscitation may require a higher dose of vasopressor, and the results of this study support this hypothesis. In this study it was found that non-survivors received significantly less median fluid resuscitation within 24 hours compared to survivors (3,490 [1,825-5,463] vs. 4,320 [2,840-5,840] ml, respectively; p-value=0.004); however, they received a significantly higher median dose of vasopressor (0.73 [0.52-0.73] vs. 0.57 [0.40-0.76] mcg/kg/min, respectively; p-value<0.001) compared to survivors. Multivariate analysis also found receiving resuscitation fluid lower than 3,000 mL during the first 24 hours of septic shock resuscitation to be an independent predictor of 28-day mortality. Association between vasopressor dosage and septic shock mortality, and between fluid resuscitation volume and septic shock mortality was also reported by Roberts, et al.[11] It may, therefore, be possible that early, aggressive fluid administration during the early phase of septic shock resuscitation may reduce the dose of vasopressor; which is a modifiable risk factor that may improve patient outcomes.

Strengths and limitations

This study has some important strengths. First, the evaluated and reported dose of vasopressor were in weight-based units. This is important because the effects of vasopressors may be influenced by patient body weight, and there is no established recommendation for this strategy in the current guideline. Second, the identified time to maximum dose of vasopressor could impact patient outcomes. Although, the maximum dose and the optimal way to uptitrate vasopressors is not yet known, the findings of this study will open the door to further exploration concerning these important topics.

This study also has some mentionable limitations. First, the findings may be biased by unmeasured confounding factors, due to the single-center retrospective nature of this study. Thus, the relationships identified in this study should be confirmed by a larger multi-center study. Second, the specific type of fluid resuscitation was not clarify. Different fluid resuscitation; especially crystalloid versus colloid as well as albumin versus another colloid, may influence patient outcomes. However, the main type of fluid resuscitation used at this center during the study period was crystalloid; either 0.9% NaCl or balance solution, so there would have been no difference in type of fluid resuscitation between the low-dose and high-dose vasopressor groups. Third, a norepinephrine equivalent dose was used to define the maximum dose of vasopressor. However, different types of vasopressors have different effects that can result in different adverse consequences. By way of example; cardiac arrhythmia more commonly occurs after epinephrine administration than after norepinephrine administration. Moreover, the pattern of titration and dynamic change of vasopressor dosage was not explored. Fourth, the incidence of cardiac arrhythmia from electrocardiographic monitoring was collected once the patient was admitted to the ICU. However, some patients received vasopressor before they were transferred to the ICU, so arrhythmia that developed or occurred before ICU admission would not have been recognized nor reported, which would have resulted in underreporting of cardiac arrhythmia. Fifth and finally, the reported adverse events, which were higher among those who receive vasopressor >0.2 mcg/kg/min, may not have been caused by the vasopressor itself. Generalized tissue hypoperfusion, internal sympathetic stimulation, and systemic inflammatory response due to septic shock, could also be suspected causes of the adverse events reported in this study.

Conclusion

The results of this study revealed a higher maximum dose of vasopressor being greater than 0.2 mcg/kg/min, time to achieving maximum dose vasopressor as being longer than 24 hours, a baseline SOFA score >10, receiving fluid resuscitation in the first 24 hours <3,000 mL, and pneumonia to be independent predictors of 28-day mortality in adult septic shock patients. Of these 5 independent predictors, 3 are modifiable, which indicates that their adjustment or optimization may improve patient outcomes in septic shock management. Further well-designed prospective studies are needed to evaluate and verify these findings.

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Conflict of interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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