Original Article

Septic Shock Outcome and Factors Associated with Mortality in the Intensive Care Unit in Vietnam

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Objective: To evaluate the mortality rate of septic shock patients and to learn about the associated risk factors for death.

Materials and Methods: Septic shock is a life-threatening subset of sepsis with profound circulatory, cellular, and metabolic abnormalities. The authors conducted an analytical cross-sectional study on adult patients diagnosed with septic shock using Sepsis-3 criteria between May 2016 and May 2018 at an intensive care unit at a hospital in Vietnam. Data on patients' outcomes and associated factors were collected through questionnaires and the patient medical records. To measure the association between independent variables and outcomes, odds ratio (OR) and 95% confidence interval (CI) were calculated using logistic regression.

Results: One hundred fifty patients with septic shock were enrolled in the present study. Septic shock occurred in 71.3% of the 60-years-old patients and 54% were men. The mean age was 68.5±15.52 years. The mortality rate was 62% and 17.3% of patients died within 24 hours after being diagnosed with septic shock. The median length of ICU stay was four days. The initial mean SOFA and APACHE II scores were significantly higher in the death group. Septic shock patients with comorbidities had a higher mortality risk compared to those without comorbidity (OR 2.9, 95% CI 1.116 to 7.700). Patients who developed septic shock in the hospital were at greater death risk (OR 7.8, 95% CI 3.3 to 18.2). Septic shock due to pneumonia had a higher mortality risk in comparison with those due to the other causes (OR 5.2, 95% CI 2.4 to 11.0).

Conclusion: The mortality rate of patients with septic shock in Vietnam was considerably high. Many factors were identified as risks, such as nosocomial infection and respiratory tract diseases.

Keywords: Septic shock; Outcome; Risk factors; Vietnam

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Along with an increase in the global burden of sepsis, septic shock is also a serious health problem. The annual rate of new septic shock cases reported by the World Health Organization is about 24 million[1]. Epidemiological studies from high-income countries suggest high incidence rates of hospital-treated sepsis, ranging from 194 to 580 per 100,000 inhabitants[2]. The burden of septic shock is even higher in low and middle-income countries[1]. In recent years, despite many advances in management, the rate of septic shock-related death remains high and appears to be trending higher. In the United States, septic shock was the leading cause of death among patients in intensive care units (ICU)[3]. Studies in the U.K. showed that septic shock accounted for 19.9% of patients admitted to ICUs with a mortality rate of 56%[4]. Research conducted at 150 Asian hospitals reported that the incidence of septic shock was 10.9% and the mortality rate stood at 44.5%[5]. In Vietnam, septic shock was one of the most fatal conditions, representing 13% of the total immediate causes of death in hospitals[6]. Mortality rates of septic shock in some Vietnamese hospitals were reported to vary between 40% and 60%. At Can Tho Central General Hospital, the rate was alarmingly high, at 71.7%[7] according to a recent study. The present study institution is among the few central hospitals in Vietnam and plays an important role in taking care of patients in the Mekong Delta. To better understand and improve treatment results of septic shock in this area, the current study aimed to assess the mortality rate of septic shock patients and to learn about the associated risk factors for death in Vietnam.

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Materials and Methods

Study population

The present study was analytical cross-sectional study conducted on septic shock patients admitted to the ICU of Can Tho Central General Hospital between May 2016 and May 2018.

Sample size calculation:

$$n = Z^2_{1-\frac{\alpha}{2}} \times \frac{p(1-p)}{d^2}$$

Z=1.96 (95% confidence interval)

d: allowable error=7.5%

p=71.7% (mortality rate of septic shock patients[7])

n: sample size=139 (at the end of the recruiting period, we enrolled 150 patients)

The authors recruited all patients met the criteria (i) 18 years old or older, and (ii) diagnosed with septic shock. Septic shock patients were defined according to Sepsis-3 criteria, which included three points, (i) patients were diagnosed with sepsis with evidence of infection plus SOFA score elevated at least 2 from baseline, (ii) persisting hypotension that had to be corrected by vasopressor, and (iii) serum lactate concentration greater than 2 mmol/L[8]. The exclusion criteria were patients who were diagnosed with cardiogenic shock such as hypotension with prominent clinical pulmonary congestion symptoms and impaired end-organ perfusion, and anaphylactic shock such as shock symptoms developed minutes to hours after exposure to a likely allergen. Data were collected prospectively through the patient medical records at the ICU of Can Tho Central General Hospital. The study received approval by the Ethics Committee of Can Tho University of Medicine and Pharmacy and Faculty of Medicine (no. 1224/D. CTUMP).

Variables

The following information were recorded, demographic characteristics, admission category, comorbidities, preexisting organ insufficiency, clinical and laboratory features, source of infection, cultures, antibiograms of blood, and suspected infection source specimens. Risk factors for multi-resistant pathogen infection were defined as patients having at least one of these features, (i) had been admitted for more than five days, (ii) had been through invasive procedures, and (iii) had been treated with broad-spectrum antibiotics for more than three days before being diagnosed with septic shock. Nosocomial infection was defined as an infection that appeared after at least 48 hours in the hospital. The Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score on the first day of ICU were recorded to evaluate the severity of illness. For empirical antibiotic therapy appropriateness, the treatment was labeled as appropriate if it resulted in improvement of the patient infection status after at least 48 hours of follow-up, or the chosen empirical antibiotics were sensitive according to the culture results of blood cultures or cultures from the suspected sources of infection, otherwise, it was called not appropriate. All the patients who died within 48 hours and had no positive cultures were grouped as unidentified.

Outcome measures

All enrolled patients were followed until death in the hospital, hospital discharge, or until May 30, 2018. The primary outcome measure was hospital mortality rate, time to death, ICU length of stay, and hospital length of stay. Patients who were still hospitalized on May 30, 2018, were defined as survivors.

Statistical analysis

SPSS Statistics software, version 16.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. For qualitative variables, results were displayed as rate, ratio, and percentage. For quantitative variables that exhibited normal distributions, data were presented as mean and standard deviation (SD), otherwise, using median and interquartile range (IQR). Independent samples t-test for independent groups was applied to data with a normal distribution. Mann-Whitney U-test was used for independent groups when normality was rejected. For categorical variables, the chi-square or Fisher's exact test was applied where appropriate. To determine independent predictors for hospital mortality of septic shock patients, odds ratios (ORs) and respective 95% confidence intervals (CIs) were used, which were estimated using multivariate logistic regression analysis. Variables including demographics, underlying diseases, source of infection, the severity of illness were entered into the model if they had p-value less than 0.2 in univariate analysis. The Hosmer-Lemeshow test was used to assess the calibration of the regression model. All comparisons were unpaired, and all tests of significance were two-tailed. A p-value of less than 0.05 was considered statistically significant.

Results

Population characteristics

Between May 2016 and May 2018, 150 eligible patients were included in the present study and 54%

Table 1. Characteristics and outcomes of patients with septic shock

Variables	All patients (n=150); n (%)	Survivors (n=56); n (%)	Non-survivors (n=94); n (%)	p-value
Age (year); mean±SD	68.5±15.52	64.6±14.76	70.8±15.57	0.016***
Sex: male	81 (54.0)	31 (55.4)	50 (53.2)	0.797
Nosocomial infection	61 (40.7)	8 (14.3)	53 (56.4)	<0.001*
With comorbidities	130 (86.7)	44 (78.6)	86 (91.5)	0.024*
Source of infection				<0.001**
Respiratory system	67 (44.7)	12 (8.0)	55 (36.7)	
Gastrointestinal system	45 (30.0)	26 (17.3)	19 (12.7)	
Skin and soft tissue	13 (8.7)	7 (4.7)	6 (4.0)	
Urinary system	12 (8.0)	6 (4.0)	6 (4.0)	
Neural system	3 (2.0)	0 (0)	3 (2.0)	
Undetermined	10 (6.7)	5 (3.3)	5 (3.3)	
Risk of multi-resistant pathogen	50 (33.3)	6 (10.7)	44 (46.8)	<0.001*
Positive blood culture	26 (17.3)	12 (21.4)	14 (14.9)	0.374
Lactate (mmol/L); median	5.4	5.8	4.8	0.658
APACHE II score; mean±SD	22.0±7.01	18.27±6.38	24.1±6.46	<0.001***
SOFA score	10.1±2.69	8.8±2.17	10.9±2.70	<0.001***
Length of ICU stay (days); median [min-max]	4 [1 to 88]	5 [2 to 52]	4 [1 to 88]	
Length of hospital stay (days); median [min-max]	9 [1 to 88]	14 [4 to 66]	5.5 [1 to 88]	

SD=standard deviation; APACHE II=Acute Physiology and Chronic Health Evaluation II Score; SOFA=Sequential Organ Failure Assessment Score; ICU=intensive care unit

* Fisher's exact test; ** Chi-square test; *** Independent samples's t-test

Table 2. Life-support management for septic shock patients

Methods	Number of cases; n (%)
Second vasopressor	12 (8.0)
Inotropes	69 (46.0)
Hydrocortisone	86 (57.3)
Mechanical ventilation	104 (69.3)
Continuous renal replacement therapy	13 (8.7)

were male. The rate of patients over 60 was 71.3% and the mean age was 68.5±15.52 years. Some other characteristics of patients are shown in Table 1.

Outcome of patients

Throughout the treatment, 94 patients died (62.7%). Twenty-six patients died within 24 hours after being diagnosed with septic shock, accounting for 17.3%. Four patients had lived for more than 28 days. The median length of stay at ICU was five days for survivors and four days for non-survivors (Table 1).

For septic shock patient management, only 8% had more than one vasopressor or noradrenaline as the first line, plus dopamine or adrenaline, and 69.3% had been mechanically ventilated. More than half of septic shock patients were treated with hydrocortisone (Table 2).

Antibiotics were used empirically in all patients. Clinical or microbial appropriateness was found in 95 patients (63.7%). In this group, 51.6% survived and 48.4% did not. Alternatively, 80.6% of patients who did not receive appropriate empirical therapy died, resulting in a significant difference compared to the appropriate group (p=0.001) (Table 3).

After adding seven variables, which are age, APACHE II score, SOFA score, nosocomial infection, respiratory tract infection, risk of the multi-resistant pathogen, and comorbidity in the multivariate model, the authors recorded three variables that were independent risk factors for hospital mortality (Table 4).

Discussion

The rate of septic shock death was 62.7% according to the present study results, which was lower than a study conducted at the same hospital several years ago (71.7%)[7]. Based on this finding, it was evident that the septic shock death rate has decreased, possibly suggesting an improvement in

Table 3. Empirical antibiotic therapy appropriateness

Level of appropriateness	Number of cases; n (%)	Survivors; n (%)	Non-survivors; n (%)	p-value
Appropriate	95 (63.7)	49 (51.6)	46 (48.4)	0.001*
Clinically and microbially	21 (14.0)			
Clinically only	49 (32.7)			
Microbially only	25 (16.7)			
Not appropriate	13 (24.0)	7 (19.4)	29 (80.6)	
Unidentified	19 (12.7)			

* Fisher's exact test, all unidentified cases (19 patients) were omitted before calculating the p-value

Table 4. Multivariate logistic regression analysis of independent predictors of hospital mortality in patients with septic shock

Risk factors	OR (95% CI)		p-value	
	Univariate	Multivariate	Univariate	Multivariate
Nosocomial infection	7.756 (3.308 to 18.188)	4.402 (1.217 to 15.922)	<0.001	0.024*
Respiratory tract infection	5.18 (2.421 to 10.989)	3.379 (1.447 to 9.947)	<0.001	0.007*
SOFA score	1.418 (1.206 to 1.668)	1.308 (1.057 to 1.619)	<0.001	0.013*
With comorbidities	2.93 (1.116 to 7.700)	3.375 (0.887 to 12.841)	0.024	0.074
Age	1.027 (1.004 to 1.049)	1.011 (0.981 to 1.041)	0.018	0.488
Risk of multi-resistant pathogen	7.333 (2.868 to 18.749)	1.465 (0.357 to 6.011)	<0.001	0.596
APACHE II score	1.156 (1.087 to 1.230)	1.072 (0.990 to 1.161)	<0.001	0.086

OR=odds ratio; CI=confidence interval; APACHE II=Acute Physiology and Chronic Health Evaluation II Score; SOFA=Sequential Organ Failure Assessment Score

* Statistically significant at p<0.05 in the multivariate logistic regression

the management capacity of the department for the condition. However, this rate was higher compared to many other studies in Asian ICUs (44.5%)[5], Germany (50.9%)[9], France (42.0%)[10], and England (55.5%)[4]. Japan was higher at 63.6%[11]. Many factors could explain this disparity. For an ICU in a developing country, lack of material facilities and medical supplies, a high proportion of healthcare-associated infections, and the medical staff's heavy workload may all contribute to a high septic shock death rate[12]. In addition, high treatment costs of the disease could interfere with decisions by low-income patients and their families, resulting in choices to shorten the critical care treatment. Overall, the high rate of death from septic shock in these studies in Asia affirmed the challenges faced by ICU in the management of this condition.

The present study showed statistically significant differences in mean age between non-survivor and survivor groups (71.0±15.56 and 64.4±14.69, respectively). Aged patients tend to have many comorbidities and a higher possibility of preceding exposure to medications such as antibiotics and corticosteroids that may lead to drug-resistant infection, compromised immune system and therefore, higher treatment failure rate. These findings revealed consistency with other study results[9,13,14].

Patients who developed nosocomial infection had a higher mortality risk compared to those with community-acquired infection (p<0.001). This result resembled a multi-center study by Quenot et al in which patients with hospital-originated infection experienced higher mortality rates at 3, 7, and 28 days in comparison with community infection (p<0.0001)[10]. However, Baharoon et al found no difference between outcomes of community-acquired and hospital-acquired severe sepsis and septic shock patients (p=0.12)[15]. Baharoon et al enrolled a small number of patients (n=96), which might lead to non-significant results, as they discussed in their article. Pathogens in hospital-acquired infection, especially in the setting of the ICUs in developing countries, are becoming more resistant to antibiotics due to antibiotic misuse, especially broad-spectrum agents, low adherence to hand hygiene process, and insufficient hand hygiene facilities and personal protective equipment. Nosocomial infection, hence, resulted in much higher mortality[12].

Patients without comorbidities had a higher chance of recovery from septic shock in contrast to ones having at least one comorbidity. This difference was statistically significant (p=0.029), which was similar to other studies' results[10,16]. Usually, septic shock disrupts the patients' conditions, causing exacerbation of chronic diseases, which could worsen outcomes. Known conditions such as diabetes, end-stage organ failures, and cancer were all well demonstrated to associate with a poor outcome.

Septic shock from the respiratory tract infection had a higher death rate compared to that of other sources (p<0.001). The present study record differed from Quenot and Zhou et al[10,16], in which bloodstream infection patients were at higher risk. The authors enrolled 150 septic shock patients, a relatively small number. Complications such as infections of the nervous system, endomyocarditis, and others, were therefore, rarely encountered. Consequently, the present study finding may not represent the true relation between the source of infection and outcomes.

The initial mean value of SOFA points and APACHE II points in the non-survivor group were higher than those of the survivor group, which was statistically significant (p<0.001). A resemblance was found when compared to other studies[7,10,16] confirmed that SOFA and APACHE II scores fairly associated with treatment outcomes. The fact that these parameters can be evaluated easily upon hospital admission may give rise to better outcome prediction and a more intense treatment plan.

The median length of ICU stay was four days, which was shorter than that of Self et al study (6.3 days)[17], Quenot et al study (9 days)[10], Marx et al study (11 days)[9], and Castaño et al study (11 days)[18]. This difference may be related to the high mortality rate of septic shock patients in the present study. Other contributors could be the shortage of treatment facilities, such as continuous renal replacement therapy (CRRT) for acute kidney injury patients, and the high rate of antibiotic-resistant pathogen infections. Moreover, inadequate ICU beds often drive the clinicians to quickly refer the patients to other departments or hospitals, sometimes very early in the course of care.

According to the present study results, the rate of septic shock patients receiving invasive mechanical ventilation was higher than that of Self et al study[18] but markedly lower than that of Vallabhajosyula et al study (81.9%)[19] and Quenot et al study (83.9%)[10]. Only 8.7% of patients had been treated by CRRT, which was low compared to Quenot et al study (32.5%)[10]. This difference can be explained because the present study was conducted at an ICU in a middle-income country, where medical facilities often were in shortage. Furthermore, this costly treatment technique may not be affordable for very low-income patients, even those with health insurance. Hydrocortisone was indicated and administered in 57.3%, which was equivalent to other studies[5,10].

Empirical antibiotic appropriateness was found in 95 patients (63.7%), which was much higher than that of Trà and Thảo study result (27.6%)[20]. This difference was possibly due to location of the present study (ICU) versus the emergency department in the study of Trà and Thảo[20]. Thanks to adequate examination and laboratory tests to determine the source of infection and anticipate underlying pathogens, septic shock patients admitted in the ICUs may have more appropriate antibiotic use than those in the emergency departments. Independent risk factors associated with increased mortality in septic shock included higher SOFA score, nosocomial infection, and infection from the respiratory tract. Except for the SOFA score, the two other risk factors were not the familiar findings across sepsis and septic shock studies[16,21,22]. The small number of enrolled patients may limit the present study findings. The authors suggest a larger study to further determine accurate prognostic factors for septic shock patients.

Conclusion

The mortality rate of patients with septic shock in the present study center in Vietnam is high, demonstrating that this condition is a true major health problem. Many factors were identified as risks, such as nosocomial infection and respiratory tract diseases. Further studies should be focused on how to optimize patient outcomes in the context of a developing country.

What is already known on this topic?

Septic shock is a fatal condition among patients treated in ICUs across the world. Some factors were determined as risk factors for death, such as higher age and high SOFA and APACHE II scores.

What this study adds?

This study's results add knowledge about septic shock characteristics and the death rate in Vietnam, a middle-income country where data about septic shock may be scarce. The study also demonstrated some important findings about septic shock risk factors

for death, such as nosocomial infection and infection from the respiratory system.

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Authors' contributions

All the authors played an active role in the study. TNTP and NVT conceived and designed the study. TNTP performed the study. TNTP, VPMT, and DTT analyzed the data. Finally, TNTP and DTT wrote the paper.

Disclaimers

All the views expressed in this article are our own and not the official position of the institution.

Conflicts of interest

No conflict of interest exists.

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