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Original Article

Use of hemodynamic and laboratory monitoring tools to reduce the risk of mortality from pediatric septic shock

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Abstract

Background Early recognition of septic shock in terms of clinical, macrocirculatory hemodynamic, and microcirculatory laboratory parameters is a fundamental challenge in the emergency room and intensive care unit for early identification, adequate management, prevention of disease progression, and reduction of mortality risk.

Objective To evaluate for possible correlations between survival outcomes of post-resuscitation pediatric septic shock patients and parameters of clinical signs, macrocirculatory hemodynamics, as well as microcirculatory laboratory findings.

Methods This prospective, study was conducted in the PICU at Saiful Anwar Hospital, Malang, East Java. Inclusion criteria were children diagnosed with septic shock according to the *2005 Surviving Sepsis Campaign* (SSC) criteria, aged >30 days-18 years, who were followed up for 72h after resuscitation. The measured variables such as cardiac index (CI), systemic vascular resistance index (SVRI), stroke volume index (SVI) were obtained from ultrasonic cardiac output monitor (USCOM). Blood gas and lactate were obtained from laboratory findings. Heart rate, pulse strength, extremity temperature, mean arterial pressure (MAP), systolic blood pressure (SBP), capillary refill time (CRT), Glasgow coma scale (GCS), and diuretic used were obtained from hemodynamic monitoring tools. Survival outcomes of post-resuscitation pediatric septic shock patients were noted.

Results There was a significant correlation between the outcomes of the pediatric septic shock patients 72h after fluid resuscitation and clinical, macrocirculatory hemodynamic, and microcirculatory laboratory parameters. After the 6th hour of observation, strong pulse was predictive of survival, with 88.2% area under the curve (AUC). At the 12th hour of observation, MAP >50th percentile for age was predictive of survival, with 94% AUC.

Conclusion For pediatric patients with septic shock, the treatment target in the first 6 hours is to improve strength of pulse, and that in the first 12 hours is to improve MAP >50th percentile for age to limit mortality. **[Paediatr Indones. 2023;63:35-48; DOI: https://doi.org/10.14238/pi63.1sup.2023.35-48**].

Keywords: *clinical parameters; macrocirculatory hemodynamics; microcirculatory laboratory findings; survival outcome; septic shock*

Sepsis is a systemic inflammatory response syndrome (SIRS) with suspected or proven infection. Septic shock is a severe infection that results in cardiovascular dysfunction (including hypotension, need for vasoactive drug therapy, or impaired perfusion). To reduce early mortality, resuscitation efforts in cases of septic shock should be aimed at achieving targets of macrocirculatory and microcirculatory parameters, especially those that have been shown to be associated with early mortality.[1,2]

Early recognition and adequate resuscitation of patients with sepsis-associated circulatory disorders are a fundamental challenge in the emergency department. Clinical sepsis can range from peripheral perfusion abnormalities that are difficult to recognize to septic shock with circulatory collapse, mottled skin, prolonged capillary refill time, abnormal body temperature, decreased consciousness, weak pulse, and decreased diuresis. Macrocirculatory hemodynamic

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parameters include blood pressure, cardiac index (CI), mean arterial pressure (MAP), and systemic vascular resistance index (SVRI). Microcirculatory laboratory parameters include serum lactate, central venous pressure (CVP), central venous oxygen saturation ($ScvO_2$), mixed venous oxygen saturation (SvO_2), HCO_3, and base excess.[3,4]

Advanced hemodynamic monitoring tools are only available in large hospitals or in developed countries, while in developing countries monitoring is often only based on clinical evaluation. Often, predicting hemodynamic condition with monitoring devices (ultrasound, pulmonary artery catheter) is not always relevant with the clinical condition. Children generally compensate well, and clinical parameters, especially blood pressure, may remain good, even though the patient's condition is in the final stages.[5]

We aimed to analyze for possible correlations between survival outcomes of post-resuscitation patients and clinical, macrocirculatory hemodynamic, as well as microcirculatory laboratory parameters. Such correlations would improve clinical assessments in places with limited facilities and sharpen clinical assessment of patients with septic shock, even without laboratory parameters and hemodynamic monitoring equipment. We also explored the relationship between clinical parameters and those of advanced monitoring tools to emphasize the importance of hemodynamic and laboratory monitoring tools in the management of septic shock to reduce the risk of mortality.

Methods

A prospective study was conducted from August to December 2020 at the pediatric intensive care unit (PICU) in Dr. Saiful Anwar Hospital, Malang, East Java. Subjects were aged 1 month to 18 years who were diagnosed with septic shock based on clinical and laboratory findings according to the *Surviving Sepsis Campaign Guidelines*.[6] The exclusion criterion was congenital heart disease. The minimum required sample size was 48 patients, with 80% power of study and 95% level of significance. The subjects were followed up for 72 hours after resuscitation. The assessment involved arterial blood taken using a 3 mL syringe. The specimen was loaded into the CG4+ blood gas and lactate cartridge up to the maximum limit on the cartridge (maximum 2 mL volume), and the cartridge was inserted into the *i-STAT* analyzer (*PT. Transmedic Indonesia*) for blood gas and serum lactate analysis.

The parameters CI, SVI, and SVRI were obtained from ultrasound cardiac output monitoring (USCOM) (3.3 MHz frequency). With the patient in a supine position, USCOM was performed by placing the probe in the suprasternal notch to look for a clear picture of early systolic to end systolic, complete systolic time, and velocity time curve (VTI). The curve displays on the monitor screen as a velocity time curve. Measurements with USCOM were carried out three times and the average value was taken.

Septic shock was defined as severe sepsis accompanied by cardiovascular dysfunction. Parameters of pediatric cardiovascular dysfunction were: 1) decrease in blood pressure $<5^{th}$ percentile for age or systolic blood pressure <2 SD below normal for age; or 2) Need of vasoactive drug to maintain blood pressure in normal range (dopamine >5 μg/kg/minutes or dobutamine, epinephrine, or norepinephrine at any dose); or 3) two of the following: Unexplained metabolic acidosis: base deficit >5.0 mEq/L; increased arterial lactate >2 times upper limit of normal; oliguria (urine output 0.5 mL/kg/hr); prolonged capillary refill >5 seconds; or core to peripheral temperature gap >3°C. Thus, in this study, we use some parameters such as extremity or peripheral temperature, systolic blood pressure $>5^{th}$ percentile for age, and capillary refill time as ones of observation parameters.[7]

In pediatric septic shock patients, the target of first hour resuscitation are maintaining airway, oxygenation, and ventilation; maintaining circulation (defined as normal perfusion and blood pressure); maintain threshold heart rates according to patients' age; achieving normal perfusion pressure (MAP-CVP or MAP-IAP) appropriate for age; and achieving superior vena cava or mixed venous oxygen saturation of >70%; or maintaining CI of >3.3 L/min/m^2 and <6.0 L/min/m^2. Therapeutic end points were capillary refill >2 seconds; normal pulses with no differential between peripheral and central pulses; warm extremities; urine output >1 mL/kg/hour; normal mental status; CI >3.3 and <6.0 with normal perfusion pressure (MAP-CVP or MAP-IAP) for age; and superior vena cava or mixed venous oxygen saturation >70%; and maximizing preload to

maximizing CI.[8]

Mean arterial pressure was monitored to determine tissue perfusion pressure. Clinical formula for calculation of mean arterial pressure (MAP) (5th percentile of age at 50th height percentile) in pediatric: 1,5x age in years+40, whereas MAP (50th percentile of age at 50th height percentile): 1,5x age in years+55.[9] We were using MAP target between the 5th and 50th percentile for age and 45% reported using MAP target of greater than 50th percentile for age.[10] We used some criteria of observation, such as: peripheral or extremity temperature, systolic blood pressure, mean arterial pressure, and oxygen saturation.

In this study, we also classified patients according to patient's age. Nutritional status were categorized as severe malnutrition, underweight, well-nourished, overweight, and obesity. Nutritional status was assessed using *WHO* curve for age under 5-year-old and using *CDC* curve for age above 5-year-old.[11,12] According to *WHO* guideline, children below 5 years old were categorized as well-nourished if weight for height plot are in -2 until +2 SD. They were categorized as underweight if weight for height plot are in <-2 SD. They were categorized as overweight if weight for height/length or body mass index for age plot were above +2 SD and categorized as obesity if weight for height/length or body mass index for age were above +3 SD.[13] Using *CDC Curve 2000* for children above 5-year-old, children were categorized as in well-nourished condition if percentage of actual body weight according to ideal body weight was in the range of 90-110% (Waterlow criteria). It was categorized as underweight if actual body weight percentage according to the ideal body weight was in the range 70 until <90% (Waterlow criteria). Then, it was categorized as severe malnutrition if actual body weight percentage according to the ideal body weight was below 70% (waterlow criteria).[14] If the actual body weight percentage was above 110%, then body mass index should be plotted. Body mass index >P85 according to the age was categorized as overweight and if body mass index >P95 was categorized as obese.[12]

Statistical analyses were performed using *SPSS version 26PS* software. The Committee for Medical Research Ethics of Saiful Anwar Hospital approved this study. Informed consent was obtained from all subjects' parents.

Results

Subjects were initially comprised of 56 children, but 4 patients dropped out. A total subjects of 52 children met the inclusion criteria and remained throughout the study period. The data observed included basic characteristics such as sex, age, nutritional status, and primary disease, presented in a tabulated form in **Table 1**.

Spearman's Rho analysis for correlations between survival outcomes and several clinical parameters, namely, HR, pulse, SBP, MAP, CRT, and extremity temperature are showed in **Table 2**. Pulse strength was the only category analyzed in 72 hours of observation, because some patients were died in 72 hours of observations thus subjects were lack and not being analyzed in the other categories (heart rate, systolic blood pressure, GCS, CRT, and diuresis). In this study, a moderately strong correlation was found between clinical variables and outcomes, such as: HR (heart rate) at 6 hours, 12 hours, and 24 hours of observation, with a negative direction; pulse strength at 6, 12 hours, 24 hours, and 72 hours, with a positive correlation direction; SBP at 6, 12 hours, 24 hours,

Table 1. Demographic characteristics of subjects

Characteristics	(N=52)
Gender, n(%)	
Male	31 (59.6)
Female	21 (40.4)
Age, n(%)	
1 month - 1 year	22 (42.3)
2-5 years	4 (7.6)
6-12 years	17 (32.6)
13-18 years	9 (17.3)
Mean age (SD), years	6.2 (5.5)
Nutritional status, n(%)	
Severe malnutrition	26 (50)
Underweight	8 (15.3)
Well-nourished	16 (30.7)
Overweight	1 (1.9)
Obesity	1 (1.9)
Median weight (range), kg	17 (2.6-59)
Primary disease, n(%)	
Pneumonia	36 (69.2)
CNS infection	15 (28.8)
Malignancy	13 (25)
Outcome, n (%)	
Survived	23 (44.2)
Died	29 (55.7)

Table 2. Analysis of clinical parameters at the 6th, 12th, 24th hour and the survival outcome of pediatric septic shock patients 72 hours after fluid resuscitation

Variables observation	Correlation coefficient (r)	P value
Heart rate and survival		
16h	-0.599	0.000
12h	-0.419	0.011
24h	-0.828	0.000
72h	-	-
Pulse strength and survival		
6h	0.434	0.002
12h	0.450	0.006
24h	0.761	0.000
72h	0.466	0.022
SBP and survival		
6h	0.408	0.003
12h	0.567	0.000
24h	0.761	0.000
72h	-	-
GCS and survival		
6h	0.071	0.626
12h	0.074	0.675
24h	0.208	0.289
72h	-	-
CRT and survival		
6h	0.515	0.000
12h	0.705	0.000
24h	0.790	0.000
72h	-	-
Diuresis and survival		
6h	-0.021	0.882
12h	0.068	0.692
24h	0.127	0.511
72h	-	-
Temperature and survival		
6h	0.393	0.005
12h	0.468	0.004
24h	0.761	0.000
72h	-	-
MAP and survival		
6h	0.475	0.000
12h	0.695	0.000
24h	0.759	0.000
72h	-	-

SBP=systolic blood pressure, CRT=capillary refill time, MAP=mean arterial pressure

with a positive correlation direction; MAP at 6, 12 hours, and 24 hours, with a positive direction; CRT at 6, 12 hours, and 24 hours, with a positive direction; extremity temperature at 6, 12 hours, and 24 hours.

Spearman's Rho correlation test for correlation between survival and macrocirculatory hemodynamic parameters are showed in **Table 3**. In this study, a correlation was found between the macrocirculation hemodynamic variables and the outcomes. A weak correlation was found between the SVRI variables and the outcome at 6 and 12 hours, with a positive direction. However, at the 24th hour, afairly strong correlation was found between the SVRI variables and the outcomes.

Spearman's Rho correlation test for correlation between survival and microcirculatory laboratory parameters are shown in **Table 4**. In this study, a correlation was found between the 12th hour HCO_3 and the outcomes. There was a significant correlation in a positive direction. The strength of the correlation

was strong. In the Spearman Rho correlation test between the 24th hour HCO_3 and the outcomes, there was a significant correlation in a positive direction. The strength of the correlation was moderate. As well as obtained a correlation between BE and outcomes variables at 12th hour observation with a weak positive correlation coefficient.

Spearman's Rho correlation test in **Table 5** shows significant correlation analysis between clinical parameters and the macrocirculatory hemodynamic parameters. In this study, a correlation was found between clinical variables and macrocirculation hemodynamic variables, namely: positive correlation between CRT and CI at 12th hours of observation with weak correlation strength; positive correlation between CRT and SVRI at the 12th hours of observation with moderate correlation strength; positive correlation between CRT and SVRI at the 24th hours of observation with moderate correlation strength; positive correlation between MAP and SVRI at the 6th hour of observation with moderate correlation strength; positive correlation between MAP and SVRI at the 12th hour of observation with moderate correlation strength; last, positive correlation between MAP and SVRI at the 24th hour of observation with strong correlation power.

Table 3. Analysis of macrocirculatory hemodynamic parameters at the 6th, 12th, and 24th hours and the survival outcome in pediatric septic shock patients 72 hours after fluid resuscitation

Variables observation	Correlation coefficient (r)	P value
CI and survival		
6h	0.137	0.342
12h	0.143	0.249
24h	0.039	0.842
SVI and survival		
6h	0.056	0.697
12h	0.030	0.861
24h	0.000	1.000
SVRI and survival		
6h	0.361	0.010
12h	0.367	0.028
24h	0.482	0.008

CI=cardiac index, SVI=stroke volume index, SVRI=systemic vascular resistance indeX

Table 4. Analysis of microcirculatory laboratory parameters and the survival outcome in pediatric septic shock patients 72 hours after fluid resuscitation

Variables observation	Correlation coefficient (r)	P value
Lactate and survival		
6h	0.024	0.870
12h	0.223	0.191
24h	0.053	0.784
HCO_3 and survival		
6h	0.064	0.660
12h	0.633	0.000
24h	0.567	0.001
BE and survival		
6h	-0.031	0.830
12h	0.376	0.024
24h	0.260	0.055

CI=cardiac index, SVI=stroke volume index, SVRI=systemic vascular resistance index

Table 5. Analysis of correlation between clinical parameters and macrocirculatory hemodynamic parameters in pediatric septic shock patients

Variables observation	Correlation coefficient (r)	P value
Pulse strength and CI		
6h	0.108	0.456
12h	0.245	0.150
24h	0.054	0.780
72h	0.316	0.142
Pulse strength and SVI		
6h	0.047	0.745
12h	-0.154	0.369
24h	-0.026	0.892
72h	0.054	0.806
Pulse strength and SVRI		
6h	0.119	0.409
12h	0.200	0.243
24h	0.262	0.170
72h	0.298	0.167
CRT and CI		
6h	0.174	0.226
12h	0.389	0.019
24h	0.039	0.842
72h	0.316	0.142
CRT and SVI		
6h	0.047	0.745
12h	-0.093	0.591
24h	0.000	1.000
72h	0.422	0.045
CRT and SVRI		
6h	0.221	0.123
12h	0.446	0.006
24h	0.482	0.008
72h	0.132	0.547
MAP and CI		
6h	0.224	0.117
12h	0.236	0.165
24h	-0.128	0.517
72h	0.335	0.127
MAP and SVI		
6h	-0.007	0.964
12h	-0.179	0.296
24h	-0.213	0.277
72h	0.417	0.054
MAP and SVRI		
6h	0.437	0.002
12h	0.455	0.005
24h	0.601	0.001
72h	0.141	0.532

Spearman's Rho correlation test between clinical parameters and microcirculatory laboratory in **Table 6** revealed one significant negative correlation between lactate and MAP at the 72nd hour of observation after resuscitation, with moderate correlation strength.

Multivariate analysis was carried out by selecting variables with a Pvalue <0.25 based on the results of the bivariate test, namely: between the variables HR at 6 and 12 hours, pulse at 6 and 12 hours, SBP at 6 and 12 hours, CRT at 6 and 12 hours, extremity

temperature at 6 and 12 hours, SVRI at 6 and 12 hours, MAP at 6 and 12 hours, lactate at 12 hours, HCO_3 at 12 hours and BE at 12 hours with outcome. All variables were analyzed simultaneously at the 6th, 12th and 24th hour after resuscitation with no regression results (no P value).

Multivariate analysis withlogistic regression method followed by using of the backward selection method in **Table 7** revealed that only the pulse variable (strong) was significant at the 6th hour of observation (OR =5.698; 95%CI 1.176 to 27.602; P=0.031). An OR value > 1 means that patients with strong pulses were 5.698 times more likely to survive compared to those with weak/unpalpable pulses.

Multivariate analysis with logistic regression method followed by using of the backward selection method revealed that at the 12th hour of observation (**Table 8**), only MAP (>P5) retained significance (OR=18; 95%CI 1.496 to 216.620; P=0.023). This means that patients with MAP > P5 were 18 times more likely to survive compared to those with MAP < P5. Multivariate analysis using the backward method on observation of 24 hours after resuscitation did not produce any significant regression results.

Based on the ROC analysis, the area under the curve (AUC) of the pulse parameter (**Table 9** and **Figure 1**) as a predictor of mortality at 6 hours was 88.2%, which was in the strong range.

Table 10 and **Figure 2** show the ROC curve of the MAP parameter at the 12th hour as a predictor of mortality. The AUC was 94%, which was in the very strong range.

Table 6. Analysis of clinical parameters and microcirculatory laboratory parameters in pediatric septic shock patients

Variables observation	Correlation coefficient (r)	P value
Pulse strength and lactate		
6h	0.048	0.742
12h	0.199	0.246
24h	0.155	0.422
72h	0.405	0.056
CRT and lactate		
6h	0.048	0.742
12h	0.248	0.145
24h	0.118	0.542
72h	0.405	0.056
MAP and lactate		
6h	0.079	0.586
12h	0.199	0.246
24h	0.027	0.890
72h	-0.435	0.043

Table 7. Logistic regression analysis at the 6th hour of observation

Variables	Outcomes, n (%)		B	OR (95%CI)	P value
	Died	Survived			
Constant			-1.404		
Pulse strength					
Strong	5 (25)	15 (75)	1.740	5.698 (1.176 to 27.602)	0.031
Heart rate					
Tachycardia	11 (91.7)	1 (8.3)	2.061	7.856 (0.690 to 89.424)	0.097
Normal	5 (100)	0	-18.945	0.000	0.999
MAP					
>P5	13 (39.4)	20 (60.6)	1.580	4.854 (0.757 to 31.107)	0.096

Table 8. Logistic regression analysis at the 12th hour of observation

Variables	Outcomes, n (%)		B	OR	95%CI	P value
	Died	Survived				
Constant			-2.197			
HCO_3						
22-26	0	8 (100)	21.5	2174253501.682	-	0.999
>26	0	8 (100)	20.51	807737422.882	-	0.999
MAP						
>P5	3 (12.5)	21 (87.5)	2.890	18	1.496 to 216.620	0.023

Table 9. ROC curve analysis of the pulse strength parameter as a predictor of mortality at the 6th hour of observation

Area under the curve				
Area	Std. error	Asymptotic sig.	Asymptotic 95% CI	
			Lower bound	Upper bound
0.882	0.046	0.000	0.791	0.973

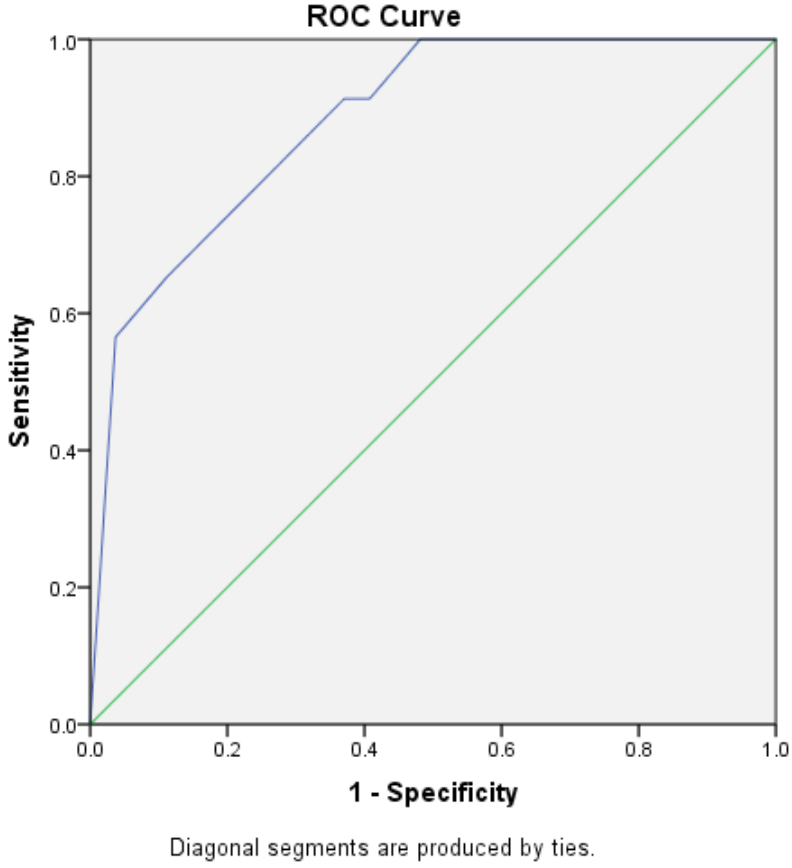

Figure 1. ROC analysis of the pulse strength variable at the 6th hour of observation

Table 10. ROC analysis of MAP (>P5) as a predictor of mortality at 12th hour of observation

Area under the curve				
Area	Std. error	Asymptotic sig.	Asymptotic 95% CI	
			Lower bound	Upper bound
0.940	0.039	0.000	0.864	1.000

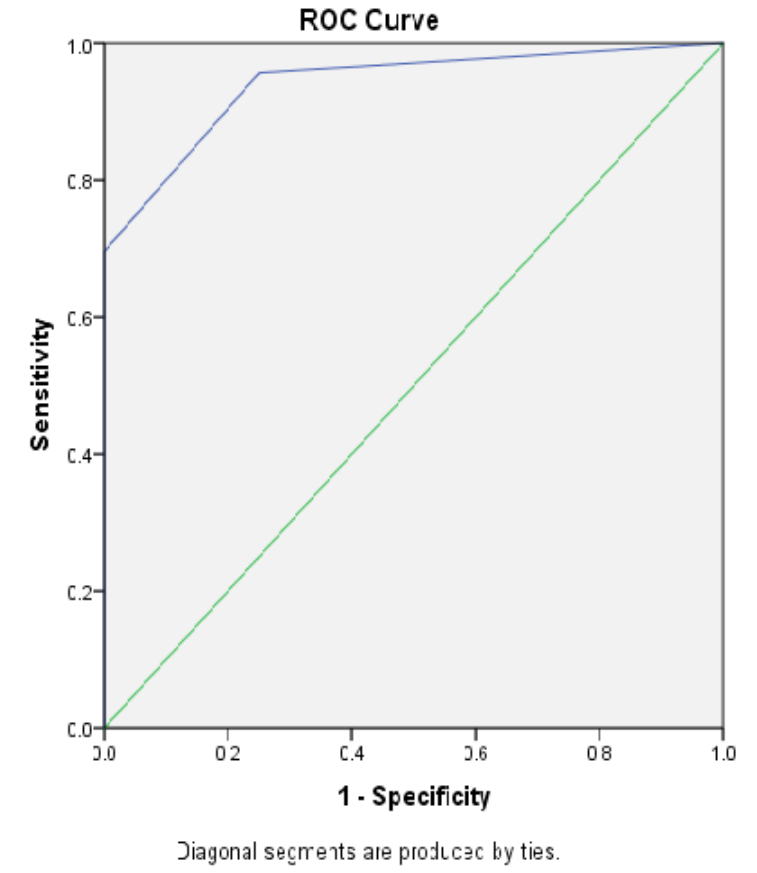

Figure 2. ROC analysis of MAP (>P5) at the 12th hour of observation

Discussion

Our subjects were predominantly male (59.6%) and had a mean age of 6.2 years. Most subjects were diagnosed with septic shock at the age of 1 month to 1 year (42.3%). Thirty-four (65.3%) patients were malnourished. The three main primary diseases causing septic shock were pneumonia (36 patients, 69.2%), central nervous system infections (15 patients, 28.8%), and malignancy (13 patients, 25%). Twenty-three children survived and 29 children died.

A previous study reported a mortality rate of 88.2% in a retrospective cohort study of 136 pediatric patients with septic shock treated in the PICU, Dr. Sardjito Hospital, Yogyakarta. Their patients' mean age was 16 months, and 52.2% were male. The main cause of septic shock was infection (54.4%), with 47 (34,5%) cases diagnosed with pneumonia. The major cause of death reported was the high incidence of fluid overload in the non-surviving group, which accounted for 58.8%.[15]

The mortality rate for septic shock in intensive

care wards in developing countries remains very high; developed countries tend to have lower mortality rates. A prospective study in India found that the mortality rate of pediatric septic shock patients was high (47%).[16] However, retrospective cohort study in the US reported mortality rate of 13.5% in pediatric septic shock patients admitted to PICU.[17] This reduction in mortality is associated with interventional care, including advances in all areas of intensive care medicine. The high mortality rate of pediatric septic shock in developing countries is associated with the time required for patient transfer into the PICU, length of PICU stay, the presence of organ dysfunction, and the *Pediatric Risk of Mortality* (PRISM) score at arrival. [15]

In our study, there was a fairly strong positive correlation between the clinical variable of HR and the survival outcomes at the 24th hour of observation. This finding indicated that patients with more normal HR at the 24th hour were more likely to survive. In addition, the pulse strength at the 6th, 12th, 24th, and 72nd hours had a strong, positive correlation outcome, i.e., patients with strong/normal pulse were more likely to survive. The same applied to SBP at the 6th, 12th, and 24th hours of observation. The positive correlation indicated that patients with higher SBP (>P5) were more likely to survive. Mean arterial pressure (MAP) at the 6th, 12th, and 24th hours of observation also demonstrated a positive correlation, meaning that higher MAP for age, P5-P50 or >P50 MAP for age (in this study we use target of P5-P50 MAP for age) indicated higher likelihood of patient survival. Capillary refill time (CRT) at the 6th, 12th, and 24th hours of observation also showed a positive correlation to survival, i.e., patients with CRT ≤ 2 seconds had good probability of surviving. Lastly, temperature of the patients' extremities at the 6th, 12th, and 24th hours of observation had positive correlations, meaning that patients with warm extremities were more likely to survive.

In our study, it could be concluded that there were correlation between HR (heart rate) at 6 hours, 12 hours, and 24 hours of observation and survival outcomes in a negative direction meaning that the more bradycardia, the more non-surviving patients; there were correlation between pulse strength at 6, 12, 24, 72 hours and survival outcome, with a positive correlation direction, which means the better the pulse (in the strong/normal direction), the more the patient will survive; there were correlation between SBP at 6, 12, 24 hours and survival outcome, with a positive correlation direction, which means the higher the systolic blood pressure (>P5), the more the patient will survive; there were correlation between MAP at 6, 12, 24 hours and survival outcome, with a positive direction, meaning that the higher the MAP (>P50), the more the patient will survive; CRT at 6, 12, 24 hours and survival outcome, with a positive direction, meaning that if the patient's CRT is ≤ 2, so the patient will survive more; Extremity temperature at 6, 12 hours, and 24 hours, in a positive direction, meaning that patients with warm extremities will survive more.

Vital signs with abnormal values, such as respiratory rate, blood pressure, heart rate, pulse, CRT, and extremity temperature, are manifestations of cellular hypoperfusion in septic shock patients. Such findings can indicate a physiological compensatory mechanism at the beginning of shock to maintain tissue perfusion by optimizing improved perfusion of vital organs. However, these abnormal values can also result from uncompensated hypoperfusion if the body's compensatory mechanisms fail to restore tissue perfusion and signs of multi-organ failure are present. As is the case when a hypoperfused patient experiences tachycardia, the high rate may be a compensatory mechanism by which the heart tries to increase its cardiac output, or it may be due to a limited filling capacity of the heart, which then leads to more severe hypoperfusion.[18] Similarly, low blood pressure may be a cause of cellular hypoperfusion in patients with low cardiac output and decreased microvascular flow. However, it can also be the result of cellular dysfunction of the cardiovascular system. Therefore, proper interpretation of vital signs in critically ill patients is needed because abnormalities can occur not only due to hypoperfusion, but also as a result of microcirculatory failure.[19]

In the early phase of shock, the body tries to compensate for impaired peripheral perfusion by vasoconstriction, causing blood to be shunted away from non-vital organs to the brain, heart, and lungs. This compensatory mechanism then causes rapid and weak pulse, cold, mottled extremity temperature, prolonged CRT, and catecholamine-induced tachycardia. If shock persists and compensatory

mechanisms fail to normalize these clinical and hemodynamic parameters, a poor outcome can be expected.[20]

Our findings were in agreement with those of a study who demonstrated clinically significant improvements in 45 children in shock after being given a fluid challenge. These clinical improvements included a decrease in the number of patients with clinical tachycardia, as well as improvement in pulse strength, extremity temperature, CRT, and diuresis.[21]

We found a correlation between macrocirculatory hemodynamic variables and patient outcomes, consisting of a weak positive correlation between the SVRI variable and survival outcomes at the 6th and 12th hours. This finding means that patients with higher SVRI were more likely to survive. However, at 24 hours, there was a moderately strong correlation between SVRI variable and survival outcome. Increased SVRI values may be related to the body's compensation to maintain perfusion.

In the early phase of shock, various compensatory mechanisms are activated. In the face of the threat of hypoperfusion, the body's sympathetic nervous system compensates by increasing HR and SVR through the release of catecholamines from the adrenal glands. The renin-angiotensin-aldosterone system is also activated, resulting in vasoconstriction and maintenance of SVR, as well as fluid retention through urine concentration. In children, vascular tone is maintained even in low-flow conditions. Therefore, children can often maintain blood pressure before progressing to a state of severe shock to maintain perfusion of vital organs.[20]

We found a significant, strong, positive correlation between microcirculatory laboratory variables and outcome, i.e., between HCO_3 at the 12th and 24th hours of observation and outcome. This finding indicates that patients with higher HCO_3 were more likely to survive. In addition, BE was significantly correlated to outcome at the 12th hour of observation, with a weak and positive correlation coefficient.

There are three ways of assessing metabolic acid-base disorders: HCO_3^-, standardized base excess (SBE), and strong ions difference (SID).[22] The use of bicarbonate ions (HCO_3^-) as a marker of acidosis/alkalosis is not appropriate because bicarbonate ions are not only influenced by metabolic acids, but also by volatile acids ($PaCO_2$, respiratory). However, the relationship between bicarbonate ion levels and $PaCO_2$ can be used to estimate the amount of body compensation. Acid-base abnormalities that occur can be inferred based on the ratio of bicarbonate or $PaCO_2$ measured with those expected from the compensation process.[22] In our study, increased HCO_3 and BE correlated with patient survival, indicating that meeting of tissue metabolic needs will increase survival in shock patients.

We found correlations between clinical variables and macrocirculatory hemodynamic variables, i.e., 12th hour CRT and CI with a positive and weak correlation as well as CRT and SVRI at the 12th hour, with a positive and moderately strong correlation. There was also a positive and moderately strong correlation between CRT and SVRI at the 24th hour of observation. The correlation between MAP and SVRI at the 6th hour of observation was positive and moderately strong. At the 12th hour of observation, MAP and SVRI had a positive and moderately strong correlation. Moreover, MAP and SVRI demonstrated a positive and strong correlation at the 24th hour of observation. These findings can be explained by the fact that, in septic shock, the ability of the heart muscle to contract is weakened, causing impaired heart function. Although cardiac output (CO) is increased (mainly due to tachycardia rather than increased stroke volume/SV), peripheral blood flow remains reduced. Hemodynamic status in septic shock that used to be thought to be hyperdynamic (vasodilation and increased blood flow). In advanced stages, is in fact more similar to hypodynamic status (vasoconstriction and reduced blood flow).[6]

The MAP and SVRI were positively correlated in our study. In cases of septic shock, this condition shows a compensation by the body to maintain MAP to maintain adequate perfusion to vital organs. MAP represents mean perfusion of the systemic circulation. It is very important to maintain a MAP above 65 mmHg to ensure that adequate cerebral, coronary artery, and renal perfusion are maintained.[20]

In our study, there was a significant correlation between clinical and microcirculatory laboratory parameters, i.e., a negative but strong correlation between MAP and lactate 72 hours after resuscitation, meaning that the lower the MAP (<P5), the higher the lactate value, and vice versa, the higher the MAP (≥P5), the lower the lactate (<2 mmol/L). This result

may still be due to adequate shock management, especially adequate oxygenation and ventilation.

Multivariate analysis with logistic regression employed the method of elimination of the backward selection of variables, revealing that a strong pulse at the 6th hour of observation could predict mortality within 72 hours, with AUC of 88.2%, which was in the strong range. Hence, improvement of pulse parameters should be a target of treatment for pediatric patients with septic shock in the first 6 hours is to prevent mortality.

In our study, multivariate logistic regression analysis with backward stepwise elimination of variables revealed that MAP at the 12th hour of observation could predict mortality within 72 hours, with AUC 94%, which was in the very strong range category. Hence, improvement of MAP parameters should be a target of treatment for pediatric patients with septic shock in the first 12 hours to prevent mortality.

Mean arterial pressure of ≥P5 indicates adequate vital organ perfusion, while MAP <P5 indicates inadequate vital organ perfusion and is a sign that shock has entered the decompensated phase because the body cannot compensate for impaired tissue perfusion and can progress to organ failure. The MAP is the average arterial pressure during one cycle of heart rate obtained from the measurement of systolic and diastolic blood pressure, and is the driving pressure for tissue or organ perfusion, especially the brain and kidneys. MAP is an important evaluation element in the management of patients in shock, with the goal of increasing the MAP to a level that permits adequate cardiac output for adequate tissue perfusion. In adults, the recommended limit is to maintain a value of 65 mmHg. The normal target of MAP in children is between P5-50 or > P50, which is the cut-off to improve tissue perfusion.[20] A previous study stated that MAP and SBP are essential evaluation elements in critically ill children.[9] However, to date, there has been no normal reference value of MAP. Systolic blood pressure is a predictor of mortality, and hypotension is associated with an increased risk of high mortality. Hypotension is one of the diagnostic criteria for uncompensated shock along with impaired perfusion in pediatric patients with septic shock. To determine the MAP value obtained from systolic and diastolic blood pressure in patients with uncompensated shock, in addition to being found with hypotension, a low MAP value also indicates low perfusion to vital organs with a risk of organ failure and an increased risk of death.[9]

The *Surviving Sepsis Campaign* (SSC) 2020 stated that they have not been able to issue pediatric recommendations about the target of MAP in children with septic shock and other sepsis-related organ dysfunctions. In the absence of evidence from RCTs, the SSC was unable to come up with a consensus to recommend specific MAP targets for children. However, in practice, the SSC states that 37% of panel members target a MAP between the 5th and 50th percentiles for age, and 45% of panel members target a MAP greater than the 50th percentile for age. It also stated that hypotension in children was acceptable if other hemodynamic variables (e.g., mental status, perfusion, urinary output, lactate) improved. In circumstances where direct measurement of MAP is less reliable, systolic blood pressure provides a reasonable alternative.[10]

Therapy to improve hemodynamics in patients with shock includes maintaining oxygen delivery above critical values and increasing the MAP to a level that can ensure optimal CO distribution to provide adequate tissue perfusion. In adults, the MAP range of 60-90 mmHg is used as the target value for end-of-life therapy to increase urine production and creatinine clearance.[24] In children, guideline by surviving sepsis campaign suggests early aggressive hemodynamic improvement, including normalization of MAP for age.[10]

However, the SSC statement was not supported by Lamontagne *et al*.[25] in a systematic review. They stated that a high MAP target (first group: 80-85 mmHg; second group 75-80 mmHg) in the management of septic shock patients who had received vasopressors > 6 hours previously may increase the risk of death compared to a low MAP target (first group: 65-70mmHg; second group: 60-65mmhg). However, it was explained that this could be because the use of vasopressors > 6 hours which could cause unfavorable side effects.

Our results suggest that when higher MAP targets are targeted earlier, the detrimental effects of the intervention are balanced by the beneficial effects obtained. On the other hand, when a patient has been on vasopressor therapy for more than 6 hours

and fails to improve rapidly, targeting a higher MAP may have an overall adverse effect because, although it does not produce any harmful effects, it does not provide further benefit. Thus, in patients who received a larger cumulative dose of vasopressor, the effect of the dose could increase, thereby increasing the target MAP to a dangerous level beyond the maximum dose threshold. This danger may not be seen in patients who improve more rapidly.[25]

The dearth of significant findings raises questions about previous guidelines that suggested the optimal MAP should be tailored to individual needs because the requirement may be higher in patients with atherosclerosis and/or hypertension. For example, a MAP of 65 mmHg may be too low in a patient with severe uncontrolled hypertension; in young patients without previously normotensive cardiovascular comorbidities, a lower MAP may be sufficient.[25]

Our study had several limitations including the small sample size, despite meeting the required minimum number of subjects. In order to achieve distribution and increase the correlation significance, further study is required with a larger sample size. In addition, we did not assess for routine drug use, vasoactive administration, or use of a mechanical ventilator. Nor was lactate clearance assessed as we used serum lactate as a comparison value for serum lactate after adequate resuscitation and ventilation.

In conclusion, there are significant correlations between several clinical parameters, macrocirculatory hemodynamic parameters, and microcirculatory laboratory parameters with the survival outcomes post resuscitation in the pediatric septic shock. Parameter at the 6th hour that can predict survival outcomes within 72 hours of observation is pulse strength, whereas parameter at the 12th hour that can predict survival outcome within 72 hours of observation is MAP.

Conflict of interest

None declared.

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References

1. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6:2-8. DOI: https://doi.org/10.1097/01.PCC.0000149131.72248.E6.
2. Alcamo AM, Pang D, Bashir DA, Carcillo JA, Nguyen TC, Aneja RK. Role of damage-associated molecular patterns and uncontrolled inflammation in pediatric sepsis-induced multiple organ dysfunction syndrome. J Pediatr Intensive Care. 2019;8:25-31. DOI: https://doi.org/10.1055/s-0038-1675639.
3. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence. 2014;5:73-9. DOI: https://doi.org/10.4161/viru.26482.
4. Gu WJ, Wang F, Bakker J, Tang L, Liu JC. The effect of goal-directed therapy on mortality in patients with sepsis-earlier is better: a meta-analysis of randomized controlled trials. Crit Care. 2014;18:570. DOI: https://doi.org/10.1186/s13054-014-0570-5.
5. Gruartmoner G, Mesquida J, Ince C. Microcirculatory monitoring in septic patients: Where do we stand? Med Intensiva. 2017;41:44-52. DOI: https://doi.org/10.1016/j.medin.2016.11.011.
6. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39:165-228. DOI: https://doi.org/10.1097/CCM.0b013e31827e83af.
7. Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care

Societies. 2005; 6:2-8. DOI: https://doi.org/10.1097/01.PCC.0000149131.72248.E6

8. Carcillo JA; Fields AI. MD (Task Force Committee Members). Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock*. Critical Care Medicine. 2002;30.1365-1378. DOI: https://doi.org/10.1097/00003246-200206000-00040
9. Haque IU, Zaritsky AL. Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. Pediatr Crit Care Med. 2007;8:138-44. DOI: https://doi.org/10.1097/01.PCC.0000257039.32593.DC.
10. Weiss SL, Peters MJ, Alhazzani W, Agus MS, Flori HR, Inwald DP, *et al.* Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020;46:10-67. DOI: https://doi.org/10.1097/PCC.0000000000002198.
11. WHO. Child growth standards [Internet]. Geneva: WHO; 2023 [cited March 4, 2022]. Available: https://www.who.int/tools/child-growth-standards/standards
12. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, *et al.* 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002;246:1-190. PMID: 12043359.
13. WHO. WHO child growth standards: Training course on child growth assessment (C. Interpreting growth indicators) [internet]. Geneva: WHO Press; 2008. [cited February 14, 2023]. Available from: https://apps.who.int/iris/bitstream/handle/10665/43601/9789241595070_C_eng.pdf?sequence=3&isAllowed=y.
14. Waterlow JC. Classification and definition of protein-calorie malnutrition. Br Med J. 1972; 3, 566-9. DOI: https://doi.org/10.1136/bmj.3.5826.566.
15. Rusmawatiningtyas D, Nurnaningsih N. Mortality rates in pediatric septic shock. Paediatr Indones. 2017;56:304-10. DOI: https://doi.org/10.14238/pi56.5.2016.304-10.
16. Singh D, Chopra A, Pooni PA, Bhatia RC. A clinical profile of shock in children in Punjab, India. Indian Pediatr. 2006;43:619-23. PMID: 16891682.
17. Kutko MC, Calarco MP, Flaherty MB, Helmrich RF, Ushay HM, Pon S, Greenwald BM. Mortality rates in pediatric septic shock with and without multiple organ system failure. Pediatr Crit Care Med. 2003;4:333-7. DOI: https://doi.org/10.1097/01.PCC.0000074266.10576.9B.
18. Jaramillo GD, Canoa JC, Galvan EV. Approach of minimal invasive monitoring and initial treatment of the septic patient in emergency medicine. Open Access Emerg Med. 2018;10:183-91. DOI: https://doi.org/10.2147/OAEM.S177349.
19. Fleming S, Gill P, Jones C, Taylor JA, Van den Bruel A, Heneghan C, *et al.* The diagnostic value of capillary refill time for detecting serious illness in children: a systematic review and meta-analysis. PloS One. 2015;10:e0138155. DOI: https://doi.org/10.1371/journal.pone.0138155.
20. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, *et al.* The American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. Crit Care Med. 2017;45:1061-93. DOI: https://doi.org/10.1097/CCM.0000000000002425.
21. Kadafi KT, Latief A, Pudjiadi AH. Determining pediatric fluid responsiveness by stroke volume variation analysis using ICON® electrical cardiometry and ultrasonic cardiac output monitor: a cross-sectional study. Int J Crit Illn Inj Sci. 2020;10:123-8. DOI: https://doi.org/10.4103/IJCIIS.IJCIIS_87_18.
22. Fikri M, Hanafie A, Umar N. Perbandingan nilai analisis gas darah, elektrolit, dan laktat setelah pemberian ringer asetat malat dengan ringer laktat untuk early goal directed therapy pasien sepsis. J Anestesi Perioperatif. 2018;6:55-62. DOI: https://doi.org/10.15851/jap.v6n1.1291.
23. Sutadi K, Pudjiastuti P, Martuti S. Faktor risiko mortalitas pada anak dengan syok di ruang perawatan intensif Rumah Sakit dr. Moewardi Surakarta. 2020;22:7-12. DOI: https://doi.org/10.14238/sp22.1.2020.7-12.
24. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345:1368-1377. DOI: https://doi.org/10.1056/NEJMoa010307.
25. Lamontagne F, Day AG, Meade MO, Cook DJ, Guyatt GH, Hylands M, *et al.* for the Early Goal-Directed Therapy Collaborative Group. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. Intensive Care Med. 2018;44:12-21. DOI: 10.1007/s00134-017-5016-5.