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Original Article

The Role of several Biomarkers and Scoring Systems Assessed During Emergency Department Admission Day in Predicting Septic Shock

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ABSTRACT

Sepsis results in a life-threatening organ dysfunction due to the dysregulation of organ dysfunction detection, risk stratification, prognosis, and treatment is crucial for sepsis and septic shock. Several widely-available biomarkers are including white blood cells count (WBC), neutrophil-lymphocyte ratio (NLR) C-reactive protein (CRP), and procalcitonin (PCT), lactate levels. Presepsin (P-SEP) and mid-regional pro-adrenomedullin (MR-ProADM), are other two important biomarkers currently under investigation. In addition, clinical scoring system such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE)-II scores are combined. Furthermore, comorbidities and the underlying infections should be considered. In this study, we evaluated the potency of septic shock predictor in sepsis patients at Dr. Kariadi Hospital Semarang, Indonesia between June and August 2019. A total number of 59 patients, consisted of 19 sepsis and 40 septic shock who fulfilled the Sepsis-3 criteria were enrolled. Biomarkers, scoring system and other variables were evaluated within 24 hours of emergency department (ED admission. Bivariate and multivariate logistic regression analyses as well as receiver operating characteristic curve analysis were used to predict the development of septic shock. A combination of five biomarkers (WBC count, PCT, P-SEP, MR-ProADM, and lactate) plus SOFA score and additional risk variables (skin and soft tissue infection, and hypertension) performed better for predicting septic shock than any single factor.

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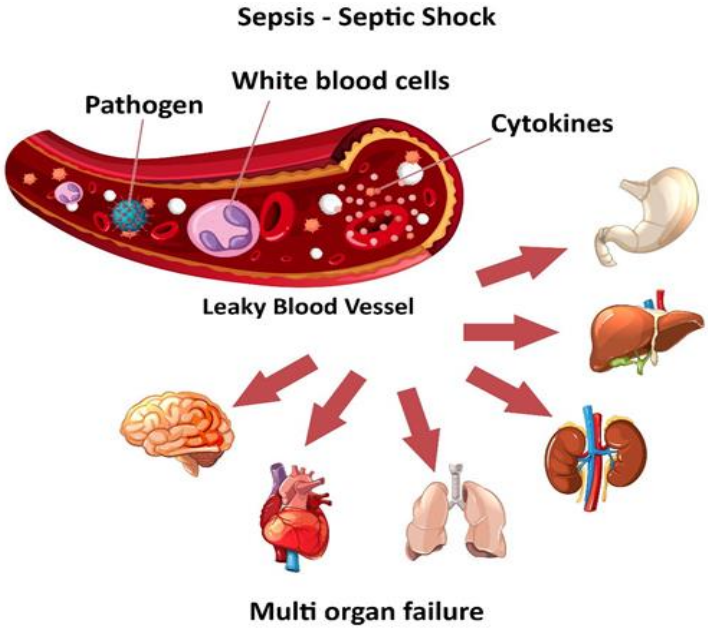
GRAPHICALABSTRACT



Introduction

Sepsis and septic shock are serious emergency issues that have been attributed to a high in-hospital mortality rate [1].

While sepsis may affect everyone across the world, there are considerable differences between regions in incidence and mortality, with lower-middle-income countries (LMICs) having the highest rates [2].

A recent study in Southeast Asia demonstrated that the 28-day mortality rate in adult patients with sepsis was 13%, with severe sepsis strongly related to 18% of adult mortality [3].

The overall outcomes of sepsis is determined by a combination of an early diagnosis and prompt treatment. Pathogen detection is based on cultivated microorganisms. However, culture analysis is time-consuming. In the emergency setting, a combination of biomarkers and clinical scoring system are commonly used as a clinical judgment. Although potentially beneficial, this may be also misleading as patient factors such as age, accompanying illness, and initial health status may influence disease progression, outcome, and mortality [4].

Importantly, biomarkers are crucial for diagnosis, early organ dysfunction detection, risk stratification, prognosis, and appropriate clinical management, including antibiotic stewardship [5].

Various biomarkers such as leukocyte number, neutrophil-lymphocyte ratio (NLR) C-reactive protein (CRP), lactate and procalcitonin (PCT) levels are widely used. The conventional biomarker WBC count is the most commonly used to measure infection, but it may be the least beneficial because septic shock may also result in leukocytosis or leukopenia [5] CRP particularly is an important inflammatory. However, it can not distinguish whether the inflammation is due to an infection or not. The NLR is typically increased by metabolic stress conditions that lead to neutrophilia and lymphopenia [6].

Since sepsis induces lymphocyte apoptosis, septic shock may worsen a significant increase in NLR more than other types of physiologi stress [7].

Procalcitonin has shown considerable potential in detecting sepsis, assessing illness severity, and guiding antibiotic administration [8]. Moreover, procalcitonin levels are often increased in bacterial infections and lower in viral infections [9].

Blood lactate is an oxygen-dependent byproduct of glucose metabolism. If the perfusion of tissue is poor and the oxygen supply is inadequate, metabolism will be affected. In those with sepsis, disease severity is directly coinciding with tissue perfusion level and oxygen supply [10].

Other promising biomarkers are Presepsin (P-SEP) and Mid-regional proadrenomedullin (MR-ProADM). Presepsin is a cleaved N-terminal fragment of CD14, an important receptor which recognizes lipopolysaccharide (LPS) binding protein complexes. One mechanism of P-SEP is associated with bacterial uptake and the disintegration of the CD14 membrane from granulocyte lysosomal enzymes during the production [11].

Several previous studies have suggested that P-SEP levels in the blood can predict the in-hospital mortality of sepsis patients during ED and ICU admission [11, 12].

MR-ProADM is a novel biomarker that acts as a surrogate marker for adrenomedullin. MR-ProADM has vasodilatory effects [13, 14] by binding to endothelial and smooth muscle cell receptors and modulating the endothelial barrier [15].

Adrenomedulin is increased in sepsis patients by direct interaction with the relaxation of vascular tone triggered by hypotensive conditions in sepsis patients [16].

According to Zhou *et al.* and Angelatti *et al.* [17], MR-ProADM has a high specificity for distinguishing sepsis from non-infectious SIRS. Furthermore, in septic patients, concomitant MR-adrenomedullin and procalcitonin increased the probability of diagnosis compared to single marker [17].

In addition to biomarkers, a scoring system consisting of clinical and laboratory parameters has been demonstrated to assess sepsis risk stratification and predicts mortality [18].

The scoring system is needed because it is easy, and practical to use. The widely used sepsis scoring system includes the Sequential Organ Failure Assessment Score (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) -II scores [19, and 20].

The SOFA score is designed to identify the function of six organ systems and the degree of organ dysfunction. The SOFA score includes assessments of respiratory organs (PaO_2/FiO_2), cardiovascular (blood pressure and vasopressor), kidney (diuresis or creatinine), hematology (platelet number), neurology (GCS), and hepatic (bilirubin) function [19-21].

The APACHE-II score is widely used in the ICU and can predict the mortality of critically ill patients in the Emergency Department. Man SY *et al.* showed that the APACHE-II score was a good predictor of mortality in ED patients. The APACHE-II scoring system consists of three variables, the first being acute physiological variables (i.e. temperature, blood pressure, cardiac rate, respiration rate, level of hematocrit, leukocyte number, serum levels of sodium, potassium, creatinine, and acidity level), or blood pH, oxygen partial pressure (PaO_2), Glasgow Coma Scale (GCS)), the second is age variable, and the third is comorbid chronic disease variable [22].

To date, the gold standard diagnostic biomarker for sepsis and septic shock is unavailable. Furthermore, most studies were performed in ICU rather than in the emergency department. Concerning these factors, it is essential to conduct more studies, to identify useful biomarkers which can predict the development of septic shock in emergency the setting.

Materials and Methods

A prospective observational study was performed at Dr. Kariadi Hospital in Semarang, Indonesia, between June and August 2019. The inclusion criteria were that in-hospitalized adult sepsis and septic shock patients (≥18 years old) according to SEPSIS-3 criteria were enrolled within 24 hours of admission to the emergency department. Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the SOFA score of 2 points or more. Septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level more than 2 mmol/L (>18 mg/dL) in the absence of

hypovolemia. Written informed consent was obtained from patients or family members. Pregnancy, shock of other origin, resuscitation status from cardiopulmonary arrest, human immunodeficiency syndrome, immunosuppressive therapy, malignancy, or cancer were excluded.

All subjects were given timely initial interventions, including empirical antibiotics. The study was approved by the local Ethics Committee Dr Kariadi Hospital according to the Declaration of Helsinki (1964). Clinical variables were age, gender, resting heart rate, respiratory rate, source of infection, comorbidities, and type of infection. Laboratium examination for complete blood count, C-reactive protein (CRP), Procalcitonin (PCT), NLR, liver function test, lactate level, renal function tests, electrolytes serum, blood cultures and cultures of specimens from the primary site of infection were done in Laboratorium of Dr. Kariadi Hospital. The severity of sepsis was scored within 24 h of diagnosis of sepsis using the SOFA and APACHE-II scores.

Blood samples for P-SEP and MR-ProADM were collected at baseline (within 24 h of admission to ED), centrifuged, aliquoted, and assayed in GAKI Laboratorium Faculty of Medicine Universitas Diponegoro. MR-ProADM plasma level was measured using Human MR-ProADM (Mid-regional pro-adrenomedullin) ELISA (Enzyme-Linked Immunosorbent Assay) Kit, Elabscience Biotechnology Inc., United States whereas presepsin plasma was measured using Human Presepsin ELISA kit, Bioassay Technology Laboratory, Shanghai, China.

Statistical analysis

The Shapiro-Wilk normality test was performed on a continuously variable to establish the cut-off. Most of the variables were abnormal. The mean was performed as the cut-off for variables that are normally distributed, while the median was used for variables that were not normally distributed. The variables were divided into two dichotomous categories of normal and abnormal.

Categorical data were presented as a percentage, and comparisons were made using the chi-square test. Bivariate and multivariate logistic regression analyses were used to investigate the independent risk factors associated with septic shock. Variables with p <0.05 and p < 0.2 in bivariate analysis were included in multivariate analysis.

The statistical tests were all two-sided, p < 0.05 and p <0.1 were considered statistically significant. The odds ratio (OR) and confidence interval (CI) were then computed. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off of variables for predicting septic shock. All data were analysed in STATA (version 15).

Results and Discussion

In this study, 59 patients were included (Figure 1); 40 patients were in septic shock group (67.8%).

Mortality of sepsis patients were 56.9% (n=13), meanwhile septic shock was 75% (n=27). Clinical characteristics of the patients in relation to sepsis and septic shock are shown in Table 1.

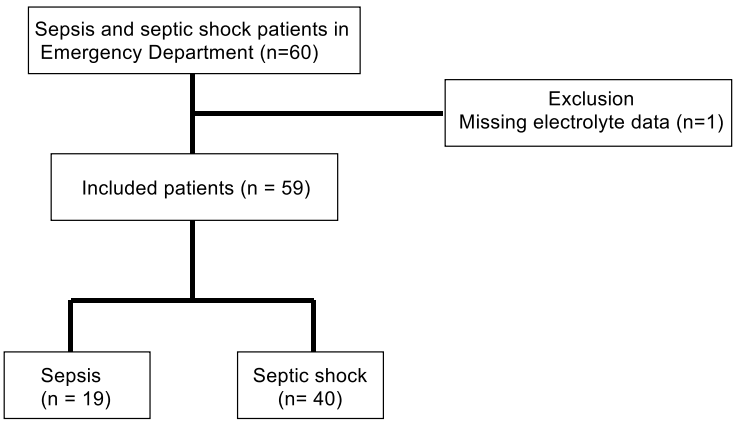


Figure 1: Flowchart of subjects study

Table 1: Baseline characteristics of study subjects

Variables (n=59)	Mean±SD	Median (Minimun-Maximum)	IQR	*p*-value
Age (years old)	59.50±15.70	61.0 (22.0-88.0)	20.0	0.005*
Temperature (^{0}C axilla)	37.40±0.75	37.20 (36.0-39.1)	0.90	0.001*
Heart rate (x/minutes)	112.53±14.08	113.00 (75.0-166.0)	19.0	0.001*
Mean arterial pressure	82.0±21.90	73.30(49.0-148.0)	31.33	0.000*
Glasgow Coma Scale	10.14±2.90	10.00 (3.0-15.0)	3.0	0.429
PaO2/FiO2 ratio	360.05±146.91	328.33 (63.8-676.2)	188.67	0.383
Haemoglobin (g/dl)	11.71±2.68	12.30 (5.7-16.8)	3.30	0.106
White blood count (x10^3/uL)	17.76±8.30	15.80 (5.5-46.3)	10.10	0.000*
Platelet (10^3/uL)	295.58±149.10	273.00 (39.0-634.0)	230.0	0.191
Blood glucose (g/dl)	241.22±191.00	157.00 (39.0-754.0)	235.0	0.000*
Total bilirubin (mg/dl)	1.78±2.57	0.96 (0.3-14.5)	1.19	0.000*
Ureum (mg/dl)	111.69±99.42	79.00 (10.0-488.0)	121.0	0.000*
Creatinin (mg/dl)	2.74±2.64	1.87 (0.3-12.9)	1.95	0.000*
Sodium (mmol/L)	134.56±11.95	133.00 (96.0-166.0)	16.00	0.113
Potassium (mmol/L)	4.38±1.09	4.30 (2.5-7.6)	1.10	0.073*
Lactate (mmol/L)	5.18±4.44	3.50 (0.9-21.0)	4.53	0.000*
NLR	12.62±10.16	9.56 (1.9-46.5)	8.50	0.000*
CRP (mg/L)	13.48±12.31	11.33 (0.1-54.6)	17.66	0.000*
PCT (ng/mL)	15.24±24.19	3.43 (0.0-108.5)	15.35	0.000*
P-SEP (mg/L)	1.51±2.34	0.45 (0.1-9.1)	0.61	0.000*
MR-ProADM (pg/ml)	21.05±23.34	11.85 (3.6-136.7)	12.82	0.000*
SOFA score	8.29±2.89	8.00 (1.0-14.0)	4.0	0.701
APACHE-II score	24.92±6.33	24.00 (14.0-41.0)	8.0	0.227

*Shapiro-Wilk test; *p<0.05 (abnormal distribution of variables).*
NLR (neutrophil-lymphocyte ratio); CRP (C-reactive protein); PCT (procalcitonin);
P-SEP (presepsin); MR-ProADM (mid-regional pro adrenomedullin), SOFA (Sequential Organ Failure Assessment) score; and APACHE-II (Acute Physiology and Chronic Health Evaluation-II) score.

Table 2 showed that 61.3 % of septic shock patients were ≥59.5 years old and most of them were males. Most septic shock patients were treated in the ward than ICU (72.2 vs. 57.1%). Cardiovascular disease was the common comorbidity in septic shock patients (64.0%) followed by diabetes mellitus (63.0%), stroke (57.10%), chronic obstructive pulmonary disease (COPD 33.30%), and hypertension (28.60%) whereas types of comorbidities in sepsis patients were diabetes mellitus (45.8%), CVD (42.40%), stroke (35.6%), hypertension (23.7%), and COPD (5.10%), respectively.

Pneumonia was the most frequent infection, followed by urinary tract infections, and skin-and soft tissue infections. A single set of blood cultures (2 bottles) was positive in 14 patients (23.3%), and gram-positive bacteria was the etiology in 11 of them (78.5%). Bivariate logistic regression analysis showed that there was a significant difference (p<0.05) for sepsis and septic shock as follows: heart rate; [OR = 4.04 (95% CI, 1.32-12.38); *p* = 0.014], WBC count; [OR = 4.04 (95% CI, 1.32-12.38); *p* = 0.014], CRP; [OR = 3.59 (95% CI, 1.18-10.93); *p* = 0.024], PCT [OR = 5.67 (95% CI, 1.78-18.08); p = 0.003], hypertension [OR = 6.15 (95% CI, 1.63-23.19); *p* = 0.014], and skin and soft tissue infection; [OR = 0.16 (95% CI, 0.04-0.61); *p* = 0.007], meanwhile for *p* < 0.2 were GCS [OR = 2.54 (95% CI, 0.81-7.91) ; *p* = 0.109] and lactate [OR= 2.95 (95% CI, 0.99-8.75) ; *p* = 0.052]. All variables with *p* <0.05 and *p* < 0.2 were candidate variables for multivariate analysis (Table 3).

Table 2: Bivariate analysis of risk factors related to septic shock

Variables	Categories/ cut-off	Total Subjects (n = 59)		Sepsis (n=23)		Septic shock (n=36)		*p*-value	OR	95% CI OR (Lower-Upper)	
		n	% [a]	n	% [b]	n	% [b]				
Demography											
Age (years old)	<59.5	28	47.5	11	39.3	17	60.7	0.964	1.00		
	>=59.5	31	52.5	12	38.7	19	61.3		1.02	0.36	2.92
Gender	Females	31	52.5	13	41.9	18	58.1	0.625	1.00		
	Males	28	47.5	10	35.7	18	64.3		1.35	0.45	3.72
Treatment room type	Ward	18	30.5	5	27.8	13	72.2	0.502	1.00		
	ICU	14	23.7	6	42.9	8	57.1		1.07	0.29	3.92
	ED	27	45.8	12	44.4	15	55.6		2.08	0.58	7.49
Vital signs											
Temperature (°C)	<37.5	38	64.4	16	42.1	22	57.9	0.509	1.00		
	≥37.5	21	35.6	7	33.3	14	66.7		1.45	0.48	4.43
Heart rate (x/minutes)	<113.0	29	49.2	16	55.2	13	44.8	0.014*	1.00		
	≥113.0	30	50.8	7	23.3	23	76.7		4.04	1.32	12.38
Glasgow Coma Scale	<10.14	36	61.0	17	47.2	19	52.8	0.109**	1.00		
	≥10.14	23	39.0	6	26.1	17	73.9		2.54	0.81	7.91
PF ratio	<360.0	34	57.6	13	38.2	21	61.8	0.891	1.00		
	≥360.0	25	57.6	13	38.2	21	61.8	0.891	0.93	0.32	2.67
Comorbidities											
Diabetes mellitus	No	32	54.2	13	40.6	19	59.4	0.778	1.00		
	Yes	27	45.8	10	37.0	17	63.0		1.16	0.41	3.33
COPD	No	56	94.9	21	37.5	35	62.5	0.554	1.00		
	Yes	3	5.1	2	66.7	1	33.3		0.30	0.03	3.51
Stroke	No	38	64.4	14	36.8	24	63.2	0.650	1.00		
	Yes	21	35.6	9	42.9	12	57.1		0.78	0.26	2.31
Hypertension	No	45	76.3	13	28.9	32	71.1	0.014*	1.00		
	Yes	14	23.7	10	71.4	4	28.6		0.16	0.04	0.61
Cardiovascular disease	No	34	57.6	14	41.2	20	58.8	0.687	1.00		
	Yes	25	42.4	9	36.0	16	64.0		1.24	0.43	3.61
Number of comorbidities	None	10	16.9	3	30.0	7	70.0	0.770	1.00		
	one	21	35.6	8	38.1	13	61.9		0.70	0.14	3.50
	≥2	28	47.5	12	42.9	16	57.1		0.57	0.12	2.68
Type of infections											
Pneumonia	No	1	1.7	0.0	0.0	1	100.0	1.000	1.00		
	Yes	58	98.3	23	39.7	35	60.3		NA	NA	NA
Urinary Tract Infection	No	42	71.2	15	35.7	27	64.3	0.650	1.00		
	Yes	17	28.8	8	47.1	9	52.9		0.78	0.26	2.31
Skin and soft tissue infection	No	49	83.1	21	42.9	28	57.1	0.007*	1.00		
	Yes	10	16.9	2	20.0	8	80.0		0.16	0.04	0.61
Tetanus	No	58	98.3	22	37.9	36	62.1	0.390	1.00		
	Yes	1	1.7	1	0.0	0	0.0		NA	NA	NA
Leptospirosis	No	58	98.3	22	37.9	36	62.1	0.390	1.00		
	Yes	1	1.7	1	0.0	0	0.0		NA	NA	NA
Meningitis	No	58	98.3	22	37.9	36	62.1	0.390	1.00		
	Yes	1	1.7	1	0.0	0	0.0		NA	NA	NA
Infective endocarditis	No	58	98.3	22	37.9	36	62.1	0.390	1.00		
	Yes	1	1.7	1	0.0	0	0.0		NA	NA	NA

Variables	Categories/ cut-off	Total Subjects (n = 59)		Sepsis (n=23)		Septic shock (n=36)		*p*-value	OR	95% CI OR (Lower-Upper)	
		n	% [a]	n	% [b]	n	% [b]				
Intra-abdominal infection	No	56	94.9	22	39.3	34	60.7	1.000	1.00		
	Yes	3	5.1	1	33.3	2	66.7		1.29	0.11	15.14
Laboratory values											
Haemoglobin (g/dl)	<11.71	27	45.8	8	29.6	19	70.4	0.179**	1.00		
	≥11.71	32	54.2	15	46.9	17	53.1		0.48	0.16	1.40
WBC count (x10^3/uL)	<15.80	29	49.2	16	55.2	13	44.8	0.014*	1.00		
	≥15.80	30	50.8	7	23.3	23	76.7		4.04	1.32	12.38
Ureum (mg/dl)	<79.00	28	47.5	9	32.1	19	67.9	0.308	1.00		
	≥79.00	31	52.5	14	45.2	17	54.8		0.58	0.20	1.66
Creatinine (mg/dl)	<1.87	29	49.2	11	37.9	18	62.1	0.871	1.00		
	≥1.87	30	50.8	12	40.0	18	60.0		0.92	0.32	2.61
Total bilirubin (mg/dl)	<0.96	30	50.8	10	33.3	20	66.7	0.367	1.00		
	≥0.96	29	49.2	13	44.8	16	55.2		0.62	0.21	1.77
Sodium (mmol/L)	<134.56	32	54.2	13	40.6	19	59.4	0.778	1.00		
	≥134.56	27	45.8	10	37.0	17	63.0		1.16	0.41	3.33
Potassium (mmol/L)	<4.38	33	55.9	13	39.4	20	60.6	0.942	1.00		
	≥4.38	26	44.1	10	38.5	16	61.5		1.04	0.36	2.99
Lactate (mmol/L)	<3.50	29	49.2	15	51.7	14	48.3	0.052**	1.00		
	≥3.50	30	50.8	8	26.7	22	73.3		2.95	0.99	8.75
Blood glucose (g/dl)	<157.00	29	49.2	11	37.9	18	62.1	0.871	1.00		
	≥157.00	30	50.8	12	40.0	18	60.0		0.92	0.32	2.61
Biomarkers											
NLR	<9.56	30	50.8	12	40.0	18	60.0	0.871	1.00		
	≥9.56	29	49.2	11	37.9	18	62.1		1.09	0.38	3.11
CRP (mg/L)	<11.33	30	50.8	16	53.3	14	46.7	0.024*	1.00		
	≥11.33	29	49.2	7	24.1	22	75.9		3.59	1.18	10.93
PCT (ng/L)	<3.43	29	49.2	17	58.6	12	41.4	0.003*	1.00		
	≥3.43	30	50.8	6	20.0	24	80.0		5.67	1.78	18.08
P-SEP (mg/L)	<0.45	32	54.2	11	34.4	21	65.6	0.430	1.00		
	≥0.45	27	45.8	12	44.4	15	55.6		0.65	0.23	1.88
Mr-ProADM (pg/ml)	<11.85	28	47.5	10	35.7	18	64.3	0.625	1.00		
	≥11.85	31	52.5	13	41.9	18	58.1		0.77	0.27	2.20
Score systems											
SOFA score	<8.29	30	50.8	16	53.3	14	46.7	0.024*	1.00		
	≥8.29	29	49.2	7	24.1	22	75.9		3.59	1.18	10.93
APACHE-II score	<24.92	30	50.8	12	40.0	18	60.0	0.871	1.00		
	≥24.92	29	49.2	11	37.9	18	62.1		1.09	0.38	3.11

*Chi-Square test ; significant if *p < 0.05 ; ** p<0.2 ; NA* : not applicable/observation*

[a]*calculate percentage in total subjects of recruitement (n = 60)*

[b]*calculate percentages in a row*

Table 3: Multivariate analysis of risk factors related for septic shock

Variables	Categories or Cut-off	*p* value	OR	95 % CI (Lower-Upper)	
Biomarkers/score system					
WBC count (×10³/uL)	15.8	0.082**	4.98	0.81	30.51
PCT (ng/L)	3.43	0.192	2.94	0.58	14.88
P-SEP (mg/L)	0.45	0.249	0.33	0.05	2.16
MR-ProAdm (mg/L)	11.85	0.042*	0.10	0.01	0.92
SOFA score	8.29	0.013*	24.72	1.97	310.52
Lactate (mmol/L)	3.50	0.051**	6.17	0.99	38.34
Type of infection/comorbidity					
Skin and soft tissue infection	-	0.058**	18.42	0.91	373.28
Hypertension	-	0.019*	0.05	0.00	0.61

**p<0.05, **p<0.1; p-value of Hosmer-Lemeshow Goodness of Fit (GoF) = 0.548;*
Cox and Snell R2 square = 0.439 or 43.9%.

Table 4: Sensitivity, specificity, and area under the receiver operating curve (AUC) of biomarkers as risk factors for septic shock

Biomarkers/score system	Cut-off	Sensitivity	Specificity	AUC
WBC count (×10³/uL)	15.8	63.89%	69.57%	0.667
PCT (ng/ml)	3.43	66.67%	73.91%	0.703
P-SEP (mg/L)	0.45	41.67%	47.83%	0.448
MR-ProADM (mg/L)	11.85	50.00%	43.48%	0.467
SOFA score	8.29	61.11%	69.57%	0.653
Lactate (mmol/L)	3.5	61.11%	65.22%	0.631
Skin and soft tissue infection	NA	11.11%	56.52%	0.338
Hypertension	NA	22.22%	91.30%	0.568

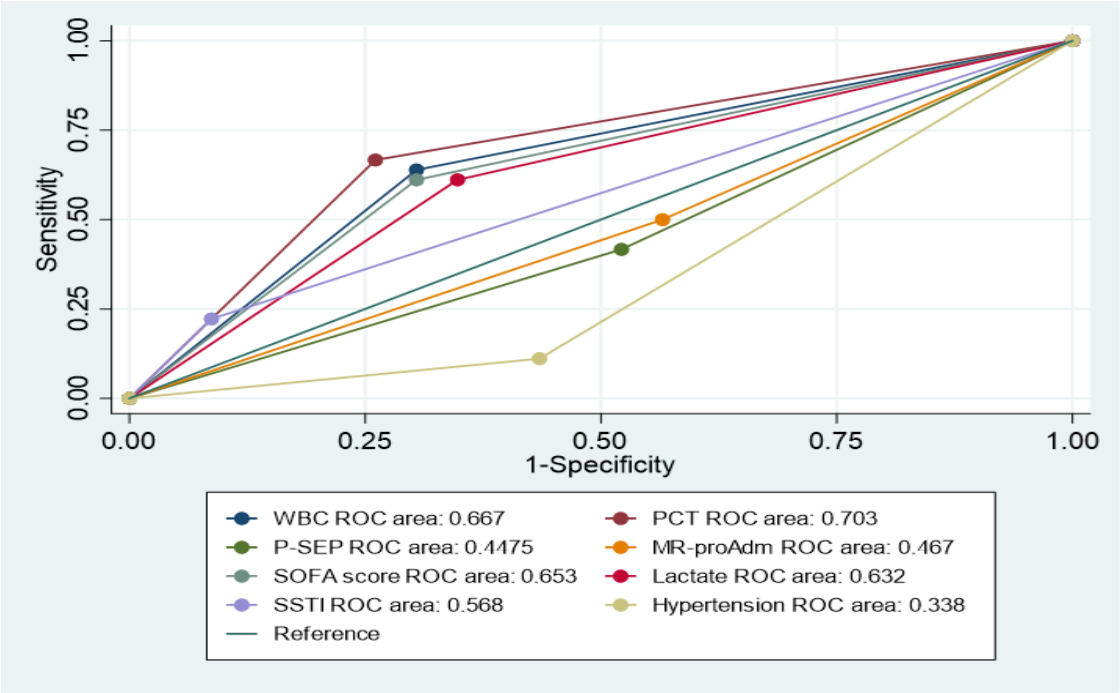


Figure 2: ROC curve multivariate analysis of single predictor septic shock of WBC, PCT, P-SEP, MR-ProADM, SOFA score, lactate, skin, and soft tissue infection, hypertension

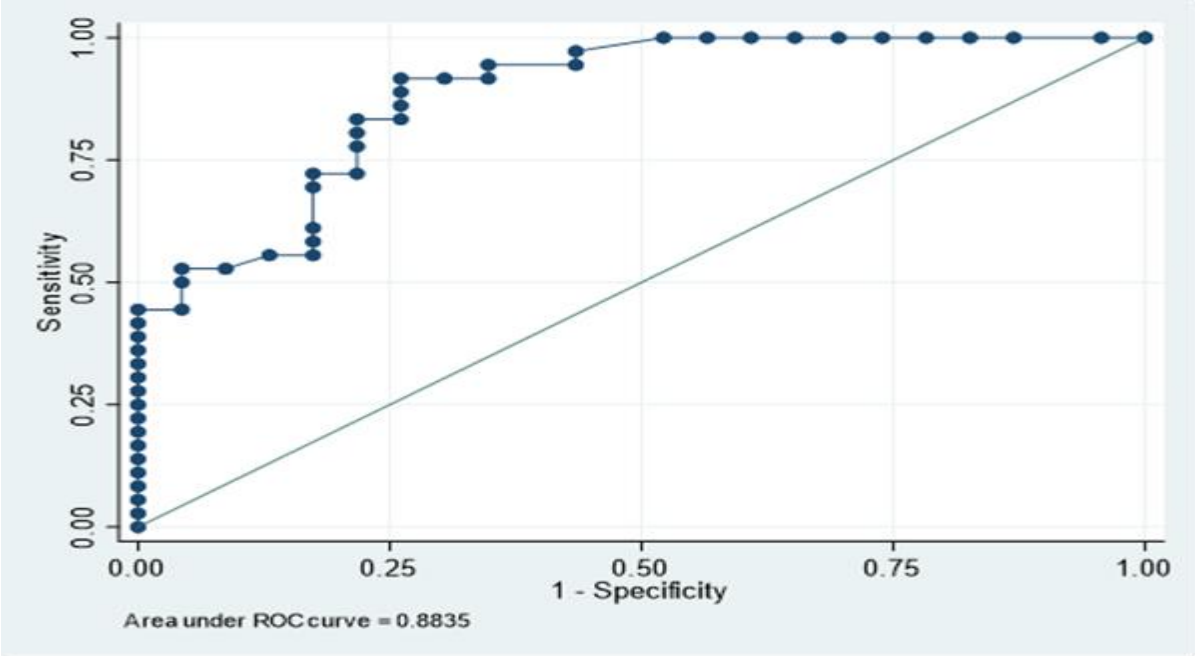


Figure 3: ROC curve multivariate model combination of WBC count, PCT,P-SEP, MR-ProADM, SOFA score lactate, skin and soft tissue infection, hypertension (AUC=0.883)

Table 3 indicated the multivariate analysis of predictors related to septic shock. The significance threshold can be $p < 0.05$ and $p < 0.1$. The predictors for septic shock were as followed: WBC count (OR = 4.98; 95% CI, 0.81-30.51; p = 0.082); PCT (OR = 2.94; 95%CI 0.58-14.88; p = 0.192); P-SEP (OR = 0.33; 95%CI 0.05-2.16; p = 0.249); MR-ProADM (OR = 0.10; 95% CI, 0.01-0.92; p = 0.042); SOFA score (OR = 24.72; 95% CI, 1.97-310.52; p = 0.013); lactate (OR = 6.17 95% CI, 0.99-38.34; p = 0.051); skin and soft tissue infection (OR = 18.42; 95% CI, 0.91-373.28; p = 0.058); and hypertension (OR = 0.05; 95% CI, 0.00-0.61; p = 0.019).

Although P-SEP, WBC count, PCT, and skin and soft tissue infection were not statistically significant for $p < 0.05$, it was critical to keep these four variables in the model.

Eliminating these four variables diminishes the significance of the remaining predictor variables. If the analysis of an important variable was not significant, it might still be included in the multivariate model. For instance, in this study, using the GoF and R2 parameters yielded positive results.

We measured the R2 coefficient, which results in Cox and Snell values of 0.439, indicating that the variability of the dependent variable, which can be explained by a set of predictors is 43.9%, or approximately 56.1% of the rest is explained by factors outside the model, meaning that the model is unable to explain it. SOFA score was the highest odd ratio followed by skin and soft tissue infection, lactate, WBC count, PCT, P-SEP, MR-ProADM, and hypertension, respectively.

Table 4 and Figure 2 showed the ability of selected biomarkers and SOFA score to predict septic shock patients based on ROC curve analysis. The optimal cut-off value for WBC count was 15.8×10^3 uL with sensitivity of 63.89% and specificity of 69.57% (AUC 0.667; 95% CI 0.81-30.5); 3.43 ng/mL for PCT with sensitivity of 66.67% and specificity 73.91% (AUC 0.703; 95% CI 0.58-14.88); 0.45 mg/L for P-SEP with sensitivity of 41.67% and specificity of 69.57% (AUC 0.448; 95% CI 0.05-2.16); 11.85mg/L for MR-ProADM wih sensitivity of 50.0% and specificity of 43.48% (AUC 0.467; 95% CI 0.01-0.92); cut-off 8.29 for SOFA score wih sensitivity of 61.11% and specificity of 69.57% (AUC 0.653; 95% CI 1.97-310.52); 3.5 mmol/L for lactate with sensitivity of 61.11 % and specificity of 65.22% (AUC 0.631; 95% CI 0.99-38.34); for skin and soft tissue infection the sensitivity of 11.11% and the specificity of 56.52% (AUC 0.338; 95% CI 0.91-373.28); for hypertension the sensitivity of 22.22% and the specificity of 91.30% (AUC 0.568; 95% CI 0.00-0.61). Procalcitonin was the highest

AUC, followed by WBC count, SOFA score, lactate, hypertension, MR-ProADM, P-SEP, and skin and soft tissue infection (0.703; 0.667; 0.653; 0.631; 0.568; 0.467; 0.448; 0.338).

Figure 3 depicts the WBC count, PCT, P-SEP, MR-ProADM, SOFA score, lactate, skin and soft tissue infection, and hypertension together generating a fit model to predict a septic shock.

The ROC of the logistic regression model showed higher than the ROC of the predictor alone. It was possible to predict septic shock in a patient using information from eight predictors and the ROC value of the model was 0.883 (95% CI 0.796-0.971).

The *p*-value of Hosmer-Lemeshow Goodness of Fit (GoF) was 0.548 or not significant, and Cox and Snells R Square was 0.439 or 43.9%. These prediction models were able of predicting septic shock at an emergency department.

Sepsis and septic shock are life-threatening conditions that necessitate immediate diagnosis and treatment since admitted to ED.In fact, sepsis and septic shock have a significant fatality rate. Various factors play a role in the aggravation of these illnesses [23].

In this study, we found that the combination of WBC count, PCT, P-SEP, MR-ProADM, SOFA score, and lactate, not only biomarkers and scoring systems, but also types of infection and comorbidity such as skin soft tissue infection and hypertension, may predict septic shock. These combinations had higher ROC, sensitivity, and specificity than single analyses of predictors. A biomarker should be accurately measured and reliable. In the ideal situation, the biomarker or combination of biomarkers would have high specificity and sensitivity for identifying a health condition [5].

Several studies have shown that the combination of several variables increases the AUC value, sensitivity, and specificity.

In this study, the cut-off WBC count was 15.8 ($\times 10^3$/uL) in septic patients. The WBC count is the most common test used for infectious diseases. Septic shock may cause leukopenia or leukocytosis of normal count [5].

The number of neutrophils increases in the early stages of septic shock in most patients. During septic shock, an overabundance of neutrophils destroys organ parenchymal cells and causes numerous organ dysfunctions [24].

This study found that cut-off PCT was 3.43ng/ml (AUC 0.703) and P-SEP was 0.45 (AUC 0.448) in septic shock patients. In this study, PCT value was higher in sensitivity and specificity than P-SEP. Procalcitonin increases in the first 4 hours in response to injury or infection, with a peak in the initial 6 hours with duration of 8-24 hours, and will return to baseline values in 2-3 days [25].

Previous studies found that P-SEP, which is part of CD14, can be detected in the blood and its level elevates closely related to the immune response to LPS and typically elevates earlier than PCT [26, 27]. The P-SEP level increases within 2 h and reaches the peak in 3 h after infection [26].

P-SEP might be a better biomarker for sepsis during the early stages of sepsis than in later stages [28, 29]. Wu *et al.* found no significant difference between presepsin and PCT in either EDs (AUC 0.90 and 0.88) or ICUs (AUC 0.87 and 0.82). Furthermore, it is not suggested as a sole test for sepsis diagnosis, but it may be beneficially combined with some sensitive biological markers [27].

According to Haang *et al.* [30], the MR-ProADM cut-off value is 1.75 nmol/L, and the combination of MR-ProADM and SOFA-score improves the 30-day mortality risk higher (area under the curve (AUC) 0.87) than the SOFA-score alone (AUC 0.81). The AUC value of a combination of presepsin and the SOFA score was significantly larger than that of the SOFA score alone (AUC: 0.817 vs. 0.793, P=0.041) [31].

There is inadequate circulation in sepsis to support an appropriate metabolism, resulting in septic shock. Elevated lactate levels during critical illness or septic shock can be caused by tissue hypoxia, reduced hepatic clearance, or significant ß-adrenergic activation of Na/K-ATPase, which leads to an increase in aerobic glycolysis [30, 31]. In this study, cut-off lactate level was 3.50 mmol/L and a significant predictor of septic shock. In critically ill patients with sepsis, trauma, organ failure, and shock caused by septic, cardiogenic, or hemorrhagic etiologies, a sustained increase in lactate > 2 mmol/l is an independent predictor of mortality [32-35].

In this study, the cut-off SOFA score was 8.29, with the highest odd ratio and significant predictors of septic shock (OR = 24.72; 95% CI, 1.97-310.52; p = 0.013). It was higher than Sepsis study in Southeast Asia, those who died had a considerably higher total SOFA score than those who survived (6.7 vs. 4.6, p 0.001). The AUROC of SOFA score for septic shock was 0.653 slightly different with lie at.al 0.68 (95% confidence interval: 0.62-0.74) [36]. MR-ProADM median was 11.85 pg/ml higher than the study by Andaluz-Ojeda *et al.* and Elka *et al.*, 4.49 pg/ml, and 11.47 pg/ml [37, 38].

In this study, the levels of MR-ProADM were significantly higher in septic shock than in sepsis (p=0,042). MR-ProADM is mainly produced by vascular endothelial cells and smooth muscle cells. MR-ProADM has effects on vasodilatation, which are involved in some clinical manifestations of sepsis and septic shock as refractory hypotension [39].

Levels of MR-ProADM may represent the severity of organ failure, even in the early stages of the disease, as well as the progression of systemic inflammatory response, the progression from sepsis to septic shock, and the mortality risk of septic patients. Moreover, MR-ProADM may be a good alternative to SOFA score [40].

Skin and soft tissue infection admission to the ED is one of the most common causes of sepsis [39]. Skin and soft tissue infections can induce sepsis or septic shock because organisms from the outside can enter the blood of vulnerable people through cracks in the skin and enter the blood. The skin has a large circulatory system within it that, when disrupted, has adverse effects. Extensive skin involvement, wound depth, diabetes mellitus, and age are all risk factors for sepsis in SSTI [41-43]. Besides that, in this study, 98% of patients had pneumonia, thus exacerbating the condition of septic shock. Furthermore, in this study, 98% of patients had other concomitant infection with pneumonia, aggravating the situation of septic shock. Furthermore, 57 % of patients had more than two comorbidities. Wang *et al.* investigated the relationship between baseline chronic medical problems and the possibility of future sepsis occurrences [44].

Previous studies related medical comorbidities to the severity of sepsis or the degree of organ dysfunction [45, 46].

However, the comorbidities that facilitate organ dysfunction differ depending on the underlying infection. The risk of sepsis effects varied substantially depending on the number of comorbidities. The presence of any of a number of comorbidities, including hypertension, advanced age, and heart illness, may result in worsening results in sepsis and septic shock [45, 46].

The study had limitations. First, the study had a limited number of samples size and here is a discrepancy between the number of patients with sepsis compared to that of patients with septic shock. Second, we did not evaluate various treatments, or other potential variables such as genetic polymorphisms that might have effect to sepsis and septic shock conditions.

Conclusion

In this study, biomarkers should not be used as a single test, but always in conjunction with other risk factors of septic shock. Diagnosis and prognosis are often the result of a combination of several factors. The combination of five biomarkers (white blood cells count, procalcitonin, presepsin, MR-Proadrenomedullin, and lactate) and clinical scoring (SOFA score) plus additional risk variables such as skin and soft tissue infection, and hypertension performed better in predicting septic shock than any single factor.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the article and agreed to be responsible for all the aspects of this work.

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