ORIGINAL ARTICLE

CONTENTS

Inflammatory cytokines as risk factor of septic shock in patients with sepsis

Dwi Retnoningrum[1,2], Nyoman Suci Widyastiti[2], Meita Hendrianingtyas[2], Edward Kurnia Setiawan Limijadi[2], Villa Sekar Cita[2], Nur Farhanah[3], Banundari Rachmawati[2]

[1]DOCTORAL STUDY PROGRAM OF MEDICAL AND HEALTH SCIENCE, UNIVERSITAS DIPONEGORO, SEMARANG, INDONESIA
[2]DEPARTMENT OF CLINICAL PATHOLOGY, FACULTY OF MEDICINE, UNIVERSITAS DIPONEGORO, SEMARANG, INDONESIA
[3]DIVISION OF TROPICAL MEDICINE AND INFECTIOUS DISEASES, DEPARTMENT OF INTERNAL MEDICINE, FACULTY OF MEDICINE, UNIVERSITAS DIPONEGORO, DR. KARIADI HOSPITAL, SEMARANG, INDONESIA

ABSTRACT

Aim: To prove pro-inflammatory and anti-inflammatory cytokines as risk factors of septic shock in patients with sepsis.

Materials and Methods: This study used a prospective observational study. The target population were sepsis patients who were admitted to the emergency room of Dr Kariadi Hospital. TNF-α, IL-6, IL-10, and IL-4 levels were examined using the ELISA method. Bivariate and multivariate logistic regression analyses as well as receiver operating characteristic curve analysis were used to predict septic shock.

Results: Patients with septic shock had higher levels of IL-6, TNF-α, and IL-10 compared to those with sepsis. Multivariate analysis results showed that IL-6 and IL-10 were independent risk factors for septic shock. IL-6 level ≥11.4 pg/ml had an OR of 7.02, CI 95% 1.78-27.70 (p = 0.005), and IL-10 level had an OR of 3.89, CI 95% 1.13-13.45 (p = 0.031), as risk factors for septic shock.shock.

Conclusions: IL-6 and IL-10 are risk factors of septic shock in sepsis. Meanwhile, TNF-α and IL-4 levels are not associated with shock in sepsis.

KEYWORDS: sepsis, interleukin, tumor necrosis factor, septic shock

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by an inappropriate body response to infection [1]. An estimated 49 million cases of sepsis and 11 million sepsis-related deaths occurred worldwide in 2017, accounting for approximately 20% of all causes of death globally. The incidence and mortality of sepsis vary greatly across regions, with the highest incidence in sub-Saharan Africa, Oceania, South Asia, East Asia, and Southeast Asia [2, 3]. A systematic review and meta-analysis by Fleischmann et al. in 2020 reported that from 51 studies, the pooled incidence of sepsis was 189 cases per 100,000 population per year, with an estimated mortality rate of 26.7%. The estimated incidence of sepsis in the intensive care unit (ICU) was 58 per 100,000 people per year, with an estimated mortality rate of 41.9% [4]. The prevalence of sepsis in Asia was reported by Li et al. (2022) from 386 ICUs in 22 Asian countries, with a prevalence of sepsis of 22.4% and a 90-day mortality rate of 36.6% [5]. Research by Purba et al. in Indonesia found that the mortality rate of sepsis patients was 58.3% [6]. The study by Valles et al. reported that 55.5% of deaths from sepsis occurred in the ICU within 72 hours of treatment [7].

Septic shock is a more severe condition than sepsis and is a critical condition involving acute circulatory dysfunction that requires vasopressors to correct hypotension, decreased urine output, and changes in the patient's level of consciousness. Septic shock is defined as sepsis accompanied by persistent hypotension after the administration of 30 ml/kg of intravenous (IV) crystalloid fluid within 1 hour of sepsis identification, requiring vasopressors to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg and serum lactate levels > 2 mmol/L (18 mg/dL). Using this criterion, the mortality rate for septic shock increases to 40% [8, 9].

In sepsis, the balance between pro-inflammatory and anti-inflammatory cytokines is critical. Pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, stimulate systemic inflammation. Anti-inflammatory cytokines such as IL-10 and IL-4 work to restore immunological balance. Sepsis can cause tissue and organ damage if pro-inflammatory cytokines are produced

in excess. Levels of pro- and anti-inflammatory cytokines increase significantly in patients with sepsis [10]. Several studies have indicated that the most important pro-inflammatory cytokine that plays a significant role in the pathogenesis of acute inflammatory responses is tumor necrosis factor-alpha (TNF-α). TNF-α is a pro-inflammatory cytokine that affects antimicrobial and anti-inflammatory responses by activating leukocytes, increasing cell proliferation, differentiation, and lymphocyte apoptosis. According to Deng et al., TNF-α is an inflammatory cytokine associated with sepsis-induced cardiomyopathy [11]. Research by Zhai et al. in patients with abdominal injuries found that TNF-α levels were higher in sepsis than in non-sepsis ($p < 0.001$). TNF-α plays a central role in the systemic inflammatory response due to its ability to release other cytokines in the early stages of infection and its direct effect on septic shock, and plasma TNF-α levels are associated with mortality from sepsis [12, 13].

The hyperinflammatory state in sepsis is also characterized by increased levels of IL-6 as a proinflammatory cytokine. Interleukin 10 (IL-10) is a pleomorphic cytokine with various phenotypic roles released by granulocytes, dendritic cells, macrophages, B cells, and T cell subsets. IL-10 is a major anti-inflammatory cytokine with immunomodulatory effects that suppress the production of pro-inflammatory cytokines [14]. The study by Zhang et al. reported differences in IL-10 levels between sepsis and non-sepsis infections. In sepsis patients, IL-10 correlated with leukocyte count and IL-6 and IL-8 levels [15].

Interleukin-4 (IL-4) is an anti-inflammatory cytokine that plays an important role in modulating the immune response during sepsis. IL-4 functions by inhibiting the production of pro-inflammatory cytokines such as TNF-α and IL-1β, as well as reducing the expression of adhesion molecules on endothelial cells, which collectively help control the excessive inflammatory response that occurs in sepsis. However, the role of IL-4 in sepsis remains controversial. Some studies suggest that IL-4 may have a protective effect by suppressing excessive inflammatory responses, while other studies indicate that IL-4 may contribute to excessive immunosuppression, increasing susceptibility to secondary infections [16]. Research by Schrijver et al. reports that interleukin-4 (IL-4) has the ability to suppress acute inflammation while inducing trained immunity in monocytes. To take advantage of this paradoxical property of IL-4 in the body, they developed a fusion protein between apolipoprotein A1 (apoA1) and IL-4, which was then integrated into lipid nanoparticles. Therapy using IL-4 in the form of these nanoparticles successfully overcame immunoparalysis in mice with hyperinflammation induced by lipopolysaccharides [17].

AIM

To prove pro-inflammatory and anti-inflammatory cytokines as risk factors of septic shock in patients with sepsis.

MATERIALS AND METHODS

This study was a prospective observational study. The study was conducted from March to October 2025. Physical examinations, medical history, and informed consent for research subject screening were conducted at the emergency room of Dr. Kariadi Hospital in Semarang. Complete blood tests and laboratory examinations were performed at the hospital laboratory. Tests for IL-6, TNF-α, IL-10, and IL-4 levels were performed at the GAKI Laboratory, Faculty of Medicine, Universitas Diponegoro, Semarang.

The inclusion criteria were a sepsis diagnosis according to SEPSIS-3 criteria, enrollment within 24 hours of admission to the emergency department, age >18 years, and being free of radiotherapy or chemotherapy. Septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and a serum lactate level more than 2 mmol/L (>18 mg/dL). Exclusion criteria were patients with immunosuppressive therapy, a history of autoimmune disease, and malignancy. IL-6, TNF-α, IL-10, and IL-4 were examined using the ELISA (Enzyme Linked Immunosorbent Assay) kit, Elabscience Biotechnology Inc., United States.

STATISTICAL ANALYSIS

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 $p < 0.25$ in bivariate analysis were included in multivariate analysis. The odds ratio (OR) and confidence interval (CI) were then computed. The Mann-Whitney test was used to test the difference in IL-6, TNF-α, IL-10, and IL-4 levels between shock and sepsis. The cut-off levels for the variables were determined based on the Youden index from the Receiver Operating Characteristic (ROC) curve or from the literature. The study received ethical clearance from the Health Research Ethics Committee of Dr Kariadi General Hospital, Semarang, No. 16447/EC/KEPK-RSDK/2025.

AI STATEMENT

The author states that no AI tools were used in writing this article.

FRAMEWORK
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RESULTS

This study involved 82 subjects consisting of 44 males (53.7%) and 38 females (46.3%). The subjects in this study ranged in age from 18 to 77 years. Most subjects required ICU care, with a mortality rate of 54.9%. Diabetes mellitus was the most prevalent comorbidity among patients, with cardiovascular diseases and hypertension coming in second. Patients had an average SOFA score of 7.7 and a maximum score of 14. The average hemoglobin level of the research participants was 10.03 g/dL, which suggested mild anemia. While the median platelet count stayed within the normal range at $248 \times 10^3/\mu L$, leukocyte counts tended to be higher at $14.28 \times 10^3/\mu L$. With median values of 83.5 mg/dL and 1.9 mg/dL, respectively, the majority of patients had increased urea and creatinine levels. The NLR, which measures systemic inflammation, and serum lactate levels were both high, with median values of 3.7 mmol/L and 9.1, respectively. The basic characteristics of the research population are shown in Table 1.

Table 2 showed bivariate analysis of risk factors associated with septic shock. The bivariate analysis revealed that males are at higher risk of developing septic shock (OR 2.60, p=0.037, CI 1.05–6.43). Among vital signs, systolic blood pressure and an increased heart rate were associated with a higher risk of septic shock (OR 5.01, p = 0.001, and CI 1.95–12.92 and OR 5.67, p = 0.001, and CI 2.18–14.74, respectively). Based on the source of infection, this study found that intra-abdominal infections carry a higher risk of septic shock compared to other infections (OR = 9.00, p = 0.04, CI 1.03–78.57).

The results of the bivariate laboratory analysis revealed that elevated levels of bilirubin and serum lactate, as well as a high NLR, were risk factors for septic shock compared to other laboratory findings (OR = 2.54, p = 0.047, CI 1.00–6.41; OR = 5.00, p = 0.001, CI 1.93–12.96; OR = 3.10, p = 0.016, CI 1.22–7.86, respectively). Meanwhile, a bivariate analysis of inflammatory cytokines revealed that higher levels of IL-6, TNF-α, and IL-10 were risk factors for septic shock (OR = 8.06, p = 0.001, CI 2.66–24.46; OR = 3.8, p = 0.008, CI 1.39–10.41; OR = 3.59, p = 0.005, CI 1.43–9.00, respectively).

Table 3 showed the differences in pro-inflammatory and anti-inflammatory cytokines between sepsis and septic shock. The Mann-Whitney U test results showed a difference in IL-6, TNF-α, and IL-10 levels between sepsis and septic shock (p = 0.001, p = 0.019, and p = 0.008), while no difference was found in IL-4 levels between sepsis and septic shock (p = 0.352). The level of IL-6, TNF-α, and IL-10 was higher in septic shock than in sepsis.

Based on Table 4, the results of the bivariate analysis with a p-value < 0.25 were included in the multivariate analysis. Thus, the variables gender, WBC, total bilirubin, sodium, lactate, NLR, intra-abdominal infection, IL-6, TNF-α, and IL-10 were included in the multivariate analysis. Table 4 indicated a multivariate analysis of inflammatory cytokines and other risk factor-related septic shocks. The risk factors of septic shock were as followed: lactate serum (OR=6.02; 95% CI, 1.6-22.65, p=0.008), intraabdomen infections (OR=16.76, 95% CI, 1.04-269.44, p=0.047, IL-6 (OR=7.02, 95% CI, 1.78-27.70, p=0.005) and IL-10 (OR=3.89, 95% CI, 1.13-13.45, p=0.031).

Table 5 showed the cut-off value of inflammatory cytokines and other risk factors with area under the curve, sensitivity and specificity. The area under the curve (AUC) values from the ROC curve for IL-6, IL-10, intra-abdomen infection, lactate and the incidence of septic shock were 0.709, 0.673, 0.428 and 0.696. IL-6 has the best AUC value (Fig. 1).

Fig. 1 showed the Receiver Operating Characteristic (ROC) curves comparing the diagnostic capabilities of IL-6, IL-10, lactate levels, and the presence of intra-abdominal infection in predicting the study outcome. As shown in the graphical representation, for most of the 1-specificity range, the IL-6 curve is farther above the reference line than the other biomarkers, demonstrating the best discriminatory ability. The curves for lactate and IL-10 also showed a fairly satisfactory discriminatory capacity, as they are above the reference line, but their performance is still inferior to IL-6. On the other hand, the intra-abdominal infection variable has the curve closest to the reference line, which indicates low predictive ability.

DISCUSSION

The results of this study indicate that being 60 years or older was not associated with septic shock, but males were found to have a higher risk of developing septic shock than females. In general, males are more susceptible to sepsis than females. Several studies have reported a higher incidence of sepsis in males and varying mortality rates between the sexes. Females tend to have a better immune response, which is thought to be due to the role of the hormone estrogen in enhancing the adaptive immune system and higher levels of anti-inflammatory mediators in females, while males often show a weaker cellular immune

Table 1. Characteristics of Research Subjects

Variable (n=82)	n (%)	Mean ±SD	Median (Min-Max)	p-value
Gender				
Male	44 (53.7)			
Female	38 (46.3)			
Age (yr)		54.67±14.12	58.5 (18-77)	0.001*
Sepsis state				
Sepsis	46 (56.1)			
Septic shock	36 (43.9)			
Outcome				
Survive	37 (45.1)			
Non-survive	45 (54.9)			
Ward				
ICU	45 (54.9)			
Non-ICU	37 (45.1)			
Blood pressure				
Systole (mmHg)		108.89±26.62	100 (60-180)	0.001*
Diastole (mmHg)		69.04±16.35	68 (39-107)	0.047*
Heart rate (bpm)		100.30±23.90	98 (60-172)	0.073
Temp (°C)		36.74±0.69	36.7 (35.6-39.1)	0.001*
Respiratory rate (bpm)		23.88±3.33	24 (18-36)	0.001*
Comorbidity				
DM	34 (41.5)			
Hypertension	27 (32.9)			
CKD	3 (3.7)			
Cardiovascular disorder	19 (23.2)			
SOFA score		7.70±2.95	8 (2-14)	0.099
Hemoglobin (g/dL)		10.03±2.53	9.5 (4.9-18.1	0.039
WBC (x10^3/µL)		16.6±10.45	14.28 (3.0-63.3)	0.001*
Platelet (x10^3/ µL)		273.78±166.54	248 (9-785)	0.002*
Blood glucose (mg/dL)		154.46±104.9	122 (34-631)	0.001*
Urea (mg/dL)		97.60±60.76	83.5 (20-262)	0.005*
Creatinine (mg/dL)		2.67±2.67	1.9 (0.3-14.0)	0.001*
Total bilirubin (mg/dL)		2.08±3.8	0.71 (0.15-25.54)	0.001*
Sodium (mmol/L)		133±8.03	134 (107-162)	0.017*
Potassium (mmol/L)		4.09±1.09	4.0 (1.5-7.0)	0.005*
Lactate (mmol/L)		4.88±3.09	3.7 (0.7-15.5)	0.001*
NLR		11.11±7.93	9.10 (0.10-30.01)	0.001*
IL-6 (pg/mL)		20.55±17.99	15.04 (1.31-98.01)	0.001*
TNF-α (pg/mL)		28.29±28.37	17.88 (12.58-161.2)	0.001*
IL-10 (pg/mL)		29.66±28.98	15.73 (1.13-99.19)	0.001*
IL-4 (pg/mL)		49.69±38.89	39.03 (0.84-154.4)	0.001*

p: Kolmogorov-Smirnov, *p<0.05: abnormal distribution of variable, ICU: intensive care unit,
DM: diabetes mellitus, CKD: chronic kidney disease, SOFA: Sequential Organ Failure Assessment, WBC: white blood cells, NLR: neutrophil lymphocyte ratio, IL: interleukin, TNF: tumour necrosis factor.
Source: compiled by the authors of this study

response, possibly due to the suppressive effects of testosterone [18, 19]. Aa complex network of cytokine, immune, and endothelial cell interactions occur and disturbances in the microcirculation cause organ dysfunction or even failure leading to high mortality in those patients. In this respect, numerous experimental and clinical studies indicate sex-specific differences in infectious diseases and sepsis. Female gender has been demonstrated to be protective under such conditions, whereas male gender may be deleterious

Table 2. Bivariate analysis of risk factors associated with septic shock

Variables	Cut-off	Total subject (n=82)		Sepsis		Septic shock		p-value	OR	95% CI (Lower-Upper)
		n	%[a]	n	%[b]	n	%[b]			
Demography										
Age (yr)	≥ 60	37	45.1	20	54.1	17	45.9	0.735	1.16	0.48-2.79
	< 60	45	54.9	26	56.6	19	42.2			
Gender	Males	44	53.7	20	45.5	24	54.5	0.037*	2.60	1.05-6.43
	Females	38	46.3	26	68.4	12	31.6			
Ward	ICU	45	54.9	22	48.9	23	51.1	0.147**	1.90	0.79-4.71
	Non-ICU	37	45.1	24	64.9	13	35.1			
Vital Sign										
Systole (mmHg)	<100	36	43.9	12	33.3	24	66.7	0.001*	5.01	1.95-12.92
	≥100	46	56.1	34	73.9	12	26.1			
Heart rate (bpm)	≥102	39	47.6	15	38.5	24	61.5	0.001*	5.67	2.18-14.74
	< 102	43	52.4	31	72.1	12	27.9			
Temperature (°C)	≥37.5	26	31.7	17	65.4	9	34.6	0.248	0.569	0.22-1.49
	<37.5	56	68.3	29	51.8	27	48.2			
Respiratory rate (bpm)	≥ 22	43	52.4	41	95.3	26	60.5	0.049*	0.317	0.10-1.03
	< 22	39	47.6	5	12.8	10	25.6			
Comorbidities										
Diabetes mellitus	Yes	34	41.5	21	61.8	13	38.2	0.384	0.67	0.28-1.65
	No	48	58.5	23	47.9	23	47.9			
Hypertension	Yes	27	32.9	19	70.4	8	29.6	0.068**	0.41	0.15-1.08
	No	55	67.1	27	49.1	28	50.9			
CKD	Yes	3	3.7	2	66.7	1	33.3	0.592	0.75	0.15-3.80
	No	79	96.3	44	55.7	35	44.3			
Cardiovascular	Yes	8	9.8	5	62.5	3	37.5	0.502	0.75	0.17-3.35
	No	74	90.2	41	55.4	33	44.6			
Type of infection										
Pneumonia	Yes	66	80.5	36	54.5	30	45.5	0.565	1.39	0.45-4.27
	No	16	19.5	10	62.5	6	37.5			
Urinary tract infection	Yes	19	23.2	12	63.2	7	36.8	0.479	0.68	0.24-1.97
	No	63	76.8	34	54.0	29	46.0			
Skin and soft tissue infection	Yes	6	7.3	4	66.7	2	33.3	0.461	0.62	0.11-3.58
	No	76	92.7	42	55.3	34	44.7			
Leptospirosis	Yes	2	2.4	1	50.0	1	50.0	0.688	1.14	0.28-4.67
	No	80	97.6	45	56.3	35	43.8			
Intra-abdominal infection	Yes	7	8.5	1	14.3	6	85.7	0.040*¥	9.00	1.03-78.57
	No	75	91.5	45	60.0	30	40.0			
Laboratory values										
Hemoglobin (g/dL)	<10.4	50	61.0	30	60.0	20	40.0	0.373	0.67	0.27-1.63
	≥10.4	32	39.0	16	50.0	16	50.0			
WBC (x10^3/µL)	≥15.6	34	41.5	16	47.1	18	52.9	0.165**	1.88	0.77-4.57
	<15.6	48	58.5	30	62.5	18	37.5			
Platelet (x10^3/µL)	<150	21	25.6	12	57.1	9	42.9	0.911	0.94	0.35-2.57
	≥150	61	74.4	34	55.7	27	44.3			
Blood glucose (mg/dL)	≥ 122	41	50.0	25	61.0	16	39.0	0.373	0.67	0.28-1.61
	<122	41	50.0	21	51.2	20	48.8			

Table 2. Cont.

Urea (mg/dL)	≥85	40	48.8	21	52.5	19	47.5	0.522	1.33	0.56-3.19
	<85	42	51.2	25	59.5	17	40.5			
Creatinine (mg/dL)	≥1.2	55	67.1	32	58.2	23	41.8	0.587	0.77	0.31-1.95
	<1.2	27	32.9	14	51.9	13	48.1			
Total bilirubin (mg/dL)	≥1.2	29	35.4	12	41.4	17	58.6	0.047*	2.54	1.00-6.41
	<1.2	53	64.6	34	64.2	19	35.8			
Sodium (mmol/L)	≥143.5	5	6.1	1	20.0	4	80.0	0.093**¥	5.63	0.60-52.72
	<143.5	77	93.9	45	58.4	32	41.6			
Potassium (mmol/L)	<4	39	47.6	22	56.4	17	43.6	0.957	0.98	0.41-2.34
	≥4	43	52.4	24	55.8	19	44.2			
Lactate (mmol/L)	≥4.46	33	40.2	11	33.3	22	66.7	0.001*	5.00	1.93-12.96
	<4.46	49	59.8	35	71.4	14	28.6			
NLR	≥7.15	36	43.9	10	27.8	26	72.2	0.016*	3.10	1.22-7.86
	<7.15	46	56.1	25	54.3	21	45.7			
Inflammatory cytokine										
IL-6 (pg/ml)	≥11.4	51	62.2	20	39.2	31	60.8	0.001*	8.06	2.66-24.46
	<11.4	31	37.8	26	83.9	5	16.1			
TNF-α (pg/ml)	≥15.9	53	64.6	24	45.3	29	54.7	0.008*	3.80	1.39-10.41
	<15.9	29	35.4	22	75.9	7	24.1			
IL-10 (pg/ml)	≥21.6	36	43.9	14	38.9	22	61.1	0.005*	3.59	1.43-9.00
	<21.6	46	56.1	32	69.6	14	30.4			
IL-4 (pg/ml)	≥48.9	32	39.0	17	53.1	15	46.9	0.664	1.22	0.50-2.98
	<48.9	50	61.0	29	58.0	21	42.0			

Chi-Square test; ¥: Fisher exact test, significant if *p < 0.05; ** p<0.25; [a]: calculate percentage in total subjects of recruitment (n = 82), [b]: calculate percentages in a row.
Source: compiled by the authors of this study

Table 3. Comparison of inflammatory cytokines between sepsis and septic shock

Variable	Sepsis Median (min-max)	Septic shock Median (min-max)	p
IL-6	10.08 (1.31-52.30)	18.45 (4.84-98.01)	0.001*
TNF-α	16.34 (12,58-119,5)	20.43 (12.65-161.2)	0.019*
IL-10	13.15 (1.13-97.85)	29.19 (3.06-99.19)	0.008*
IL-4	40.38 (3.27-154.4)	33.54 (0.84-152.2)	0.352

p= Mann-Whitney U test; * p<0.05
Source: compiled by the authors of this study

due to a diminished cell-mediated immune response and cardiovascular functions. Male sex hormones, i.e., androgens, have been shown to be suppressive on cell-mediated immune responses. In contrast, female sex hormones exhibit protective effects which may contribute to the natural advantages of females under septic conditions. Thus, the hormonal status has to be considered when treating septic patients. Therefore, potential therapies could be derived from this knowledge. In this respect, administration of female sex hormones (estrogens and their precursors

The mortality rate of sepsis in this study was quite high, with more than 50% of patients dying within 28 days of treatment. These results are consistent with a study by Purba et al., which found a mortality rate of 58.3% among sepsis patients in Indonesia, with the national burden of sepsis estimated at US$130 million per 100,000 patients. The cost of ICU care is much higher, with an average of US$1,618 per patient [6]. The study by Valles et al. reported that 55.5% of deaths from sepsis occurred in the ICU within 72 hours of treatment, with an average mortality rate related

Table 4. Multivariate analysis of risk factors and inflammatory cytokine of septic shock

Variable	Cut-off	p values	OR	95% CI (Lower-Upper)
Gender	-	0.082	0.32	0.09-1.16
WBC (x10^3/µL)	15.6	0.080	3.16	0.87-11.42
Total bilirubin (mg/dL)	1.2	0.980	1.02	0.26-4.03
Sodium (mmol/L)	143.5	0.094	20.68	0.60-717.35
Lactate (mmol/L)	4.46	0.008*	6.02	1.60-22.65
NLR	7.15	0.194	2.44	0.63-9.40
Intra-abdominal infection	-	0.047*	16.76	1.04-269.44
IL-6 (pg/ml)	11.4	0.005*	7.02	1.78-27.70
TNF-α (pg/ml)	15.9	0.943	1.05	0.25-4.14
IL-10 (pg/ml)	21.6	0.031*	3.89	1.13-13.45

*p<0.05

Source: compiled by the authors of this study

Table 5. Area under the curve, sensitivity and specificity biomarker and inflammatory marker as risk factor of septic shock

Variable	Cut-off	AUC	Sensitivity	Specificity
WBC (x10^3/µL)	15.6	0.526	50.0 %	62.2%
Total bilirubin (mg/dL)	1.2	0.692	47.2%	73.9%
Sodium (mmol/L)	143.5	0.455	11.1%	97.8%
Lactate (mmol/L)	4.46	0.696	61.1%	76.1%
NLR	7.15	0.668	72.2%	54.3%
Intra-abdominal infection	-	0.428	16.7%	97.8%
IL-6 (pg/ml)	11.4	0.709	86.1%	56.5%
TNF-α (pg/ml)	15.9	0.652	80.6%	47.8%
IL-10 (pg/ml)	21.6	0.673	61.1%	69.6%

Source: compiled by the authors of this study

to septic shock of 25.8% in the ICU and 29.6% in the hospital [7].

The most common comorbidities in the subjects of this study were diabetes mellitus and hypertension. This is consistent with studies by Xia et al. and Sun et al., in which diabetes mellitus and hypertension were the highest comorbidities causing sepsis mortality [20, 21]. Diabetes, as a metabolic disorder characterized by chronic hyperglycemia, has widespread effects on various physiological systems, including immune function, endothelial integrity, and inflammatory response, all of which are critical in the development and outcome of sepsis. Diabetes mellitus is associated with several immune dysfunctions, such as impaired neutrophil function, decreased phagocytic activity, and altered cytokine production, which can increase susceptibility to infection. Hypertension is associated with chronic inflammation that can exacerbate the inflammatory response to sepsis, thereby increasing the risk of mortality. Research indicates that the use of ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) to manage hypertension in sepsis patients who have not yet experienced septic shock can reduce in-hospital mortality rates [21-23].

The most common source of infection in this study was pneumonia, although pneumonia is not statistically a risk factor for septic shock. This is consistent with previous studies, which found that the most common source of infection causing sepsis was pneumonia [24]. This study found that intra-abdominal infection sources are a risk factor for septic shock. Intra-abdominal infections can cause shock in sepsis through an uncontrolled systemic inflammatory cascade, starting with the translocation of bacteria and endotoxins into the bloodstream. An excessive immune response triggers a cytokine storm that damages the vascular endothelium, causing massive vasodilation, capillary leakage, and refractory hypotension. This leads to tissue hypoperfusion, myocardial depression, and multiple organ failure [25-27].

Lactate is a metabolic product produced primarily by anaerobic metabolism when oxygen to tissues is insufficient for aerobic respiration. In septic shock, there is an increase in serum lactate levels indicating

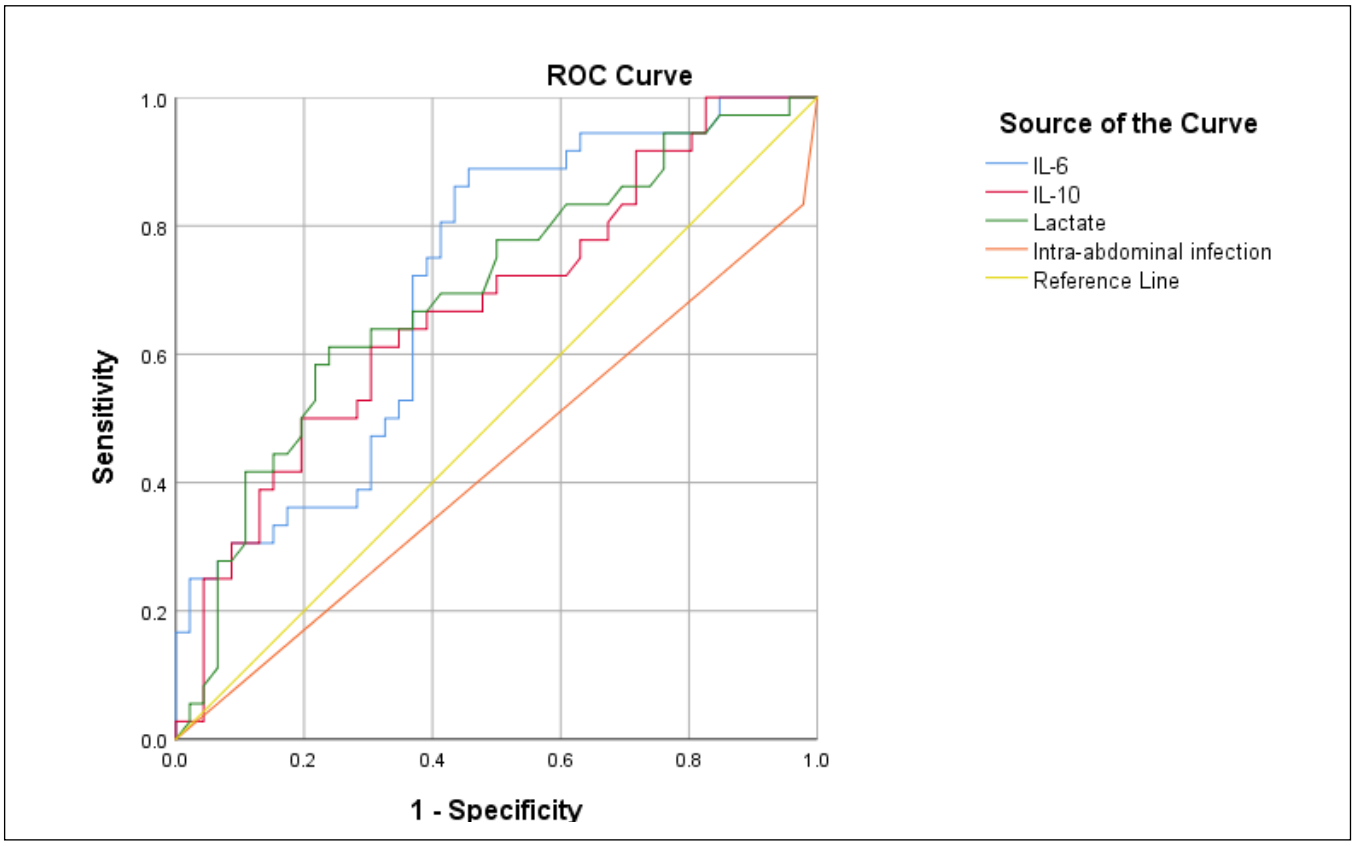


Fig 1. ROC multivariate analysis of single risk factor septic shock of IL-6, IL-10, lactate and intra-abdomen infection with incidence of shock septic
Picture taken by the authors

tissue hypoperfusion and cellular hypoxia, reflecting an imbalance between oxygen supply and demand. This accumulation is caused by increased anaerobic glycolysis and impaired clearance by the liver and kidneys. Elevated lactate is used clinically as a biomarker to assess the severity of sepsis, guide resuscitation efforts, and predict patient outcomes [28, 29]. This study found a mean lactate value of 4.88 mmol/L with a median of 3.7 mmol/L. Multivariate analysis results showed that lactate levels above 4.46 were a risk factor for septic shock. Song et al. reported lactate levels as predictors of sepsis mortality on days 7 and 28. Lactate levels ≥4 mmol/L had odds ratios (OR) of 1.286 and 1.346 in patients with septic shock who received appropriate treatment in the emergency department [30]. A study by Putri et al. found that lactate levels were positively correlated with SOFA scores. This is consistent with the finding that higher lactate levels indicate relatively greater organ dysfunction [31].

The analysis of differences in pro-inflammatory and anti-inflammatory cytokines between patients with sepsis and septic shock revealed a difference in IL-6, TNF-α, and IL-10 levels. Meanwhile, no differences were found in IL-4 levels. After conducting a multivariate analysis of other factors that could be risk factors for septic shock, only IL-6 and IL-10 levels were found to be statistically independent risk factors for septic shock. IL-6 levels above 11.4 pg/mL had a 7.02 times higher risk of septic shock compared to patients with lower IL-6 levels. This observation is consistent with a study by Vivas et al. (2021), which showed significant differences in plasma IL-6 levels between patients with sepsis and septic shock during the first 48 hours after admission to the ICU. In patients with pure sepsis, this study found a significant decrease in serum IL-6 levels, with the average value decreasing from 60.00 pg/mL at admission to 7.00 pg/mL 48 hours later ($p = 0.002$). In contrast, in patients who progressed to septic shock, IL-6 levels remained high and stable during the same period, from 70.00 pg/mL at admission to 50.00 pg/mL at 48 hours ($p = 0.001$). This difference indicates that the persistence of high IL-6 levels is a marker of clinical deterioration toward septic shock, while the progressive decrease in IL-6 reflects a controlled inflammatory response in sepsis without shock [32]. Research by Smok et al. shows that serum levels of IL-6, procalcitonin, and C-reactive protein at hospital admission are statistically significantly higher in sepsis compared to the control group (21.4 pg/ml, 0.6 ng/ml, and 24.9 mg/l vs. 3.48 pg/ml, 0.0 ng/ml, and 1.0 mg/l [33].

Interleukin-6 is synthesized by mononuclear phagocytes, endothelial cells, fibroblasts, and some activated

T cells in response to pathogen-associated molecular patterns (PAMPs), IL-1, and TNF-α. IL-6 stimulates acute-phase protein synthesis by the liver, production of neutrophils from the bone marrow, and differentiation of TH17 T helper cell subsets. In severe sepsis that progresses to septic shock, high IL-6 concentrations are associated with a poor prognosis, and high serum IL-6 levels are closely related to increased inflammatory severity and the development of organ dysfunction. The occurrence of septic shock is primarily mediated by TNF-α, which stimulates the release of other cytokines, including IL-6, thereby causing the amplification of the excessive inflammatory response characteristic of septic shock [32, 34].

In this study, TNF-α levels in sepsis differed from those in septic shock; however, after multivariate analysis, no results were found to indicate that TNF-α is a risk factor for septic shock. A prospective multicenter study of 163 adult patients in the ICU showed that plasma TNF-α levels were significantly higher in the septic shock subgroup (median 57.3 pg/mL) compared to sepsis without shock (median 42.9 pg/mL, $p = 0.0007$). [13] Sepsis has diverse etiologies (Gram-negative vs. Gram-positive, abdominal vs. non-abdominal), causing variable TNF-α responses. Patients with comorbidities or different stages can show inconsistent TNF-α levels, making them non-independent in multivariate analysis. Meta-analyses highlight the divergent effects of TNF-α, with some studies showing adaptive rather than maladaptive effects of TNF-α in experimental studies [35].

The results of the study found that IL-10 levels above 21.6 ng/ml had a 3.89 times higher risk of shock. Research by Fabri et al. (2021) showed that in patients with septic shock, IL-10 production by monocytes and CD4 T cells increased, which was associated with a decrease in HLA-DR expression and a decrease in TNF-α production by monocytes. This data indicates the development of an immunosuppressive profile with increased IL-10, which may contribute to immune dysfunction in septic shock [36]. Research by Mazer et al. demonstrates the dual effect of IL-10 on the immune system of sepsis patients, whereby IL-10 suppresses TNF-α production and HLA-DR expression in monocytes but actually increases IFN-γ production in T cells, indicating the complex modulatory role of IL-10 in post-sepsis immune balance. This indicates that IL-10 acts as an anti-inflammatory cytokine and has the potential to play a stimulatory role in some aspects of the adaptive immune response during sepsis [37]. Research by Harviendo et al. showed that there was a moderate positive correlation between IL-10 levels and APACHE II scores, with a correlation coefficient of 0.430 and a p-value of 0.010. Interleukin-10 is an anti-inflammatory cytokine that functions to stop inflammation in sepsis. High levels are usually associated with a state of homeostatic immunological tolerance or as a counter-response (negative feedback) to increased pro-inflammatory cytokines [38].

In the present study we demonstrated that both IL-6 and IL-10 were significant predictors of poor clinical outcomes in sepsis. These results are consistent with a recent systematic review showing that IL-6 is one of the most sensitive early inflammatory response biomarkers. IL-10, on the other hand, is a compensatory anti-inflammatory response and development of sepsis-associated immunosuppression. However, the current evidence seems to indicate that the concomitant increases in IL-6 and IL-10 are indicative of the presence of hyperinflammation and immune dysregulation, which are now considered defining characteristics of the pathophysiology of sepsis, rather than being in opposition to biological pathways. Moreover, recent extensive reviews highlight that no single inflammatory biomarker is adequate for prognostic assessment and propose the use of complementary panels of biomarkers to enhance risk stratification. Therefore, the co-predictive value of IL-6 and IL-10 in this study demonstrates that a combination of biomarkers reflecting both pro- and anti-inflammatory pathways could be a better predictor of disease severity and prognosis than each cytokine alone [39, 40].

Although IL-6 and IL-10 are not yet part of routine sepsis management protocols, both may be useful as additional biomarkers for early risk stratification because they reflect complementary biological mechanisms of the host response. IL-6 is a pro-inflammatory mediator associated with the early hyperinflammatory phase, while IL-10 reflects compensatory anti-inflammatory and immunoregulatory activity. Current sepsis guidelines remain dependent on clinical assessment of the patient and on markers already in routine use. These guidelines recommend blood lactate measurement in suspected sepsis, use of periodic lactate measurements to guide resuscitation and use of procalcitonin in conjunction with clinical evaluation to assist in deciding when to cease antimicrobial therapy. In this context, one should think of IL-6 and IL-10 as investigative, not decision-making, tools by themselves. Both may be useful, in combination with lactate and procalcitonin, to improve early prognosis and identify patients at higher risk of worsening or death. Hence, their complementary roles are particularly precious at the time of patient presentation or early in ICU admission when the balance of inflammatory activation, tissue hypoperfusion, and

immune suppression may not be fully reflected by a single biomarker [41].

IL-4 levels in this study were not found to be associated with septic shock. This is consistent with the study by Wu et al., in which plasma IL-4 levels did not differ significantly between patients who survived and those who died from sepsis [42]. In other infections such as COVID-19, research by Ivanov et al., also reported that IL-4 was not associated with severity [43]. Interleukin 4 (IL-4) functions as an anti-inflammatory cytokine that regulates the immune response during sepsis and septic shock. IL-4 serves to inhibit the activation of proinflammatory immune cells, suppress T and B lymphocyte activity, and assist in regulating the equilibrium between proinflammatory and anti-inflammatory responses during sepsis. However, some studies suggest that IL-4 mRNA expression may be associated with the survival rate of patients with severe sepsis. Studies analyzing the IL-4delta2/IL-4 ratio suggest that this ratio may serve as an immunological indicator, but IL-4 expression does not have a direct relationship with the occurrence of sepsis or septic shock in general [42].

The study has limitations that should be considered when interpreting the results. The study was performed at a single center and thus, the results may not be generalizable to other health care settings and patient populations with different demographic and clinical characteristics. Second, the sample size was rather small, which would have reduced the statistical power to detect small associations and the precision of the estimated predictive performance of the biomarkers. Third, this study did not perform a complete evaluation of potential confounding factors and pre-existing comorbidities such as obesity, diabetes mellitus and other underlying diseases that impact the course of sepsis and the development of septic shock. As a result, a comprehensive assessment of the potential contribution of these factors to the observed relationships was not possible. However, in spite of these limitations, the validation of the considerable predictive value of IL-6 and IL-10 supports the validity of the present findings.

CONCLUSIONS

In this study, IL-6 and IL-10 are independent risk factors for septic shock, whereas TNF-α and IL-4 are not independent risk factors for septic shock in patients with sepsis. Additional multicenter studies in larger and more heterogeneous cohorts, with appropriate adjustment for relevant comorbidities and other potential confounders, are needed to confirm our findings and to further define the therapeutic utility of these biomarkers for risk stratification in sepsis patients.

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A complete list of references can be requested from the Authors.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Banundari Rachmawati
Universitas Diponegoro Semarang
I. Prof. Soedarto, Tembalang, Kec. Tembalang,
Kota Semarang, Jawa Tengah 50275, Semarang, Indonesia
e-mail: banundaridr@fk.undip.ac.id

ORCID AND CONTRIBUTIONSHIP

Dwi Retnoningrum: 0000-0003-1606-0078 A B D
Nyoman Suci Widyastiti: 0000-0002-4083-1293 C E
Meita Hendrianingtyas: 0000-0003-1554-2876 A B C

Edward Kurnia Setiawan Limijadi: 0000-0002-8476-2971 D E
Villa Sekar Cita: 0000-0003-1580-3917 B C
Nur Farhanah: 0000-0002-7385-3325 A E F
Banundari Rachmawati: 0000-0002-9181-5832 E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

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