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Analysis of procalcitonin and urine nitrite to predictor sepsis patients

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ABSTRACT

Background: Sepsis is a significant health problem worldwide. Various sepsis biomarkers have been studied before, but few data link PCT and urinary nitrite levels to culture result in septic patients.

Purposes: This study compares PCT, Urine Nitrite on culture results against their sensitivity to determine variables that can be used to predict sepsis patients.

Methods: This is a cross-sectional study by taking data on patients with sepsis aged ≥18 years in 207. Diagnostic tests were performed to determine sensitivity and specificity of PCT, Urine Nitrite, and Blood Culture of septic patients. A Chi-square test was carried out to see the relationship between two parameters and the outcome of sepsis.

Results: PCT sensitivity was higher than Urine Nitrite: 74.5%. Specificity of Urine Nitrite was higher than PCT: 88.2%. Procalcitonin has a significant relationship with sepsis patient outcomes ($p<0.005$).

Conclusion: PCT can predict septic patients because it has a higher sensitivity than urine nitrite.

INTRODUCTION

Sepsis is an organ dysfunction due to the body's response to uncontrolled life-threatening infection, as defined in the Sepsis Committee 3 of 2016. Sepsis can be caused by microorganisms such as Gram-negative and Gram-positive bacteria, viruses, fungi, and parasites. One of the causes of sepsis is a urinary tract infection which is also known as urosepsis. The pathogenesis of sepsis is closely related to the immune response system and the coagulation-fibrinolysis system as predisposing genetic elements, which interact mutually to form a network.[1-4]

Sepsis is a significant health problem worldwide. This can be seen from the high incidence, mortality, health costs required to treat a patient with severe sepsis and septic shock, and the persistent increase in the incidence from year to year. A prospective cohort study in the United States showed that 415,280 cases of severe sepsis and septic shock were diagnosed in 2003 and increased to 711,736 cases in 2007, with a mortality rate of 29.1%. Research in 2009 in 150 intensive care rooms in 16 Asian countries (including Indonesia) showed severe sepsis and septic shock by 10.9% with a mortality rate of 44.5%.[1-4]

Procalcitonin (PCT) is a precursor to the peptide calcitonin produced by C cells of the thyroid gland and neuroendocrine cells of the lung and intestine in response to bacterial toxins. Procalcitonin is also a protein involved in the immunopathogenesis of sepsis. Increased PCT occurs in immunocompetent patients with sepsis and bacterial meningitis. A study conducted by Meynar in 2010 and colleagues concluded that PCT levels were better than other markers of bacterial sepsis (such as C-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), interleukin-6 (IL-6)) in differentiate SIRS and sepsis in critically ill patients. If the PCT level in the first 24 hours of ICU admission was below 2ng/mL, sepsis due to bacterial infection could be excluded, or the negative predictive value (NPV) was 97%. If the PCT level is more than 10ng/m.[5-10]

Nitrite is the result of nitrate oxidation carried out by Enterobacteriaceae bacteria. Urine nitrite examination is one of the parameters found in urinalysis that can be used to determine the presence or absence of bacteriuria. Normal urine contains a chemical called nitrate. If bacteria get into the urinary tract, nitrates can turn into chemicals called nitrites.[11-13]

Culture is the gold standard for diagnosing sepsis, interpreting the results by counting the number of bacteria present in the culture media. Culture results are essential for isolating specific organisms and adjusting antibiotic therapy. According to a previous study conducted by Koichi et al. in 2013, conducted at the Urology Department of West Osaka Hospital, blood culture is a particular method for detecting and confirming septicemia. However, test results will be available after 24 hours. The blood culture is confirmed positive if the same organism is found in the urine culture. Procalcitonin test results can also be used to diagnose and monitor the effectiveness of treatment in severe bacterial infections or septic patients. This may be associated with positive culture results with PCT levels in septic patients.[13-16]

Various septic biomarkers have been studied previously, but data is still lacking for analyzing PCT and urine nitrite in septic patients. Therefore, this study aimed to compare PCT, Urine Nitrite on culture results against their sensitivity to determine variables that can be used to predict sepsis patients.

METHOD

Study Design

This is a crossectional study design.

Setting and Respondent

This research was conducted at RSUP Dr. Wahidin Sudirohusodo from January 1st, 2018, to December 31st, 2020. The data were 207 septic patients who met the inclusion criteria aged 18 years who had three examinations, namely procalcitonin, urine nitrite, and culture results. Patients with a history of kidney and liver disease were excluded. Septic patients were diagnosed by clinicians based on history, physical examination, investigations, and SOFA scores.

The Variable, Instrument, and Measurement

Procalcitonin levels, urine nitrite, and culture results support examinations in the clinical pathology laboratory of sepsis patients recorded in the medical record. Cut off point of procalcitonin levels was <2 ng/mL, using a serum sample measured using the Biomerieux VIDAS instrument. Nitrite examination was obtained from the urinalysis using the FUS-100 device and was categorized as positive and negative.

Data Analysis

Analysis of the data obtained was processed by statistical tests using SPSS software. The statistical method used is the calculation of the frequency distribution, using a diagnostic test table 2x2 to determine the sensitivity and specificity, and to determine the relationship between PCT and Urine Nitrite with the outcome of sepsis patients using the chi-square test.

Ethical Consideration

The research permit was obtained from the Health Research Ethics Commission, Faculty of Medicine, Hasanuddin University with the number: 252/UN4.6.4.5.31/PP36/2021.

RESULTS

The research data shows that from 207, there were 97 (46.9%) female patients and 110 (53.1%) male patients. The age group based on medical record data obtained an average age of 52 years, with the 18-65 year age category totaling 153 (73.9%) and the >65 year age category are totaling 54 (26.1%). The outcome of sepsis patients recovered 48 (23.2%), died 159 (76.8%). Procalcitonin 2 was 152 (73.4%), PCT <2 was 55 (26.6%). Positive urine nitrite is 28 (13.5%), while urine nitrite is negative 179 (86.5%). Positive blood cultures were 55 (26.6%), while negative blood cultures were 152 (73.4%). The most common type of bacteria found in the blood culture results of sepsis patients was Klebsiella Pneumonia amounting to 19 (9.2%). In the literature, gram-negative bacteria (mainly Escherichia coli, Klebsiella species, and Pseudomonas aeruginosa) and gram-positive cocci (Staphylococcus and Streptococcus) are microbes is often found in patients with sepsis and septic shock (Table 1).

Table 1. Characteristics of the Patient

Characteristics	Result
Gender	
Woman	97 (46.9%)
Man	110 (53.1%)
Age	
18-65 Years, mean±SD, Min-Max	153 (73.9%), 43.85±14.9, 18-65
>65 Years, mean±SD, Min-Max	54 (26,1%), 74.35±6.73, 66-92
Output	
Get Well	48 (23.2%)
Died	159 (76.8%)
Procalcitonin:	
2.0 ng/mL, mean±SD, Min-Max	152 (73.4%), 40.7±56.5, 2.07->200
< 2.0 ng/mL, mean±SD, Min-Max	55 (26.6%), 0.813±0.55, 0.06–1.94
Urine Nitrit	
Positive	28 (13.5%)
Negative	179 (86.5%)

Blood Culture	
Positive	55 (26.6%)
Negative	152 (73.4%)
Bacteria Type: (n=55)	
Klebsiella Pneumonia	19 (9.2%)
Escherichia coli	6 (2.9%)
Burkholderia Cepacia	6 (2.9%)
Acinobacter Baumanii	6 (2.9%)
Pseudomonas aeruginosa	4 (1.9%)
Staphylococcus aureus	4 (1.9%)
Kocuria Kristinae	2 (1.0%)
Streptococcus Mitis	2 (1.0%)
Cryptococcus Laurentii	1 (0.5%)
Enterobacter Aerogenes	1 (0.5%)
Other bacteria	4 (2.0%)

The PCT and Urine Nitrite Diagnostic Test results showed that the PCT sensitivity was higher than the Urine Nitrite sensitivity, which was 74.5%. Meanwhile, the specificity of Urine Nitrite was higher than that of PCT, which was 88.2%. The results of the diagnostic test can be seen in Table 2 and Table 3.

Table 2. PCT Diagnostic Test Results on Culture Results

		Blood Culture		Total
		Positive	**Negative**	
PCT	**2ng/mL**	41	111	152
	<2ng/mL	14	41	55
	Total	55	152	207

Sensitivity: [A : (A+C)] x 100% = [41 : 55] x 100% = 74,5%
Specificity: [D : (B+D)] x 100% = [41 : 152] x 100% = 26,9%
Positive predictive value: [A : (A+B)] x 100% = [41 : 152] x 100% = 27,0%
Negative predictive value: [D : (C+D)] x 100% = [41 : 55]x100% = 74,5%

Table 3. Urine Nitrite Diagnostic Test Results on Culture Results

		Blood Culture		Total
		Positive	**Negative**	
Nitrite	**Positive**	10	18	28
	Negative	45	134	179
	Total	55	152	207

Sensitivity: [A : (A+C)] x 100% = [10 : 55] x 100% = 18.2%
Specificity: [D : (B+D)] x 100% = [134 : 152] x 100% = 88.2%
Positive predictive value: [A : (A+B)] x 100% = [10 : 28] x 100% = 35.7%
Negative predictive value: [D : (C+D)] x 100% = [134 : 179]x100% = 74.9%

From tables 2 and 3, it can be seen that the Negative Predictive Value PCT (74.5%) and Urine Nitrite (74.9%) have almost the same presentation. In comparison, the Positive Predictive Value PCT (27.0%) and Urine Nitrite (35.7%) presentation are much different so that in terms of This,

urine nitrite has a higher probability. PCT sensitivity (74.5%) and urine Nitrite Sensitivity (18.2%), PCT specificity (26.9%). Urine Nitrite Specificity (88.2%), seen from the presentation of PCT sensitivity, is higher than urine nitrite. PCT can be used more to predict sepsis patients, while the presentation of specificity indicates that urine nitrite is higher than PCT.

Table 4 above shows a significant relationship between PCT and the outcome of sepsis patients (p <0.05). From 152 PCT ≥2 ng/mL, 43 (28.3%) recovered outcomes were found, while from 55 PCT <2 ng/mL, 5 (9.1%) recovered outcomes were found with RR = 3.11, meaning that the recovered outcomes were 3, 11 times greater in PCT ≥2 ng/mL than PCT <2 ng/mL.

Table 5 above shows that the results of Urine Nitrite, both positive and negative, have a fairly high mortality rate, namely 67.9% and 78.2%. There was no significant relationship between Urine Nitrite and the outcome of sepsis patients. X2(df) = 6.49, p=0.334.

DISCUSSION

This research is in line with research conducted by Sudhir et al. in India in 2011, that the PCT sensitivity with value cut off 0.5 ng/mL in septic patients was reported to reach 94%. We end up using the cut-off point of PCT 2ng/mL cause PCT in the first 24 hours of ICU admission was below 2ng/mL, sepsis due to bacterial infection was excluded. These results confirm the previous findings that pointed to PCT as one of the best markers of sepsis for screening.[17]

Procalcitonin is a precursor of the hormone calcitonin produced by the CALC-1 gene located on chromosome 11; mRNA is translated into pre-procalcitonin, which will be modified into a sequence of amino acids. Procalcitonin consists of 116 amino acid proteins with a molecular size of 13 kDa. Procalcitonin is produced in the neuroendocrine cells of the thyroid, lung, and pancreas. PCT levels in the blood will rise 3 to 6 hours after infection.[18] Urine nitrite specificity is much higher than PCT, with urinary nitrite specificity value reaching 88.2%. These results are in line with research conducted by Rangaiahagari A in Rwanda in 2015, with a high Urine Nitrite specificity reaching 99.6% to 100%.[19]

Research conducted by Novita et al. at Dr. Hospital. Sutomo Surabaya In 2019, PCT was used as a marker for the diagnosis of sepsis but could not determine the severity of sepsis. This can also be seen in the results of our study, that PCT 2 ng/mL was more in patients with a cured outcome. This is because PCT levels rapidly increase early in the first 3-6 hours of infection. peak within 12 to 48 hours and decrease in 48 to 72 hours.[18,20]

Table 4. Relationship between PCT and Outcome in Sepsis Patients

		Outside		Total	RR	p-value
		Get Well	Died			
PCT	2 ng/mL	43 (28.3%)	109 (71.7%)	152 (100%)	3.11	0.007
	<2 ng/mL	5 (9.1%)	50 (90.9%)	55 (100%)		
	Total	48 (23.2%)	159 (76.8%)	207 (100%)		

Table 5. Relationship between Urine Nitrite and Outcome in Sepsis Patients

		Outside		Total	RR	p-value
		Get Well	Died			
Urine Nitrite	Positive	9 (32.1%)	19 (67.9%)	28 (100%)	-	0.334
	Negative	39 (21.8%)	140 (78.2%)	179 (100%)		
	Total	48 (23.2%)	159 (76.8%)	207 (100%)		

Analysis of the $x2$ test on Urine Nitrite with the outcome there is no significant relationship because Urine Nitrite may be specific in helping the diagnosis of sepsis. However, suppose it is associated with the outcome. In that case, many factors affect the outcome of sepsis, especially the administration of antibiotics, including accuracy in choosing the antibiotic and the dose and timing of administration an Antibiotics. In addition, infection-causing bacteria that can convert nitrate to nitrite are the Enterobacteriaceae group. While in this study, the most common causative bacteria were Klebsiella Pneumoniae. Other factors that can influence the outcome of sepsis are the presence of comorbidities and the severity of organ dysfunction.

CONCLUSIONS AND RECOMMENDATION

Sensitivity PCT is higher than Urine Nitrite. The specificity of Urine Nitrite is higher than PCT. Procalcitonin has a significant relationship with sepsis outcome, so that PCT can be used as a predictor of outcome. Meanwhile, Urine Nitrite has no significant relationship with sepsis outcome, so Urine Nitrite cannot be used as a predictor of sepsis outcome, so Urine Nitrite can help diagnose sepsis.

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