

PLASMA LACTATE VERSUS C-REACTIVE PROTEIN AS PROGNOSTIC INDICATOR IN UROSEPSIS

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ABSTRAK

Urosepsis terjadi pada 20-30% kasus septic. Diagnosis dini penting untuk meningkatkan hasil manajemen sepsis. Konfirmasi bakteriologi mungkin sulit untuk didapatkan dan kultur yang negatif tidak mengecualikan adanya infeksi. Peningkatan pemahaman mekanisme inflamasi menyebutkan beberapa indikator infeksi dan prognosis. Pengukuran laktat pada pasien dengan infeksi dan sepsis dapat membantu mengidentifikasi pasien berisiko tinggi kematian untuk menerapkan terapi yang agresif. Elevasi serum C-reactive protein (CRP) juga dikaitkan dengan peningkatan risiko kematian pada pasien dengan infeksi. Tujuan penelitian ini adalah menentukan laktat plasma dan kadar CRP pasien dengan urosepsis sebagai indikator prognostik. Penelitian ini merupakan penelitian observasional analitik untuk membandingkan korelasi dan signifikansi laktat plasma dan CRP dengan prognosis urosepsis. Subjek diukur kadar laktat plasma dan serum CRP pada saat penerimaan. Semua subjek dikelola sesuai dengan standar protokol. Pada hari ke-14 dari pengobatan, pasien dievaluasi dengan skor keparahan klinis. Hasilnya diklasifikasikan sebagai berikut: 1=kondisi baik/membaik, 2=morbid/memburuk dan 3=kematian. Analisis statistik yang digunakan uji Spearman rho, $p < 0,05$. Hasil: Terdapat 25 subjek dengan urosepsis terdiri 14 pasien yang septic, 9 pasien memiliki sepsis berat dan 2 pasien syok septic. Rata-rata tingkat laktat plasma pada pasien berdasarkan pada hasil (membaik/memburuk/kematian) adalah 2,08 mmol/L; 4,16 mmol/L dan 5,27 mmol/L. Nilai rata-rata dari CRP adalah 13,41 mg/L; 22,28 mg/L dan 24,62 mg/L. Secara statistik signifikan ($p 0,008$ vs $0,016$) dalam menentukan outcome dari pasien urosepsis. Koefisien korelasi lebih baik dengan laktat plasma dari CRP ($0,517$ vs $0,475$). Simpulan, pengukuran laktat plasma dan tingkat CRP bisa digunakan sebagai penanda prognostik untuk hasil pasien dengan urosepsis. Laktat plasma menunjukkan korelasi yang lebih tinggi dengan hasil urosepsis dari CRP. (FMI 2017;53:113-117)

Kata kunci: Laktat plasma, CRP, Urosepsis

ABSTRACT

Urosepsis occurs in 20-30 % of septic case. Early diagnosis were undoubtedly important to improve the results of sepsis management. Bacteriological confirmation may be difficult to obtain and negative cultures do not exclude the presence of infection. Increased understanding of inflammatory cascade mechanisms provided several indicator of infection and prognosis. Lactate measurement in patients with infection and possibly severe sepsis to help identify patients at high risk of death in order to apply aggressively therapy. Elevation in serum C-reactive protein (CRP) is also associated with an increasing risk of death in patients with infection. This study was to determine the plasma lactate and CRP levels of patients with urosepsis as a prognostic indicator. This is an analytic observational study to compare the correlation and significance of plasma lactate and CRP with prognosis of urosepsis. Each subject was measured for plasma lactate and serum CRP at time of admission. All subjects were managed according to standard protocol. At the 14th day of treatment, patients were evaluated with a clinical severity score. The outcome was classified as follows: 1=good condition/improved, 2=morbid/worsened and 3=death. The statistical analysis used Spearman's rho test, $p < 0.05$ was considered to indicate significance. We enrolled 25 subjects with urosepsis. 14 patients who were septic, nine patients had severe sepsis and 2 patients had septic shock. Mean plasma lactate level in patients based on outcome (improved/worsened/death) was 2.08 mmol/L; 4.16 mmol/L and 5.27 mmol/L. The mean value of CRP was 13.41 mg/L; 22.28 mg/L and 24.62 mg/L. These were statistically significant ($p 0.008$ vs 0.016) in determining the outcome of the urosepsis patient. The coefficient correlation is better with plasma lactate than CRP (0.517 vs 0.475). In conclusion, the measurement of plasma lactate and CRP level can be used as a prognostic marker for the outcome of patient with urosepsis. Plasma lactate showed higher correlation with outcome of urosepsis than CRP. (FMI 2017;53:113-117)

Keywords: Plasma lactate, CRP, Urosepsis

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INTRODUCTION

Urosepsis occurs in 20-30 % of septic case. Urosepsis defined as sepsis caused by urinary tract infection (UTI). (Bone et al 1992, Lever & Mackenzie 2007, Marx & Reinhart 2008) Sepsis is characterized by signs and symptoms of SIRS (Sistemic Inflammatory Response Syndrome), the clinical manifestations are body temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$, tachycardia ≥ 90 beats/min, tachypnea ≥ 20 breaths/min, respiratory alkalosis ($\text{PaCO}_2 \leq 32$ mmHg), and leucocytes $\geq 12,000$ μL or ≤ 4000 μL . (Bone et al. 1992, Schiefer & Diemer 2007, Wagenlehner et al. 2008). Sepsis also known as a systemic illness caused by microbial invasion of normally sterile parts of the body. When accompanied by evidence of hypoperfusion or dysfunction of at least one organ system, this becomes "severe sepsis." Finally, where severe sepsis is accom-panied by hypotension or need for vasopressors, despite adequate fluid resuscitation, the term "septic shock" applies.

Early diagnosis and therapy were undoubtedly important to improve the results of sepsis management. Nowadays, diagnosis and monitoring of sepsis therapy usually using clinical parameters. Many other clinical biomarkers must be considered. Some study using biomolecular marker to determine the disease severity and to predict the outcome of urosepsis, such as plasma lactate and C-reactive protein. (Bakker et al 2013, Shapiro & Howell 2005, Suzana et al 2003)

Bakker et al. (2013) and Shapiro et al (2005) concluded that lactate measurement in patients with infection and possibly severe sepsis to help identify patients at high risk of death in order to apply aggressively therapy in their study. Elevation in serum CRP (C-reactive protein) has also associated with an increasing risk of death in patients with infection. (Suzana et al 2003, Vincent & Beumier 2013) Besides its use in the diagnosis of sepsis, Lactate and CRP have also been evaluated as prognostic markers. (Bakker et al 2013, Shapiro & Howell 2005, Suzana et al 2003)

The first and ultimate step in the diagnosis of sepsis is isolation of bacteria. This process usually requires 24 hours, but another 24 hours are needed to achieve more detailed information in order to identify the bacteria. Thus the identification of bacteria has to be accelerated, or other clinical and laboratory findings must be relied on to reach an initial diagnosis. It is well known that a large proportion of patients (at least 15-30%) appear to be clinically septic have negative blood cultures. (Von Landenberg & Shoefeld 2001, Wagenlehner et al 2008) There are two major reasons to explain this phenomenon. One possibility might be that patients are indeed

septic with bacteremia but the organisms in the sample did not grow under normal circumstances in the culture medium. The second possibility is that the apparently septic state may have resulted not from bacteremia but from pyrogenic cytokine activation, either by previous and transient bacteremia or derived from a non-bacterial origin.

The classification of the sepsis syndrome follows different levels of criteria: (Schaeffer 2010, Schiefer & Diemer 2007)

Criteria I: Proof of bacteraemia or clinical suspicion of sepsis.

Criteria II: Systemic Inflammatory Response Syndrome (SIRS)

Body temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$

Tachycardia ≥ 90 beats/min

Tachypnoea ≥ 20 breaths/min

Respiratory alkalosis $\text{PaCO}_2 \leq 32$ mmHg

Leucocytes $\geq 12\,000$ μL or ≤ 4000

μL or bandforms $> 10\%$

Criteria III: Multiple Organ Dysfunction Syndrome (MODS)

Heart, circulation: Arterial systolic blood pressure ≤ 90 mmHg or mean arterial blood pressure ≤ 70 mmHg, ≥ 1 hour despite adequate fluid or vasopressure agents resuscitation.

Kidney: Production of urine < 0.5 mL/kg body weight/hour despite adequate fluid resuscitation.

Lung: $\text{PaO}_2 \leq 75$ mm Hg (breathing room air) or $\text{PaO}_2/\text{FiO}_2 \leq 250$ (assisted respiration) [(PaO_2 , arterial O_2 -partial pressure; FiO_2 , inspiratory O_2 -concentration)].

Platelets: Platelets $< 80\,000$ μL or decrease $\geq 50\%$ in 3 days.

Metabolic Acidosis: Blood pH ≤ 7.30 or base excess ≥ 5 mmol/L; plasma lactate ≥ 1.5 fold of normal.

Encephalopathy: Somnolence, agitation, confusion, coma.

Following these criterion, the sepsis syndrome is classified into 3 levels:

Sepsis: Criteria I + ≥ 2 criteria II. Associated lethality: 2 criteria II – 7%; 3 criteria II – 10%; 4 criteria II – 17%.

Severe sepsis: Criteria I + ≥ 2 criteria II + ≥ 1 criteria III. Associated lethality: For each affected organ: $\pm 15 - 20\%$.

Septic shock: Criteria I + ≥ 2 criteria II + refractory arterial hypotension ≤ 90 mm Hg. Associated lethality: 50–80%.

In the case of urosepsis, the clinical evidence of UTI is based upon symptoms, physical examination, sonographic and radiological features and laboratory data, such as bacteriuria and leucocyturia. Many clinical and laboratory variables used to determine the severity and prognosis of the disease, assessed an adequate therapy in patients with critical disease including urosepsis. Some of the measurement was plasma lactate and CRP levels. This measurement does not represent all the parameters, but it was nearing the diagnostics needs. (Bakker et al 2013, Schuetz et al 2008, Suzana et al 2003, Vincent & Beumier 2013)

MATERIALS AND METHODS

This is an analytic observational study. We enrolled 25 subjects with urosepsis. Each subject was assigned to the test for plasma lactate and CRP level at the time of admission. All of subjects was managed according to standard urosepsis therapy. At the 14th day of treatment, patients were evaluated with a clinical severity score and compared to condition at the first day admission, then we classified the outcome as follows: 1=good condition/improve, 2=morbid/getting worse and 3=mortality.

The inclusion criteria were patients with clinically suspicious urosepsis (SIRS criteria), pre-operative or post-operative (urological procedure) patients with SIRS criteria, and consent to join and sign in the research form. The exclusion criteria were urosepsis patients with source of infection from the other organ sites, history of drug consumption (salicylic acid, alcohol, methanol, metformin), patients already got antibiotic therapy, preexisting liver disease, immunocompromized patients (diabetes mellitus, drug users, immunosuppressant), patient age > 65 years old, and history of cardiovascular disease (CVA, CHD).

Descriptive statistics was used to describe the basic and demographic data of the samples. Data distribution and homogeneity were tested using the appropriate test (Kolmogorov-Smirnov test). The statistical analysis the variables were tested using the appropriate test (Spearman's rho test). In all tests, $p < 0.05$ was considered to indicate significance.

RESULTS

A total 25 patients with complete follow up were selected. The two biomarkers had examined at the first day of urosepsis (admitted to emergency department). These research found fourteen patients who were in septic condition. Nine patients had severe sepsis and 2 patients had septic shock. Examination of blood gas analysis showed an average blood pH of 7.36. Groups

of patients with lactate levels above 5 mmol/L obtained 3 patients with blood pH ranges from 7.36 to 7.41 which is not found signs of acidosis. MAP (Mean Arterial Pressure) measurements performed to assess the presence or absence of shock conditions. In this study, there were 2 patients with MAP < 70 mmHg. Description of data characteristic could be seen in Table 1.

The mean value of plasma lactate level in patient based on the outcome (improve/morbid/death) was 2.08 mmol/L; 4.16 mmol/L and 5.27 mmol/L. The mean value of CRP level was 13.41 mg/L; 22.28 mg/L and 24.62 mg/L (Table 2). Examination of microbiology (blood and urine culture) as the gold standard in the diagnosis of urosepsis was routinely performed on all samples in this study. The most pathogen organism were *Escherichia Coli* (40% in urine culture, 12% in blood culture) and *Klebsiella pneumonia* (8%) which seen in Table 3. In this study, lactate level showed significant correlation with the outcome of urosepsis ($p < 0.05$) as well as CRP, but CRP has lower correlation coefficient (0.517 vs 0.475). This data was describe in Table 4.

DISCUSSION

Characteristics of the sample obtained sexes which males are more dominant than females (64% vs. 36%). The average age of the patients was 47.12 years, with a range at 25-65 years. Risk factors for urosepsis was found in some samples in this study such as age (the older the higher risk), malignant disease, radiotherapy, chemotherapy, and presence of obstructive uropathy. (Kalra & Raizada 2009, Schaeffer 2010, Schiefer & Diemer 2007, Von Landenberg & Shoenfeld 2001). Patients in this study had a fever for most of the 1-3 days with an average of $2.04 + 0.84$ days. Acute phase of immunological response is started the first 6 hours to 36 hours, usually characterized by the synthesis of acute phase proteins such as CRP, procalcitonin, and complement (Schiefer & Diemer 2007), therefore the sample with a fever more than 3 days will be made to drop out.

Urosepsis were not adequately treated can fall in a state of severe sepsis, septic shock or even multiple organ dysfunction syndrome (MODS) which is characterized by at least two organ failures. (Bone et al 1992; Marx & Reinhart 2008; Lever & Mackenzie 2007) Defining element of the progression and the severity of sepsis including the first attack that causes sepsis, comorbidities, individual genetic condition, previous therapy and treatment time. (Bochud 2003, Gladden 2004, Schuetz et al 2008).

Table 1. Characteristic data

Characteristics	N	Min	Max	Mean	SD
Age	25	25	65	47.12	11.26
Sex					
Male	16	-	-	-	-
Female	9	-	-	-	-
Classification					
SIRS	-	-	-	-	-
Sepsis	14	-	-	-	-
Severe Sepsis	9	-	-	-	-
Septic Shock	2	-	-	-	-
Blood PH	25	7.00	7.51	7.37	.11
WBC	25	8130	43900	21349.20	8618.79
MAP (mmHg)	25	70.00	110.00	83.60	10.16
CRP (mg/L)	25	5.10	31.20	16.98	9.56
Lactate (mmol/L)	25	1.00	8.80	3.01	1.92
Day of fever	25	1.00	3.00	2.04	1.42
Rectal temp	25	35.00	39.50	38.08	1.12
Urine culture					
Positive	14	-	-	-	-
Negative	11	-	-	-	-
Blood culture					
Positive	3	-	-	-	-
Negative	22	-	-	-	-

Table 2. Biomarkers characteristic

	Improve		Morbid		Death	
	Mean	SD	Mean	SD	Mean	SD
CRP (mg/L)	13.41	8.14	22.28	9.70	24.62	9.02
Lactate (mmol/L)	2.08	0.79	4.16	2.80	5.27	1.54

Table 3. Data distribution of pathogens

Pathogenes	Urine Culture	Blood culture
<i>Eschericia Coli</i>	10 (40%)	3 (12%)
<i>Klebsiella pneumonia</i>	2 (8%)	-
<i>Pseudomonas aeroginosa</i>	1 (4%)	-
<i>Morganella Morganii</i>	1 (4%)	-
<i>Klebsiella ozaenae</i>	1 (4%)	-
<i>Micrococcus luteus</i>	-	1 (4%)
Steril	10 (40%)	21 (84%)
Total	25	25

Table 4. Statistical analysis for correlation between

Spearman's rho test		Outcome	
Lactate	Correlation coeff.	1.000	.517
	Sig. (2-tailed)	.	.008
	N	25	25
CRP	Correlation coeff.	1.000	.475
	Sig. (2-tailed)	.	.016
	N	25	25

General hemodynamic measurements reflect only a fraction of the total blood flow in the body. Microcirculation with extensive endothelial surface, is actually the largest organ in the human body. In clinical practice, microcirculation perfusion measured from several aspects such as color, capillary refill and temperature on peripheral part of the body (fingers, toes, ears, nose). (Bochud 2003, Gladden 2004, Schuetz et al 2008)

Many laboratory variables used to determine the severity and prognosis of the disease, assessed an adequate therapy in patients with critical condition including urosepsis. One of them is the measurement of blood lactate levels. It does not represent all the parameters, but lactate was nearing the diagnostics needs. (Bakker et al 2013, Suzana et al 2003)

On the other hand, CRP has long been used and trusted as an indicator of sepsis. CRP as a molecular marker, is generally used as an indicator to determine the inflammatory response associated infectious and non-infectious conditions. CRP is also often used as an indicator of prognosis in sepsis. A study mention the median value of CRP level of 70 mg/L compared with survival group (CRP 18 mg/L) showed a significant association with the incidence of mortality in patients with sepsis. (Gladden 2004)

In this study, median value of CRP levels was 16.98 + 9.56 mg/L. Plasma lactate levels was 3.01 + 1.92 mmol/L, than we performed statistical tests to compare the value and significance of the correlation between lactate levels and CRP in determining the outcome/prognosis in patients with urosepsis that treated in Soetomo general hospital.

The mean value of plasma lactate level in patient based on the outcome (improve/morbid/death) was 2.08 mmol/L; 4.16 mmol/L and 5.27 mmol/L. The mean value of CRP level was 13.41 mg/L; 22.28 mg/L and 24.62 mg/L. Based on these data, the real distribution obtained that the higher the degree of severity of sepsis followed by increased levels of CRP and lactate.

The statistical analysis in this study showed that CRP levels in urosepsis have shown significant correlation to the outcome/prognosis in the sample without assessing the classification of sepsis with a significance value of 0.016 ($p < 0.05$) and a correlation coefficient of 0.475 as well as plasma lactate, but with higher correlation coefficient (0.517).

The four patients died with initial CRP levels was 11.2 mg/L; 27.6 mg/L; 29.2 mg/L and 30.5 mg/L, with plasma lactate levels was 3.5 mmol/L; 4.8 mmol/L; 5.6 mmol/L and 7.2 mmol/L, respectively. Additional data analysis in our study showed the sample group with CRP levels >10 mg/L had a mortality rate of approximately 23.5%. Suzana et al. (2003), found that ICU patients with admission serum CRP levels >10 mg/dL were associated with higher mortality rates (36% vs 21%, $p < 0.05$) than CRP levels < 1 mg/dL. Vincent et al. (2013), in their study found that an increased CRP level was associated with a mortality rate of 60.9% in patients with CRP concentrations >10 mg/dl on ICU admission ($p < 0.05$).

Shapiro and Howell (2005) mention that mortality rates increased as lactate increased. Patients with lactate level 0-2.5 mmol/L (have a risk of 4.9% died), lactate level 2.5-4.0 mmol/L (9% died), and lactate level greater than or equal to 4.0 mmol/L (28.4% died). While the research we did, found a mortality rate of approximately 40% in the urosepsis with plasma lactate levels > 3 mmol/L.

CONCLUSION

The measurement of plasma lactate and CRP level can be used as a prognostic marker for the outcome of patient with urosepsis. Plasma lactate showed higher correlation with outcome of urosepsis than CRP.

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