Uric Acid Levels as Predictor Of Sepsis Severity Related To Sofa Scores In Patients With Sepsis At ICU Adam Malik Hospital Medan

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***Abstract*- Introduction:** Sepsis is a life-threatening condition that result in organ dysfunction and diagnosed with SOFA score. It is often accompanied by kidney disorders that inhibit uric acid excretion causing hyperuricemia.

Objective: To determine the role of serum uric acid levels as predictors of sepsis severity associated with SOFA scores.

Method: This is an analytic study conducted from June-August 2019 on 38 sepsis patients at ICU Adam Malik Hospital Medan. Sepsis severity was measured using SOFA scores, while uric acid levels was measured by enzymatic method TBHBA with Architect C8200. All examinations were performed on the first and third day. Statistical analysis was performed with Spearman Correlation test using SPSS

Results: A total of 16 (42.1%) men and 22 (57.9%) women were included in this study. There was a significant increase in SOFA scores from 4 (range 3–11) on the first day to 6 (range 2–11) on the third day ($p < 0.001$). There was also a significant increase in serum uric acid levels from 5.4 mg / dl to 6.2 mg / dl ($p < 0.01$). There was a significant correlation of uric acid levels with SOFA scores on the first day ($r = 0.4$, $p = 0.01$) with moderate correlation strength, but there was no correlation between uric acid levels with SOFA scores on the third day ($r = -0.04$, $p = 0.79$).

Conclusion: Serum uric acid levels have a significant correlation with SOFA score on the first day, and can be used as a predictor of sepsis severity

***Index Terms*-** uric acid, sepsis, SOFA

I. Introduction

Sepsis has long been known as the leading cause of death in intensive care unit (ICU) where the incidence continues to increase. Sepsis is defined as a life-threatening condition characterized by the release of various systemic inflammatory mediators that result in organ dysfunction, and the diagnosis is based on SOFA scores.

High free radicals and low levels of antioxidants in sepsis patients are believed to cause multiorgan failure, one of which is kidney dysfunction, which results in inhibition of uric acid excretion, and causes hyperuricemia[1]. In humans, uric acid is the final oxidative product of purine metabolism through the action of xanthine oxidase or xanthine dehydrogenase. About two-thirds of uric acid is excreted by the kidneys. Uric acid occurs mainly as a uric acid anion under physiological circumstances. In kidney, uric acid is filtered easily by the glomerulus and then reabsorbed by the proximal tubular cells of the kidney and excretion in the urine is around 10% (N.L. Edwards, 2008).

Previous studies found that increased serum uric acid had a positive correlation with total antioxidant capacity and APACHE II scores in patients with severe sepsis and septic shock. This suggests that uric acid can be an important contributor to the total antioxidant capacity, and hyperuricemia may be an important early predictor for worse outcome markers in patients with sepsis[3]. Uric acid examination is a simple examination that does not require sophisticated equipment and can be applied in daily clinical practice. However, so far, there has been no research that identifies the role of uric acid levels as a predictor of the severity of sepsis associated with SOFA scores. This study aims to determine the role of serum uric acid levels as predictors of the severity of sepsis patients associated with SOFA scores.

II. METHODS

This research is an analytical study with a prospective cohort design conducted in the ICU room at H Adam Malik General Hospital Medan from June to August 2019. All research procedures were approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara

A total of 38 people with sepsis aged 18-65 years were included as subjects in this study. The diagnosis of sepsis is made if the patient has a SOFA score of ≥2 accompanied by evidence of infection, clinically and microbiologically. Patients who had comorbid like chronic kidney disease and malignancy were excluded from this study.

All subjects underwent arterial blood tests for measurement of uric acid levels, and levels of bilirubin, creatinine, platelets and blood gas analysis to calculate SOFA scores. Examination of uric acid levels was carried out using the enzymatic method TBHBA (2,4,6-tribromo-3-hydroxybenzoic acid), and was read by spectrophotometer. All examinations were performed on the first and third day of treatment. For stabilizing the quality of gout use control from Multichem S Plus (Assayed), Lot. NO. 18004180, ABBOTT 65205, Germany and for calibration using

Multiconstituent Cal, Lot.NO. 81708-1. Abbot Park, IL 60064, USA.

III. RESULTS

A total of 38 people with sepsis were included in this study. The demographic and clinical characteristics of the patients who were the subjects of this study can be seen in Table 1

Table 1 Characteristic of subjects

Characteristic		n	%
Gender	Male	16	42.1
	Female	22	57.9
Age	< 40 years old	9	23.7
	40-49 years old	10	26.3
	50-59 years old	11	28.9
	≥ 60 years old	8	21.1
Total		38	100.0

Based on the underlying disease, it was found that almost half of the study subjects (63.1%) had sepsis caused by pneumonia. Other diseases that contributed to the increased incidence of sepsis were urosepsis (13.2%), peritonitis (10.5%) and surgical wounds (10.5%) in post-operative patients. The clinical and laboratory characteristics of the research subjects can be seen in Table 2.

Table 2 Clinical and Laboratoric findings of subjects

Karakteristik		**median**	**min - max**
PaO_2/FiO_2 (mmHg)	day 1	420	175 - 610
	day 3	464.5	212 - 673
GCS	day 1	9	6 - 13
	day 3	10	9 - 13
Bilirubin (mg/dl)	day 1	1.25	0.2 - 20
	day 3	1.4	0.2 - 24.8
Creatinin (mg/dl)	day 1	1.17	0.4 - 10.3
	day 3	2.32	0.2 - 7.8
Platelet ($x\ 10^3/mm^3$)	day 1	225	26 – 838
	day 3	95	90 – 571
MAP (mmHg)	day 1	91.8	54.3 - 130
	day 3	87.3	57 – 124
SOFA score	day 1	4	3 – 11
	day 3	6	2 – 11
Uric Acid (mg/dl)	day 1	5,4	4 - 16.3
	day 3	6.2	3,6 - 18.7

The main purpose of this study is to determine whether there is a significant correlation between uric acid levels and SOFA scores of patients with sepsis, with the results shown in Table 3 and Table 4 below:

Table 3. Correlation of uric acid level and SOFA score on day 1

	Uric Acid (day 1) mg/dl	
	r	**p value**
SOFA score day 1	0.41	0.01*

*) Spearman correlation

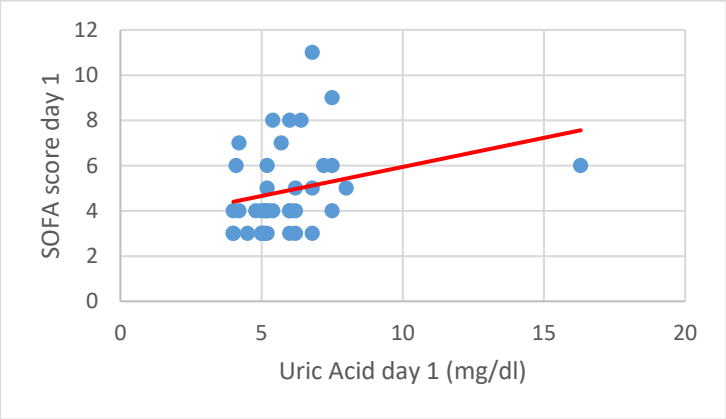
Table 4. Correlation of uric acid level and SOFA score on day 3

	Uric Acid (day 3) mg/dl	
	r	**p value**
SOFA score day 1	-0.045	0.79

*) Spearman correlation

Table 3 shows that there is a significant correlation between day 1 uric acid levels and day 1 SOFA scores, with the level of correlation strength being moderate (r = 0.41). This means that the patient's uric acid level when first diagnosed with sepsis (day 1) is related to the condition of sepsis.

In order to further clarify the relationship between uric acid levels with a patient's SOFA score, the research data are depicted in a scatter plot diagram as follows:



Picture 1. Scatter plot correlation of uric acid and SOFA score on day 1

Figure 1 shows a linear line that leads diagonally upward which means that the correlation is positive. Because the correlation coefficient is positive, it can be concluded that the higher the level of uric acid in the blood, the higher the SOFA score (day 1) of the patient.

Table 4 shows that there is no relationship between uric acid levels on day 3 and SOFA scores on day 3.

IV. DISCUSSION

In the human body, uric acid is the final oxidative product of purine metabolism through the action of xanthine oxidase or xanthine dehydrogenase. About two-thirds of uric acid is excreted by the kidneys, and the rest is excreted by the digestive tract. In addition, some uric acid will degrade in the body after reacting with oxidants or peroxynitrite. Uric acid is formed mainly in the form of uric anion under physiological pH conditions. In the kidney, the veins are easily filtered by the glomerulus and then reabsorbed by the proximal tubular cells of the kidney. Hyperuricemia is defined as the accumulation of serum uric acid beyond its solubility in water. The mechanism of hyperuricemia can be caused by excess production of uric acid, reduced secretion rate, or a combination of both[4].

Sepsis is defined as a life-threatening condition characterized by the release of various systemic inflammatory mediators that result in organ dysfunction, and is enforced using SOFA scores. The majority of intensive care unit (ICU) patients experience ischemic-reperfusion injury and inflammation with varying degrees of severity during hospitalization

Because high levels of oxidic acid and lower antioxidant levels in patients with sepsis are believed to cause multiorgan failure, measurement of uric acid levels can be used as a marker of oxidative stress in patients with sepsis. During sepsis, there is an increased level of antioxidant response to compensate for the excessive amount of proinflammatory cytokines and very high oxidative stress[3]. It seems that this oxyradical plays a role in aggravating systemic inflammatory response syndrome (SIRS) in life-threatening conditions. This imbalance in the redox state also reflects oxidative stress and tissue damage[5].

Serum uric acid, like other antioxidants is a strong free radical scavenger. Uric acid levels will increase in response to acute oxidative stress The formation of uric acid can even provide a significant antioxidant defense mechanism against nitration by peroxynitrite in rat hearts during hypoxia. Therefore uric acid is believed to be an important marker of oxidative stress[3].

This study found that there was a relationship between uric acid levels in the blood with SOFA scores on the first day of treatment. which is a parameter of disease severity, where the higher the uric acid level, the higher the SOFA score and means the severity of the disease experienced by the patient also increases ($p < 0.05$, $r = 0.41$). In other words, the level of uric acid at the beginning of the diagnosis of sepsis can be a predictor of the severity of the patient's disease.

However, it needs to be understood that there are several factors that can influence the level of uric acid in the blood and can potentially be biased in this study. The use of drugs that are nephrotoxic, high purine diet, drug interactions, dehydration status will also affect the levels of uric acid in the blood. Further research is needed for know the role of uric acid in sepsis, by conducting a quantitative analysis of more inflammatory mediators involved in sepsis.

V. CONCLUSION

Serum uric acid levels can be used as predictors of sepsis severity associated with SOFA scores. There is a significant correlation between serum uric acid levels with SOFA scores on the first day

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