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Relationship between Renal Angina Index and D-Dimer Improvement Towards Acute Kidney Injury in Covid-19 Patients in Special Isolation Room of Dr. Soetomo Hospital Surabaya

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ABSTRACT

Since the World Health Organization (WHO) declared COVID-19 as pandemic in March 2020, the number of new case findings in Indonesia has continued to increase. As happened in the city of Surabaya. Even in severe cases deterioration is rapid and progressive. One of them is the high D-dimer level in COVID-19 patients, which indicates the presence of vascular thrombosis, resulting in organ failure syndromes such as Acute Kidney Injury (AKI). Such conditions clearly indicate that this virus attacks the kidneys. It is known that the prevalence of AKI is 17%, where 77% of AKI patients experienced severe COVID-19 infection, and 52% died. For this reason, this study was prepared with the aim of knowing the relationship between increased levels of D-Dimer Renal Angine Index and the incidence of Acute Kidney Injury (AKI) in COVID-19 patients in the Special Isolation Room of Dr. Soetomo Hospital Surabaya. This study was a retrospective cohort analytic observational study with a sample size of 30. The Acute Kidney Injury criteria in this study used an increase in serum creatinine ≥ 0.3 mg / dL within 48 hours, or an increase in serum creatinine ≥ 1.5 times. Through research conducted, it is known that the Renal Angina Index can be used to predict the incidence of AKI in this study with p <0.0001 and sensitivity 71%, specificity 21% (r: 0.43; strong CC> 0.3) with a limit of 7. It can be concluded that there is a relationship which is significant between the Renal Angina Index on the incidence of Acute Kidney Injury (AKI). However, there was no significant relationship between increased D-Dimer levels and the incidence of acute kidney injury.

Keywords: renal angina index; D-dimer; acute kidney injury (AKI); COVID-19

INTRODUCTION

COVID-19 has been declared a pandemic by the World Health Organization since March 2020 (*Situation Report-55*, 2020). Even in Indonesia, especially in Surabaya, the COVID-19 virus has become a serious problem until now. Since May 2021, 25,216 people have been confirmed with COVID-19 in Indonesia with 1,520 deaths (*Coronavirus disease (COVID-19) Situation Report-132*, 2020).

It is known that someone who has been infected with COVID-19 will experience mild, moderate, and severe symptoms. A series of articles and recent research have concluded that the main clinical symptoms that often appear are fever, cough and difficulty breathing. Complementary symptoms that can appear are respiratory problems, fatigue, muscle aches, and diarrhea (*Kementerian Kesehatan Republik Indonesia*, 2020).

The patient will experience shortness of breath within one week. In severe cases there will be rapid and progressive deterioration to the point of death. This sepsis condition begins with pneumonia, metabolic acidosis due to severe kidney problems, bleeding, and disorders of the coagulation system (Klingensmith & Coopersmith, 2016).

The manifestations of coagulation disorders in COVID-19 patients appear to be dominant. One of them concerns storm cytokines, which is a strong suspicion of the occurrence of vascular thrombosis, both macro and microangiopathy (Jhaveri et al., 2020; Sun et al., 2020; Xia et al., 2018). One study showed that elevated D-dimer levels were associated with a poor prognosis for patients (Guan et al., 2020; Zhou et al., 2020). High D-dimer levels indicate vascular thrombosis.

D-dimer is a degradation product of fibrin, which is a small protein fragment in the blood after the blood clot is degraded by fibrinolysis. D-dimers are a marker of vascular thrombosis. In clinical practice, it is very important to know D-dimer levels as a determinant of the severity of coagulation disorders due to COVID-19 infection (Kroll, 2020). In a state of sepsis there is an increase in various kinds of inflammatory mediators and cytokines which can end up in cytokine storm conditions or Cytokines Storm (Thachil & Agarwal, 2020).

Storm cytokines manifest in the form of endotheliopathy and decreased vascular blood flow. As a result of these two conditions, the blood will easily experience clotting and vascular thrombosis occurs (McGonagle et al., 2020).

The thrombus on the microvascular causes organ failure syndromes that are common in COVID patients such as Acute Kidney Injury (AKI) (Guan et al., 2020; Joly et al., 2020; Thachil & Agarwal, 2020).

Acute renal failure is a condition that often occurs in critically ill patients, especially those with severe infections. Acute renal failure is often associated with high morbidity and mortality. Little attention has been paid to the incidence of acute renal failure and renal involvement is often neglected. However, currently there is increasing evidence that acute kidney failure often occurs in COVID 19 patients. Some studies have even shown that this virus directly attacks the kidneys (Gabarre et al., 2020; Huang et al., 2016).

The prevalence of acute kidney injury (AKI) was 17%. While it is known that 77% of AKI patients experience severe Covid infection, even 52% of that number are known to have died. About 5% of Covid patients who develop AKI require the use of kidney replacement therapy (Robbins-Juarez et al., 2020). The prevalence of Covid patients who experience AKI in RIK is 17.19%. Thus, early detection of AKI is necessary to prevent morbidity and mortality.

The process of understanding the pathophysiology of kidney disorders seems to have been done a lot, especially discussing the Renal Angina Index (RAI) as a score to evaluate changes in kidney function. Of the many chronic comorbidities that aggravate the condition of COVID-19 patients, one of them is a risk factor for AKI such as Diabetes Mellitus, which has been reported to be at high risk and is included in the AKI prediction model. The Renal Angina Index (RAI) has been shown to be effective in predicting persistent acute kidney injury (AKI) in adult patients admitted to the ICU (Matsuura et al., 2018).

Acute Kidney Injury (AKI) conditions caused by viral invasion due to cytokine storms will run linearly with patient severity and affect coagulation conditions and the effectiveness of RAI in predicting the incidence of AKI. Therefore, this study aims to analyze the relationship between AKI and changes in D-dimer levels and Renal Angina Index in COVID-19 patients who are in the Special Isolation Room of Dr. Soetomo Hospital Surabaya.

METHOD

This study was a retrospective cohort analytic observational study that analyzed the relationship between changes in D-dimer levels and the Renal Angina Index and the incidence of Acute Kidney Injury (AKI) in patients with confirmed COVID-19 at Dr. Soetomo Hospital Surabaya. The population in this study were patients with confirmed COVID-19 with symptoms of Acute Kidney Injury (AKI) at the Dr. Soetomo Hospital Surabaya.

Data collection on patients was carried out in several stages. The first stage was to collect data on D-Dimer levels and Renal Angina Index which were seen on the first day (D-1) and the third day (D-3). The second stage, processing and analyzing data.

In the analysis process, the data were processed using the SPSS 24.0 program, which was then presented in tables and graphs. Then, the analysis of the relationship between changes in D-dimer levels and the Renal Angina Index (RAI) with Acute Kidney Injury (AKI) in patients with confirmed COVID-19 was used as the dependent variable through the Mann-Whitney test.

RESULT AND DISCUSSION

Demographic Characteristics of Research Subjects on the Incidence of Acute Kidney Injury (AKI)

In a retrospective search of COVID-19 patients from June to August 2020, a total of fifty-eight (58) patients were found, with forty-two (42) male patients and sixteen (16) female patients. In the research data, it is known that thirty-nine (39) patients experienced acute kidney injury (AKI) with the distribution of male as much as twenty-six (26) or 66.7% and female as much as thirteen (13) or 33.3%. Meanwhile, there were nineteen (19) patients who did not experience acute kidney injury (AKI), namely sixteen (16) male patients (84.2%) and three (3) female patients (15.9%).

Medical record data also showed that the mean age of patients with acute kidney injury (AKI) was 42.5 years. Meanwhile, those who did not experience acute kidney injury (AKI) had an average age of 53.1 years. The mean BMI of patients with acute kidney injury (AKI) tended to be overweight (mean 29.3), while patients who did not experience acute kidney injury (AKI) were in the range 18.3 - 31.1 (23.6) with a significant p value. (p 0.001). On the other hand, in observing the SOFA score, it was found that the mean score of patients who experienced acute kidney injury (AKI) was 6.79, while patients who did not experience acute kidney injury (AKI) had a lower mean score (4.68) with a score p <0.01.

The complex treatment for COVID-19 makes hospital length of stay important. Through observations, the average length of stay (LOS) of patients with acute kidney injury (AKI) was 9.6 days, while patients who did not experience acute kidney injury (AKI) had an average treatment of 6.7 days. This is in line with the SOFA score, where patients who have higher SOFA scores with the incidence of acute kidney injury (AKI) require longer treatment days.

On the other hand, through the process of evaluation and observation, it was found that there was no significance in the data, leucocytes and lactate, CRP, and procalcitonin with a value of p> 0.05. Meanwhile, laboratory values with significant p values were found on serum creatinine results during treatment. This can be seen in TABLE 1 below.

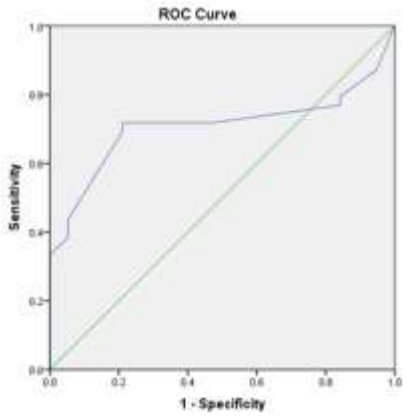
TABLE 1: Characteristics of Research Subjects on the Incidence of *Acute Kidney Injury* AKI.

Characterictics		AKI	Non-AKI	Total	*p*
Sex	Male Female	26 (66.7%) 13 (33.3%)	16 (84.2%) 3 (15.8%)	42 16	
	Total	39	19	58	
Age		23 – 71 (42.5)	39 – 70 (53.1)	23 – 71 (48.6)	
BMI		18.6 – 48.4 (29.3)	18.3 – 31.1 (23.6)	18.3 – 48.427.5	0.001
SOFA score		1 – 14 (6.79)	1 – 12 (4.68)	1 – 14 (6.1)	0.01
Sepsis Incident	Sepsis Non-Sepsis Sepsis Shock	19 (48.7%) 4 (10%) 16 (41.3%)	7 (36.8%) 8 (42.1%) 4 (21.1%)	26 12 20	
Haemoglobin		9.7 – 18.0 (13.4)	8.7 – 16.6 (13.2)	8.7 – 18.0 (13.38)	
Leukocytes		1.790 – 48.410 (14.953)	1.520 – 35.170 (14.364)	1.520 – 48.410 (14.760)	0.728

Characterictics		AKI	Non-AKI	Total	*p*
Albumin		2.5 – 3.6 (3.03)	2.4 – 3.85 (3.01)	2.4 – 3.8 (3.03)	
CRP		0.2 – 320 (23.2)	0.3 – 40.0 (12.2)	0.20 – 320.0 (19.63)	0.297
Lactate		0.43 – 2.86 (1.36)	0.5 – 3.0 (1.4)	0.43 – 3.00 (1.38)	0.875
Procalcitonin		0.04 – 100.0 (4.02)	0.12 – 4.67 (1.01)	0.04 – 100.00 (3.03)	0.278
Serum Creatinine	Basalt Day 0 Treatment Day	0.34 – 12.5 (1.28) 0.50 – 4.20 (1.40) 1.00 – 6.50 (3.01)	0.50 – 19.50 (2.32) 0.60 – 12.00 (1.90) 0.60 – 18.00 (1.98)	0.34 – 19.5 (1.62) 0.50 – 12.00 (1.56) 0.60 – 18.00 (2.67)	 0.555 0.0001

Analysis of Renal Angina Index (RAI) Data with the Incidence of Acute Kidney Injury (AKI)

One of the complications of patients with COVID-19 is acute kidney injury (AKI) which requires intervention. Renal Angina Index is a scoring that can be used to predict the incidence of acute kidney injury (AKI) in this study with p <0.0001 and a sensitivity of 71% and a specificity of 21%. The strength of the relationship from the Renal Angina Index (RAI) correlation test on the incidence of Acute Kidney Injury (AKI) is calculated as 0.43 (strong CC> 0.3) with a cutoff point of 7 which means it has a strong relationship. This analysis can be seen in the following graph.



Data Analysis of D-dimer Change (H1 with H3) with the Incidence of Acute Kidney Injury (AKI)

D-dimers suspected of being a marker of a thrombus occurring in COVID-19 patients have led to the theory that Acute Kidney Injury (AKI) is one of the consequences of the thrombus. From the data analysis of the relationship between D-dimer changes and the incidence of Acute Kidney Injury (AKI), it is known that these data do not show insignificant results (p <0.226), but the strength of the relationship is from the correlation test of D-dimer changes in the incidence of Acute Kidney Injury (AKI). amounted to 22.6%, which means that they have a moderate relationship. The analysis data can be seen in TABLE 2 below:

TABLE 2: Data on D-dimer Change with the Incidence of Acute Kidney Injury (AKI).

Characteristics		AKI	Non-AKI	Total	*P*
D-dimer Change	< 272.5	15 (38.5%)	12 (63.2%)	27	0.226
	≥ 272.5	24 (61.5%)	7 (36.8%)	31	
Total		39	19	58	

The Relationship between D-Dimer Changes in Acute Kidney Injury (AKI)

In the research conducted, it was found that the high level of serum D-dimers indicated a hypercoagulation process that was prominent in the pathological process of COVID-19. A severe inflammatory process sometimes combined with an infectious process can lead to high blood D-dimer levels (Abou-Ismail et al., 2020).

Through the results of this retrospective studied it was proven that the increase in D-dimer at the time close to the occurrence of acute kidney injury (AKI) is expected to be an unproven causal process (p 0.226). This provides other evidence that D-dimers cannot be a strong indicator to predict the incidence of Acute Kidney Injury (AKI) that a patient is experiencing.

Acute Kidney Injury (AKI) Predictors: Improving Service Quality

Acute Renal Injury (AKI) is one of the highest causes of mortality in intensive care rooms. It is known that in the last fifteen (15) years of data, it has been reported that mortality related to acute kidney injury (AKI) reaches 20-90%. COVID-19 itself is a systemic inflammatory process. Thus, efforts to determine the biomarker of Acute Kidney Injury (AKI) have been studied massively in the last decade. Neutrophil Gelatinase Associated Lipocalid (NGAL) is known to be a standard biomarker as a marker of kidney failure (Matsuura et al., 2018).

Biomarkers for acute kidney injury (AKI) have many roles that are implicated both clinically and indirectly. This is due to the heterogeneous nature of the disease and the difficulty in developing effective therapies as well as the strategies used through all the tools available in treatment. The presence of biomarkers can change the way we treat patients who may need immediate intervention.

The statistical results in this study indicate that the Renal Angina Index tested on a sample with a cut-off point of 7 shows a strong relationship (cc: 43%) and a significant p value (<0.0001). Through these data, it can be interpreted that the use of the Renal Angina Index (RAI) is relatively more cost effective when compared to the use of Neutrophil Gelatinase Associated Lipocalid (NGAL) as a biomarker in predicting Acute Kidney Injury (AKI).

On the other hand, through the results of the study, it was also found that the statistical significance of the Renal Angina Index (RAI) in predicting Acute Kidney Injury (AKI) on treatment until the seventh day has a high sensitivity. This retrospective study can show a significant relationship between the Renal Angina Index (RAI) and the incidence of Acute Kidney Injury (AKI) which has an OR value of 9.4. This shows that patients with Renal Angina Index (RAI)> 7 have a risk of experiencing Acute Kidney Injury (AKI) 9.4 times greater than patients with Renal Angina Index (RAI) <7 with a 95% confidence interval.

CONCLUSION

Based on the research conducted, it can be concluded that, first, there is a significant relationship between the Renal Angina Index and the incidence of Acute Kidney Injury (AKI) in COVID-19 patients in the Special Isolation Room of Dr. Soetomo Hospital Surabaya. Second, there is no significant relationship between increased D-Dimer levels and the incidence of Acute Kidney Injury (AKI) in COVID-19 patients in the Special Isolation Room at Dr. Soetomo Hospital Surabaya.

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