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The Association between Urinary Tissue Inhibitor Metalloproteinase 2 (TIMP-2) and Insulin-like Growth Factor Binding Protein 7 (IGFBP-7) and Renal Recovery in Acute Kidney Injury

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ABSTRACT

Background. Acute kidney injury (AKI) is a common and serious medical condition associated with significant increases in morbidity, mortality, cost of care and non recovery of kidney function that leads to progression to chronic kidney disease. Cell cycle arrest is implicated in the pathogenesis and repair process following AKI. The urinary cell-cycle arrest markers tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7) have been utilized to predict the risk of AKI in many studies from specific population with good performance. However, their use in predicting recovery is still lacking. The aim of this study was to determine the association between two novel AKI biomarkers, urinary TIMP2 and IGFBP7 and renal recovery after 7 days of treatment in AKI patients at Dr. Mohammad Hoesin Hospital Palembang. **Method.** This was a prospective cohort study conducted in dr. Mohammad Hoesin Hospital Palembang from January 2021 until March 2021. Subjects enrolled in this study were patients whom diagnosed AKI based on KDIGO 2012 criteria. Urine samples were collected upon patients' enrollment within 24 hours of AKI diagnosis. We utilized Sandwich Enzyme Linked Immunosorbant Assay (ELISA) method to detect urinary TIMP-2 and IGFBP-7 levels. The primary outcome is recovery from AKI after 7 days of treatment. Chi square test is used to analyze the association between urinary TIMP-2 and IGFBP-7 levels and renal recovery.
Results. There were 70 subjects, only 22 of them were recovered after 7 days (31%). Median of urinary TIMP-2 and IGFBP-7 was 0,0047(0,0001-0,1439) [(ng/ml)2/1000]. There was significant association between urinary TIMP2 and IGFBP7 and renal recovery (p=0,027; OR 3,19; 95% CI 1,116-9,128). **Conclusion.** There was significant association between urinary TIMP2 and IGFBP7 and renal recovery in AKI patients.

1. Introduction

Acute kidney injury (AKI) is a clinical syndrome that includes many etiologies and pathophysiological processes, characterized by a sudden decline in kidney function resulting in accumulation of nitrogen and waste products and dysregulation of extracellular volume and electrolytes. The definition of AKI used in clinical practice and epidemiological research with certain criteria continues to develop. The current definition and system staging preferred is based on the 2012 KDIGO. AKI is considered if one of the following criteria is met: (1) serum creatinine increase > 0.3 mg/dl in 48 hours; (2) increase in serum creatinine >1.5 times baseline, known or suspected to have occurred in the previous 7 days; or (3) urine volume <

0.5 ml/kg/hour for 6 hours.[1-3]

Globally, the prevalence of AKI varies greatly from <1% to 66% due to population differences and the varying classification criteria used.[4] The incidence of AKI using KDIGO criteria in 2012 reported that about 20% on normal wards and 67% in the intensive care unit.[5] In Indonesia, there are no national publications on the epidemiology of AKI. A retrospective study at Borromeus Hospital in Bandung from March 2005 to October 2006 by Roesli et al. get an AKI incidence rate of 6.1%.[6]

Although attention to AKI and research on biological markers (biomarkers) has increased rapidly in the last decade, AKI remains a significant complication due to its high morbidity, mortality and cost burden. One episode of AKI is associated with both short-term and long-term complications. Short-term complications include fluid overload, electrolyte and acid-base disturbances, immune dysfunction, bleeding complications and death. Long-term complications include decreased survival, cardiovascular complications, progression to chronic kidney disease (CKD) and end-stage kidney disease (CKD). One of the important consequences of AKI is the failure to restore renal function. An analysis of recovery of renal function after an AKI episode showed 41.2% of patients did not recover with a 1-year mortality in these patients of nearly 60%.[4,5,7-9] This study aims to explore the relationship between urinary TIMP-2 and IGFBP-7 levels with recovery of kidney function in acute kidney injury patients at RSMH Palembang.

2. Methods

This study was an observational study with a prospective cohort study design. The study was conducted in the emergency room and inpatient ward of Dr. Mohammad Hoesin Palembang, which was conducted from January 2021 to March 2021. The target population of the study were all patients diagnosed with AKI based on the 2012 KDIGO criteria. Inclusion criteria in this study were patients aged more than 18 years, patients diagnosed with AKI in less than or equal to within 24 hours in the emergency room and inpatient ward, and have signed an informed consent / statement of willingness to participate in the study. The exclusion criteria were patients with chronic kidney disease in kidney transplant therapy.

Sandwich enzyme linked immunosorbent assay (ELISA) TIMP-2

In sample preparation, the sample used was 0.5 mL of urine. The sample was put into a 1.5 mL centrifuge tube. The sample was then centrifuged at 5000 rpm for 10 minutes at 25°C. The supernatant was then separated and put into a new 1.5 mL centrifuge tube and stored at -20°C.

A total of 10 L of each sample was put into the microplate well, where the bottom of the microplate has anti-TIMP2. Then, 40 L of sample diluent was added to each microplate well. Standards were prepared using the gradient diluent concentration method to obtain standard concentrations of 0.2, 4, 8, 16, 32, 64, 128, and 256 pg/mL. Sample and standard incubation at 37°C for 30 minutes. 50 L of conjugated-secondary anti-TIMP2 HRP was added to each microplate well. Sample and standard incubation at 37°C for 30 minutes. Next, 50 L of chromogen A and B were added to each microplate well. Then, add 50 L of stop solution to each microplate well. The microplate was inserted into the ELISA reader Biorad to read the optical density at a wavelength of 450 m. The optical density value is then converted to TIMP2 levels by making a standard curve, so that TIMP2 levels are obtained in pg/mL units.

Sandwich Enzyme Linked Immunosorbent Assay IGFBP-7

In sample preparation, the sample used was 0.5 mL of urine. The sample was put into a 1.5 mL centrifuge tube. The sample was then centrifuged at 5000 rpm for 10 minutes at 25°C. The supernatant was then separated and put into a new 1.5 mL centrifuge tube and stored at -20°C.

A total of 10 L of each sample was put into the microplate well, where the bottom of the microplate has anti-IGFBP-7. Then, 40 L of sample diluent was added to each microplate well. Standards were prepared using the gradient diluent concentration method to obtain

standard concentrations of 0.2, 4, 8, 16, 32, 64, 128, and 256 pg/mL. Sample and standard incubation at 37°C for 30 minutes. Anti-IGFBP-7. conjugated-secondary HRP was added 50 L to each microplate well. Sample and standard incubation at 37°C for 30 minutes. Next, 50 L of chromogen A and B were added to each microplate well. Then, add 50 L of stop solution to each microplate well. The microplate was inserted into the ELISA reader Biorad to read the optical density at a wavelength of 450 m. The optical density value is then converted to IGFBP-7. levels by making a standard curve, so that IGFBP-7. levels are obtained in pg/mL units.

Data analysis

Data analysis was processed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM) program. Bivariate analysis used istest chi square. The multivariate analysis used was predictive logistic multivariate analysis (for independent variables which in bivariate analysis had $p < 0.25$).

3. Results

General characteristics of research subjects

In table 1 we can see the general characteristics of research subjects which include age, gender, body mass index (BMI) diagnosis at hospital admission, systolic and diastolic blood pressure (BP), mean arterial pressure (MAP), volume 24-hour urine output, AKI grade, AKI etiology, comorbidities, length of stay and recovery of kidney function 7 days.

Table 1. General characteristics of research subjects

Characteristics of subjects	N (%)	Median (range)*
Age (years)		57 (18 – 85)
Sex		
• male	44 (62.9)	
• female	26 (37.1)	
BMI		22.5 (14.9 – 48.4)
• less (<18.5)	6 (8.6)	
• normal (18.5 – 22.9)	38 (54.3)	
• more (≥23)	26 (37.1)	
BP systolic (mmHg)		120 (90 – 210)
diastolic BP (mmHg)		80 (48 – 113)
MAP (mmHg)		93 (63 – 143)
24-hour urine volume (ml/KgBW/hour)	0.8±0 ,4	
• oliguria	7 (10)	
• non-oliguric	65 (90)	
Degree of AKI		
• stage 1	18 (25.7)	
• stage 2	20 (28.6)	
• stage 3	32 (45.7)	
Etiology of AKI		
• prerenal	37 (52.9)	
• renal	24 (34 ,3)	
• postrenal	9 (12.9)	
Comorbid		
• without comorbid	9 (12.9)	
• 1 comorbid	48 (68.6)	
• ≥ 2 comorbid	13 (18.6)	
Length of stay (days)		9 (7 – 30)
Recovery of kidney function 7 days		
• recovered	22 (31.4)	
• not recovered	48 (68.6)	

*Kolmogorov smirnov test

In this study, the median age of the research subjects was 57 years with the youngest age being the subject of the study was 18 years and the oldest age was 85 years. The median body mass index in this study was 22.5 kg/m2 with the distribution of BMI less than 6 people (8.6%), normal BMI 38 people (54.3%), and BMI more than 26 people (37.1%). The median MAP in this study was 93 mmHg with median systolic and diastolic BP 120 mmHg and 80 mmHg, respectively. There were also 7 oliguric subjects (10%) and 65 non-oliguric subjects (90%) in this study. For the degree of AKI, stage 1 was 25.7%, stage 2 was 28.6%, and stage 3 was 45.7%. Prerenal was the most common etiology of AKI in this study with 52.9%, followed by renal 34.3%, and postrenal 12.9%. It is also known that the subjects in this study without comorbidities were 9 people (12.9%), with 1 comorbid as many as 48 people (68.6%), and > 2 comorbids as many as 13 people (18.6%). And there were 22 subjects (31.4%) who recovered kidney function and 48 (68.6%) who did not recover.

The description of the laboratory results of the research subjects

Table 2 shows the laboratory characteristics of the research subjects. The average hemoglobin value obtained in this study was 10.5 g/dL. The median leukocytes and platelets were also found to be 11,930 /mm3 and 310,000 /mm3 , respectively. The average uric acid value is 7.5 mg/dL, and the average sodium and potassium values are 138 mmol/L and 4.4 mmol/L, respectively. The median values of urea and creatinine H0 in this study were 78 mg/dL and 2.6 mg/dL, respectively. While the median value of urea H7 is 80 mg/dL and the mean value of creatinine H7 is 2.3 mg/dL. A median of urinary TIMP-2 was 19.4 ng/dL, urinary IGFBP7 was 0.24 ng/dL, and urinary TIMP-2 and IGFBP-7 were 0.0047.

Table 2. Characteristics of laboratory results of research subjects

Characteristics	N (%)	Mean±SB	Median (range)*
Hemoglobin (g/dL)		10.5±2.7	
Leukocytes (/mm^3)			11930(3170-37170)
Platelets (/mm^3)			310000(31000-917000)
Uric acid (mg/dL)		7.5±2.5	
Sodium (mmol/L)		138±7.5	
Potassium (mmol/L)		4.4±0.8	
Urea H0 (mg/dL)			78 (24-246)
Creatinine H0 (mg/dL)			2,6(1.3-17.5)
Urea H7 (mg/dL)			80(6-265)
Creatinine H7 (mg/dL)			2,3(1- 13.3)
Urinalysis			
• leukocyturia	29 (41.4)		
• hematuria	38 (54.3)		
• proteinuria	24 (34.3)		
• glucosuria	9 (12.9)		
• cylindruria	6 (8.6)		
urinary TIMP2 (ng/ dl)			19.4(3.5-107.4)
urinary IGFBP7 (ng/dl)			0.24(0.04-1.34)
TIMP-2 and urinary IGFBP-7			0.0047(0.0001-0 ,1439)

*Kolmogorov smirnov test

Comparison of urinary TIMP2*IGFBP7 levels between recovered and non-recovered patients

The results of Chi Square analysis in table 3 show that low urinary TIMP-2 and IGFBP-7 levels have a significant relationship with 7-day recovery of kidney function.

Table 3. Bivariate analysis of the relationship between urinary levels with recovery of kidney function

TIMP-2 and IGFBP-7TIMP-2 and IGFBP-7 (ng/ml)^2/1000	Renal function			*p
	Recovered	Not recovered	Total	
	n (%)	n (%)	n (%)	
Low (<0.004)	14 (45.2)	17 (54.8)	31 (100)	0.027
High (≥0.004)	8 (20.5)	31 (79.5)	39 (100)	

*Chi-Test square, p is significant if < 0.05.

The relative risk in the analysis of the relationship between urinary TIMP-2 and IGFBP-7 levels with recovery of kidney function was 2.2. This means that the probability of TIMP-2 and IGFBP-7 being low compared to TIMP-2 and high IGFBP-7 to experience recovery of kidney function is 2.2 times. In the general population, it is 95% believed that low TIMP2 and IGFBP7 can increase the likelihood of recovery of kidney function within 7 days by a range of 1.1 to 9.1-fold, compared to the high TIMP2 and IGFBP7 groups.

4. Discussion

General description of research subjects

Based on the basic characteristics of research subjects in table 1, it can be seen that the sample of this study is heterogeneous. This study uses subjects who have been diagnosed with AKI who are treated in the usual ward (non-ICU) with a variety of underlying medical, surgical and obstetric cases. Most AKI studies were conducted on critically ill patients in intensive care. A meta-analysis of 154 studies of AKI by Susantitaphong et al. reported that there were only 6 studies related to AKI in non-intensive adult care. Research on non-ICU heterogeneous subjects as this study is the same as that conducted by Cho et al (2020) in South Korea. [10]

The median age of the research subjects was 57 years with the youngest age being 18 years and the oldest being 85 years. The age range of this subject population is almost the same as that of Cho et al. i.e. 71±14 years and Baek et al. ie 65.8±16 years. In this study, the age range was very wide. The youngest age is 18 years and the oldest 85 years. This may be due to the diverse backgrounds of patients in this study where the subject of 18 years was a case of trauma and patients over 80 years of age in the form of cases of gastrointestinal bleeding and malignancy which were more common in old age. Most of the patients were less than 65 years old (68%). Several previous studies reported an increased risk of AKI in older patients, [11,12] but a recent study by Xu et al reported that the risk of AKI did not increase with age. [13]

Most of the subjects of this study were men with a percentage of 63%. Until now, there has been no randomized controlled study that specifically assesses gender trends as a risk factor for AKI and recovery of kidney function after AKI. In experimental models of AKI with rats, it is clear that the detrimental effects of

testosterone and the protective effect of estrogen on the pathogenesis of ischemic and septic AKI are evident, but in humans, knowledge about the cellular and molecular mechanisms of sex-related hormones is still minimal and various studies are still at the observational stage. In relation to the recovery of kidney function, the findings of this study were the same as those of Cho et al. There was no significant relationship between gender and the recovery of kidney function.[10,14,15]

The average BMI in this study was 23.3±5.3. There are several studies linking BMI with the clinical outcome of AKI with contradictory results. Some reported that obesity was a poor predictor of AKI outcome in critically ill patients. Liu et al in a multiethnic study in Asia reported that low BMI actually causes susceptibility to AKI in hospitalized patients. In relation to the recovery of kidney function in this study, there was no significant relationship between BMI and recovery of kidney function. Cho et al did not report BMI in their study.[16.17]

In this study, the systolic blood pressure (TDS) with a median of 120 mmHg (90-210) while the diastolic blood pressure (TDD) with a median of 80 mmHg (48-113). Mean arterial pressure or MAP at a median of 93 mmHg (63-143). In this study, most of the subjects had normal blood pressure (normotension). Most of the AKI studies that present data on blood pressure and MAP as research variables are intensive care studies, especially in patients with septic AKI and hepatorenal syndrome.[18] Blood pressure has long been recognized as a determinant of renal perfusion. In most cases, AKI is strongly associated with hypotension and organ dysfunction in the critically ill. However, in non-critical care cases, absolute hypotension is often absent, which is known as normotensive ischemic AKI.[19]

The 24-hour urine volume of the research subjects was 0.8 to±0.4 ml/KgBW/hour. Only 7 patients (10%) had oliguria at the initial diagnosis of AKI. This figure differs from existing data where oliguria can be found in 30-50% of AKI cases. Urinary volume is one of the diagnostic criteria and stages of AKI, but there are not many studies that specifically assess the role of oliguria as a marker of clinical outcome of AKI in both intensive care and ordinary wards.[17.19]

The degree of AKI in this study was mostly severe (stage 3) as much as 45.7%. The AKI grade group was further divided into two groups, namely the mild AKI group and the moderate-severe AKI group, but statistically there was no significant relationship between the AKI degree and the recovery of kidney function.

Another finding obtained in this study was the presence of severe AKI requiring renal replacement therapy. There were 9 patients (12.9%) who required hemodialysis. In relation to the recovery of kidney function, this hemodialysis condition was statistically significant (p= 0.047). These results are similar to those of Lee et al. who investigated a predictive model of renal function recovery in AKI patients on dialysis but Lee et al. evaluated recovery of renal function within 4 weeks of AKI onset. Dewitte et al also reported a significant relationship between hemodialysis and failure to recover kidney function in critically ill patients.[15,19]

The etiology of AKI in this study was predominantly prerenal, namely 37 people (52,9%), renal 24 people (34.3%) and postrenal as many as 9 people (12.9%). This composition is not much different from the existing data, where pathophysiologically, pre-renal AKI is found in 40-50% of cases, 5-10% post-renal, while the rest are renal AKI. The minimum length of treatment for patients in this study was 7 days and the longest was 30 days with a median of 9 days. On average, patients who were treated briefly were malignancy patients undergoing chemotherapy and patients with long treatment were patients with two or more comorbidities.[3.10]

The median leukocyte level of the patients was 11930(3170-37170)/mm^3 and there was no significant relationship between leukocytosis and recovery of kidney function. The immunopathogenesis of AKI involves a complex interaction between DAMP, PAMP, hypoxia inducible factor, oxidative stress, complement system, dendritic cells, neutrophils, lymphocytes, macrophages, platelets and various cytokines. Han et al reported a U-association shaped between leukocyte count and risk of AKI and mortality in a prospective cohort study in the ICU. Leukocytosis conditions are

associated with proinflammatory conditions and an increased risk of AKI while leukopenia conditions also result in weak protective functions.[19]

The characteristics of the urinalysis did not have a significant relationship with the recovery of kidney function. When the chi square test was carried out to find the relationship between urinalysis characteristics and biomarker levels, there was no significant relationship. This result is the same as that reported by Chandrashekar et al. who found that there was no correlation between AKI and urinalysis parameters, either with automatic or manual urine examination techniques. Previous studies reported that urinary sediment can be a predictor of worsening AKI.[16,18]

Comparison of urinary recovered and non-recovered patients

TIMP-2 and IGFBP-7 levelsThe results of Chi Square analysis regarding the comparison of urinary TIMP-2 and IGFBP-7 levels showed that low urinary TIMP-2 and IGFBP-7 levels had a significant relationship with recovery of kidney function 7 days with. The relative risk (RR) was found to be 2.2. This means that the probability of TIMP-2 and IGFBP-7 being low compared to TIMP-2 and high IGFBP-7 to experience recovery of kidney function is 2.2 times. In the general population, it is 95% believed that low TIMP-2 and IGFBP-7 can increase the likelihood of recovery of kidney function within 7 days by a range of 1.1 to 9.1-fold, compared to the TIMP-2 and IGFBP-7 groups. height.[5,9]

These results are in line with research with the setting same as this study, namely Cho et al (2020) with a population of patients who had AKI in the regular ward. Cho et al reported that urinary TIMP-2 and IGFBP-7 levels on the first day of AKI could predict recovery of renal function on discharge from the hospital with moderate performance (AUC = 0.675). In the setting intensive care is the same regardless of the outcome of various studies with different main focus. Xie et al (2020) reported low urinary TIMP-2 and IGFBP-7 concentrations in their study to be associated with high rates of renal recovery after discontinuation of CRRT and discharge from the ICU. The low urinary TIMP-2 and IGFBP-7 values used by Xie et al were ≤0.3(ng/dL)/1000. Meersch et al at the beginning of the discovery of this substance in 2014 reported a decrease in urinary TIMP-2 and IGFBP-7 levels as an accurate marker of recovery of kidney function after cardiac surgery. Urine samples were taken within 4 and 24 hours after cardiac surgery and the time used for evaluation of recovery was discharge from the hospital. The performance of these two substances is much better, namely AUC 0.79 than NGAL (AUC 0.48) in predicting the recovery of kidney function.[10,16]

5. Conclusion

There is a relationship between low urinary TIMP-2 and IGFBP-7 levels and recovery of kidney function in acute kidney injury patients in Palembang.

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