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Comparison of kidney injury molecule-1, proenkephalin and presepsin as predictors of diagnostics and severity of sepsis associated acute kidney injury

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Abstract: Kidney Injury Molecule-1 (KIM-1), proenkephalin, and presepsin are some of the new AKI biomarkers being explored recently. This study aims to compare the accuracy of the predictive value between urine KIM-1, proenkephalin, and presepsin on the incidence and severity of SA-AKI. Samples were taken on days 1, 3, and 7. A receiver operating curve (ROC) was generated to estimate the area under the curve (AUC) and optimal cutoff values. Sensitivity and specificity accommodate the index for validity. Comparative accuracy is determined by multivariate analysis. As predictors of SA-AKI diagnosis, urine KIM-1 on the third day has the highest AUC value during the study (AUC 0.628, sensitivity 66.7%, and specificity 57.9%, p=0.154). As predictors of SA-AKI severity on the seventh day, proenkephalin and presepsin achieved AUC 0.600 (80% sensitivity and 71.4% specificity, p value = 0.5 for proenkephalin, and sensitivity of 60% and specificity 85.7%, p = 0.471 for presepsin). A p value <0.05 is considered for statistical significance, and a 95% confidence interval is used for all assessments. Based on the results, neither urine KIM-1, proenkephalin, nor presepsin has been proven to be accurate, and more studies are needed to determine diagnostic and severity predictors of SA-AKI.

Keywords: *Acute kidney injury, Kidney injury molecule-1, Prespsin, Proenkephalin, Sepsis.*

1. Background

Sepsis is defined as life-threatening organ dysfunction as result of immune response dysregulation to infection [1]. With around 48.9 million cases every year and almost 11 million deaths, or 20% of the world's total mortality toll, this ailment represents a serious global health problem [2]. Sepsis-Associated Acute Kidney Injury (SA-AKI), or acute kidney dysfunction, is one of the most dangerous side effects of sepsis. This illness is a primary focus in the treatment of sepsis patients due to its extremely high rates of morbidity and mortality.

Approximately 20-50% of patients in the intensive care unit (ICU) experience complications of Acute Kidney Injury (AKI), which can progress to chronic kidney failure (CKD) requiring permanent dialysis, as well as increasing the risk of cerebrocardiovascular complications and mortality [3]. However, 20-30% of AKI cases can be prevented or treated early, having a major impact on patient prognosis and reducing the burden on the healthcare system [4]. Therefore, a deeper understanding of pathophysiology, risk factors, diagnostic methods, and therapeutic approaches is essential to optimize clinical outcomes. The pathophysiology of SA-AKI has unique characteristics that differentiate it from other types of AKI, although it is not fully understood. The 2023 28th Acute Disease Quality Initiative (ADQI) consensus explained that the underlying mechanisms of SA-AKI involve systemic

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inflammation, cardiovascular depression, immunomodulation, mitochondrial dysfunction, and metabolic reprogramming [5, 6]. Identification of these pathophysiological pathways allows a better understanding of the phenotype and sub phenotypes of SA-AKI, including subclinical forms that are difficult to detect.

The diagnosis of SA-AKI currently still uses general AKI criteria. However, advances in biomarker research have enabled more accurate detection, including recognition of the etiology, pathophysiology, mechanisms, and severity of AKI. These biomarkers not only aid diagnosis but also provide insight into specific phenotypes that can influence clinical outcomes and determine more targeted therapies. Biomarker-based AKI early detection strategies enable the implementation of personalized interventions, such as Reno protective therapy, renal replacement, or phenotype-tailored management to reduce morbidity, mortality, and socio-economic health burden.

The 2020 23rd ADQI consensus recommends the use of biomarkers for risk stratification, aetiology identification, severity assessment, and forecasting the duration and recovery of AKI in addition to routine clinical examination [7]. Numerous biomarkers have been demonstrated to have strong predictive value, including Tissue Inhibitors of Metalloproteinase-2 (TIMP-2), Liver-type Fatty Acid-Binding Protein (LFABP), proenkephalin, presepsin, Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1), and Interleukin-18 (IL-18) [8-10]. These biomarkers can identify structural or functional reasons, identify subclinical AKI early, and offer more data to help develop more effective treatment plans.

Although research on biomarkers for prediction and diagnosis of AKI shows great potential, there are still research gaps regarding the diagnostic and prognostic accuracy among biomarkers. Comparative research on the predictive value of biomarkers such as KIM-1, proenkephalin, and presepsin is still limited. Therefore, further studies are needed to evaluate and integrate these biomarkers into clinical practice, with the aim of increasing diagnostic accuracy, accelerating intervention, and reducing morbidity and mortality rates due to SA-AKI.

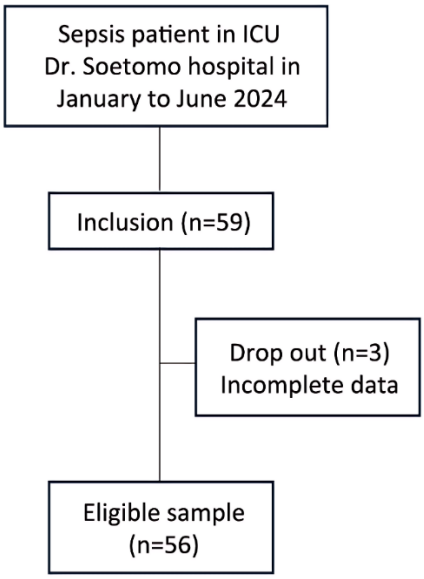

Figure 1.
Sample recruitment.

2. Material and Methods

2.1. Sample Penelitian

This study is an analytical observational diagnostic test with a cohort design which aims to analyze

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differences in the accuracy of the biomarkers KIM-1, proenkephalin, and presepsin on days 1, 3, and 7 in differentiating the incidence of Acute Kidney Injury (AKI) from non-acute kidney injury (AKI). -AKI in sepsis patients treated in intensive care. This research was carried out at RSUD Dr. Soetomo Surabaya, especially in the Resuscitation Room, Intensive Observation Room (ROI), and ICU, during the period January to June 2024.

Samples were taken using a consecutive sampling technique. Total 59 sample were enrolled and three were drop out due to incomplete data. Inclusion criteria include sepsis patients aged over 18 years who meet the Surviving Sepsis Campaign 2021 criteria (SOFA score ≥2, NEWS ≥8, or MEWS ≥3), with the approval of the patient's family through informed consent. Exclusion criteria included patients having been diagnosed with AKI in sepsis and patients in palliative care.

Measurement of Research Parameters (Scoring)

In this study, the biomarkers KIM-1, proenkephalin, and presepsin were examined using the ELISA method for each sample taken on days 1, 3, and 7. AKI severity was measured using the KDIGO score. All results are recorded on a ratio or nominal scale according to the category of each variable.

Table 1.
Research variables.

Variabel	Operational Definition	Indicator	Instrument	Scale
KIM-1	KIM-1 levels in urine were measured using the ELISA method at D1, D3, and D7	Urine examination results (ng/mL)	ELISA Kit	Rasio
Proenkefalin	Serum proenkephalin levels were measured using the ELISA method at D1, D3, and D7	Serum test results (ng/L)	ELISA Kit	Rasio
Presepsin	Serum presepsin levels were measured using the ELISA method at D1, D3, and D7	Serum test results (ng/L)	ELISA Kit	Rasio
SA-AKI	AKI that occurs within 7 days of the onset of sepsis	-	-	Nominal
Severity AKI	The severity of AKI is based on the KDIGO score	KDIGO Score	KDIGO Guidelines	Ordinal

2.2. Data Collection

Blood samples were taken from peripheral veins or central venous catheters for routine biomarker and laboratory tests. Urine sample was taken from urine catheter. Briefly, on the first day, patients with sepsis were identified and demographic data were recorded, SOFA scores were calculated, and blood samples were taken for laboratory and biomarker tests. On days 3 and 7, further evaluation of vital signs, SOFA score, and blood samples were taken again for biomarker examination. Data on clinical interventions such as fluid administration, antibiotics, and vasopressor therapy were also recorded for further analysis.

2.3. Data Analysis

To make data analysis and comprehension easier, the research findings are displayed in tabular style. Each biomarker's Area Under the Curve (AUC) and ideal cutoff value are found using the Receiver Operating Characteristic (ROC) curve. To link predictors and expected outcomes, categorical data were organized in a 2x2 table. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were then calculated. While the Kappa test assessed the degree of agreement, the McNemar test was used to examine differences in matched data. For all analyses, a 95% confidence interval was provided for a p value < 0.05, which was deemed significant. Multivariate analysis was used to compare the accuracy of several biomarkers.

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2.4. Ethical Clearance

Requests for permission from patients to be used as research samples were carried out through the Dr Soetomo Regional Hospital and the Health Research Ethics Commission.

3. Results

3.1. Demographic Characteristics

This research, which was conducted in January-June 2024, involved 56 subjects who met the inclusion and exclusion criteria at Dr Soetomo Hospital, Surabaya. The total subjects consisted of 37 men (66%) and 19 women (34%). Overall demographic characteristics are described in Table 2.

Table 2.
Demographic characteristics.

Demographic characteristics	Total	AKI	Non-AKI
Sex			
Male	37 (66%)	24	13
Female	19 (34%)	8	11
Total	56	32 (57,14%)	24 (42,86%)
Age (Year)			
Mean	52,91 ± 16,20	52,72 ± 16,07	53,57 ± 17,99
Range	18-88	18-88	20-80
Median	56	55	57
Education			
Elementary	6 (10,7%)	4	2
Junior High	33 (58,9%)	7	26
High School	13 (23,2%)	2	11
Bachelor	4 (7,2%)	1	3
Religion			
Islam	56	32	24
Ethnic			
Java	56	32	24

3.2. Clinical and Laboratory Characteristics

Clinical characteristics are described in Table 3.

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Table 3.
Clinical characteristics.

Day 1	Total	AKI	Non-AKI
Weight (kg)			
Mean	59,71 ± 8,91	59,41 ± 9,08	60,12 ± 9,07
Range	43-80	45-80	43-75
Median	60	59,5	60
Body Mass Index (kg/m^2)			
Mean	22,45 ± 3,29	22,51 ± 3,17	22,14 ± 2,99
Range	14-29	14-28	14-29
Median	23		
SOFA score	5,16 ± 2,52	5,56 ± 2,93	5,14 ± 2,80
Comorbid			
Hypertension	8 (14,29%)	4	4
Diabetes Mellitus	13 (23,21%)	5	6
Malignancy	4 (7,14%)	2	2
Stroke	4 (7,14%)	2	2
Scizophrenia	1 (1,79%)	1	0
COPD	1 (1,79%)	1	0
Hepatic cirrhosis	1 (1,79%)	1	0
Autoimmune	2 (3,57%)	2	0
Geriartric	4 (7,14%)	4	0
Case type			
Surgical	47 (83,93%)	27	20
Medical	9 (16,07%)	5	4
Source of infection			
Abdomen	20 (35,71%)	15	5
Respiratory	28 (50%)	17	11
Urinary tract	4 (7%)	4	0
Soft tissue and skin	19 (33,93%)	8	11

On the first day, most of the septic subjects with AKI suffered from grade 1 AKI. A total of 20 subjects suffered from grade 1 AKI. Seven subjects suffered from grade 2 AKI and five subjects suffered from grade 3 AKI. The severity of AKI in sepsis suffered by the subjects is reviewed in Table 4.

Table 4.
AKI severity.

AKI Severity	Day one	Day three	Day seven
Non-AKI	24	20	13
AKI	32	16	7
Total AKI and non-AKI	56	36	20
Severity of AKI			
Grade 1 AKI	20	11	4
Grade 2 AKI	7	0	2
Grade 3 AKI	5	5	1

The total number of subjects who died during observation up to day 28 was 36 of the total subjects or 64.29%. In total, up to the 28th day of observation, 18 subjects (32.14%) managed to survive. The description of mortality in this study is described in Table 5.

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Table 5.
Mortality 28 days.

Total	39 (69.64%)			
	AKI + non-AKI	AKI	Non-AKI	P value
<3 days	28	14	6	0.473
3-7 days	9	7	7	
>7 days	2	1	1	
Total	39	22	14	

Based on the characteristics of laboratory results, it was found that the mean hemoglobin decreased in sepsis patients (8.95 ± 3.68 g/dL). Subjects with AKI on the first day had lower hemoglobin levels than non-AKI (9.42 ± 5.85 g/dL compared to 10.5 ± 2 g/dL). The same phenomenon can be observed with the results of mean hematocrit levels (28.325 ± 9 vs. 29.9 ± 9.18) and albumin (1.93 ± 1.09 vs. 2.61 ± 0.68). This pattern was different from the mean neutrophils (69.78 ± 34.60 vs. 46.5 ± 40.29) and lymphocytes (58.46 ± 5.83 vs. 44.29 ± 4.32). Procalcitonin and CRP showed an increase in mean levels in sepsis patients (15.61 ± 25.73 and 20.49 ± 12.32, respectively), whereas in septic subjects with AKI, the values were (12.65 ± 24.43 vs. 9.194 ± 17 for procalcitonin and 12.058 ± 14.39 vs. 6.97 in CRP). Baseline serum creatinine ranged from 2.088 ± 1.98. A summary of laboratory results is presented in Table 6.

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Table 6.
Laboratorium test.

Day One	Total	*AKI*	*Non-AKI*
Hemoglobin (g/dL)			
Mean	8.95 ± 3.68	9.42 ± 5.85	10.5 ± 2
Range	5.6–14.5	5.6-14.5	5.7-13.8
Median	10	10	10.2
Hematocrit (%)			
Mean	30.24 ± 6.76	28.325 ± 9	29.9 ± 9.18
Range	9.5 – 42.5	9.5-42.5	10-32
Median	30.2	30.15	31.1
Albumin (g/dL)			
Mean	2.44 ± 0.53	1.93 ± 1.09	2.61 ± 0.68
Range	1-3.98	1.85-3.62	1-3.98
Median	2.34	2.24	2.57
Netrophil (%)			
Mean	85.46 ± 9.18	69.78 ± 34.60	46.5 ± 40.29
Range	54.4 – 95.6	0-95.6	0-84
Median	88.1	87.45	79.4
Limphosit (%)			
Mean	45.346 ± 41.55	58.46 ± 5.83	44.29 ± 4.32
Range	6-142.5	0-25.2	0-11.5
Median	34.1	43.5	52
Procalcitonin (ng/mL)			
Mean	15. 61 ± 25.73	12.65 ± 24.43	9.194 ± 17
Range	0.1 – 97.44	0-57.44	0-50.1
Median	2.8	0.3	0.95
CRP (%)			
Mean	20.49 ± 12.32	12.058 ± 14.39	6.97
Range	3.34 – 54.31	0-54.31	0-18.39
Median	16.95	7.315	6.22
BUN (mg/dL)			
Mean	45.34 ± 31.55	44.78 ± 32.84	10.34 ± 10.36
Range	6-142.5	0-142.5	0-33
Median	34.6	34.5	9.6
Creatinin Serum (mg/dL)			
Mean	2.088 ± 1.98	2.05 ± 2.04	0.528 ± 0.36
Range	0.5 – 11.7	0-11.7	0-1.1
Median	1.5	1.5	0.6

3.3. Results of Urine Measurements of KIM-1, Proenkephalin and Presepsin

The overall results of measuring urine levels of KIM-1, proenkhepalin and presepsin on the first (D1), third (D3) and seventh (D7) examination days are described in Table 7.

Table 7.
Results of measurements of KIM-1, proenkhepalin and presepsin levels.

Biomarker	Biomarker concentration at specific time point		
	D1	D2	D3
Urine KIM-1 (ng/mL)	1.80 ± 0.70	1.618 ± 0.79	1.406 ± 0.559
Proenkephalin (ng/L)	534.981 ± 640.715	729.724 ± 956.026	737.737 ± 1097.725
Presepsin (ng/L)	578.95 ± 1601	369.64 ± 304.21	547.185 ± 512.039

3.4. Accuracy of KIM-1, Proenkhepalin and Presepsin as Diagnostic Predictors and Severity of SA-AKI.

The results of analysis of various biomarkers (KIM-1, Proenkephalin, and Presepsin) to predict diagnostics and severity on the first (D1), third (D3) and seventh (D7) days are described in Table 8.

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For diagnostic predictions, Proenkephalin on the 7th day had the best performance with an AUC of 0.6 and an accuracy of 75.7%. For severity prediction there is also no biomarker that shows striking performance, with AUC and accuracy tending to be low throughout the observation time.

Table 8.
Accuracy test of KIM-1, Proenkhepalin and presepsin as diagnostic predictors and severity of AKI in Sepsis.

	D1			D3			D7		
	KIM-1	**Proen-kephalin**	**Presepsin**	**KIM-1**	**Proenkephalin**	**Presepsin**	**KIM-1**	**Proenkephalin**	**Presepsin**
Diagnostic Predictor									
AUC	0.443	0.586	0.595	0.628	0.409	0.547	0.443	0.6	0.6
Sensitivity	48.4	56.3	58.1	66.7	53.3	53.3	40	80	60
Specifity	45.8	62.5	62.5	57.9	47.4	68.4	85.7	71.4	85.7
Accuracy	47.1	59.4	60.3	62.3	50.35	60.85	62.85	75.7	72.85
Severity Predictor									
AUC	0.304	0.416	0.536	0.32	0.36	0.5	0.25	0.25	0
Sensitivitas	40	60	80	66.7	53.3	53.3	100	100	100
Spesifisitas	38.5	51.9	61.5	57.9	47.4	68.4	20	25	100
Accuracy	39.25	55.95	70.75	62.3	50.35	60.85	60	62.5	100

4. Discussion

4.1. Sepsis, Clinical Characteristics, and Laboratory Research

Sepsis is a medical emergency that involves a systemic inflammatory response to infection. In 2017, 48.9 million cases of sepsis were reported globally with a death toll of 11 million [2]. In Indonesia, the incidence of sepsis was reported to be more than 14 thousand cases in three years with a mortality rate of up to 58.3% [11]. This research was conducted at RSUD Dr. Soetomo Surabaya in January–June 2024 involving 56 subjects who met the inclusion and exclusion criteria.

Acute Kidney Injury (AKI) affected 57.14% of the individuals overall, whereas 42.86% did not. The average age of the subjects was 52.91 years, with 34% being women and 66% being men. AKI individuals were nearly as old (52.72 years) as non-AKI subjects (53.57 years). The study's gender distribution is in line with international research that show men are more likely than women to get sepsis [12, 13]. However, because maternal sepsis is so common in low-income nations like Malawi, women are more susceptible to sepsis [14]. The function of sex hormones like oestrogen, which has a protective impact, and testosterone, which has an immunosuppressive effect, may be one biological mechanism contributing to this discrepancy [15, 16].

Sepsis is the main cause of AKI in critically ill patients [17]. This research shows that 83.93% of AKI cases occur in surgical patients, especially emergency operations. Respiratory (39.1%) and abdominal (31.8%) infections are the main sources of sepsis [11]. Patients with AKI due to lung infection have a worse prognosis than other sources of infection.

This study's clinical and biochemical features of sepsis patients with AKI revealed a number of significant conclusions. In comparison to Zhang's study, which reported a mean score of 9.55 ± 4.17, and Wu's study, which found a median score of 10 (7–13) in the study international multicenter, the mean SOFA score was 5.16 ± 2.52 with a median of 5 (2–13). According to White, et al. [18] and Wu, et al. [19] this indicates potential disparities in severity between the research population and other populations worldwide. According to test data, the majority of individuals had anaemia, with a mean hamoglobin of 8.95 ± 3.68 g/dL. It is well established that low hamoglobin (<10.5 g/dL) raises the risk of AKI in both its early and late stages [20]. The neutrophil to lymphocyte ratio (NLR) is linked to the severity, development, and mortality of AKI in sepsis; the mean neutrophil value was 85.46 ± 9.18%, indicating a considerable increase [21, 22].

Hypoalbuminemia was also observed with a mean albumin level of 2.44 ± 0.53 g/dL, which was an independent predictor of AKI and mortality. Every 10 g/L decrease in albumin increases the risk of AKI by up to 134% [21]. Inflammatory indicators such as CRP and procalcitonin also showed

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increases. CRP had a Mean of 20.49 ± 12.32%, while procalcitonin was 15.61 ± 25.73 ng/mL, both reflecting an active inflammatory process. Elevated CRP and procalcitonin are associated with the severity of AKI [23, 24]. The mean serum creatinine was found to be 2.088 ± 1.98 mg/dL, indicating impaired renal function.

The most frequently found comorbidities were diabetes mellitus at 23.21% and hypertension at 14.29%, which is in line with research by Liu, et al. [25]. Diabetes Mellitus contributes to the risk of AKI through inflammatory mechanisms, glomerular hyperfiltration, and other renal dysfunction [25, 26]. Most of the AKI cases in this study occurred in patients with surgical cases (83.93%), compared with medical cases (16.07%), in accordance with reports that trauma, abdominal, and vascular surgery have the highest risk for postoperative AKI [18, 27]. The most common source of infection was the lungs (46%), followed by the digestive tract (22.1%) and the urinary tract (19.5%). Lung infections are known to be associated with worse renal outcomes than infections from other sources [28].

This study aims to test diagnostic accuracy in detecting AKI (Acute Kidney Injury) through certain biomarkers. Diagnostic tests are used to select the most accurate, efficient, and affordable biomarkers for disease diagnosis and screening. The KIM-1, Proenkephalin and Presepsin biomarkers were tested for their accuracy as diagnostic predictors and severity of AKI in sepsis.

4.2. Diagnostic Predictor

The diagnostic utility of serum proenkhepalin, serum presepsin, and urine biomarkers KIM-1 in predicting the occurrence of AKI in sepsis patients was assessed. Compared to KIM-1 and proenkhepalin, presepsin had the highest AUC on the first day of testing; nevertheless, the results of the kappa test ($p > 0.05$) demonstrated that presepsin was not a significant or an accurate predictor of AKI. Urine KIM-1 had the highest AUC on the third day, however it was still not statistically significant. Despite having superior sensitivity and specificity and an AUC of 0.600 on the seventh day, proenkhepalin and presepsin were not significant predictors of AKI, according to the findings of the kappa test, which indicated a p value > 0.05.

Fluctuations in presepsin levels in the course of sepsis may be caused by the body's attempt to maintain a balance between pro-inflammatory and anti-inflammatory reactions. In this study, the AUC of presepsin reached 0.595 on the first day and 0.600 on the seventh day, but was still not significant. Differences in population characteristics, such as higher CRP levels and the role of invasive surgical procedures, may influence these results. Other factors to consider include alcohol consumption, obesity, and inflammation-related diseases, which can affect presepsin levels [29]. In addition, the biomarker proenkephalin was tested, which is associated with inflammatory mechanisms that can trigger AKI. Proenkephalin showed good accuracy as an early indicator of AKI in sepsis [30] but in this study, although the highest AUC was achieved on the seventh day, the results were not significant. Other studies show differences in threshold values and accuracy of proenkephalin at various times [25, 31]. KIM-1, a biomarker of kidney injury that is elevated in sepsis, was also tested and showed the highest AUC on day 3, but remained nonsignificant. These results indicate that KIM-1 cannot be used as a predictor of AKI in this study population, even though several previous studies showed significant results [27].

Overall, this study suggests that the biomarkers presepsin, proenkephalin, and KIM-1 are not accurate enough to be used as diagnostic predictors of AKI in sepsis in this population, although these biomarkers have significant potential in other conditions. Further research is needed to explore factors influencing these outcomes and determine more appropriate thresholds in the clinical context of AKI in sepsis.

4.3. Severity Predictor

Analysis of the accuracy of urine KIM-1, serum proenkephalin, and presepsin was carried out to predict the severity of AKI in sepsis. The diagnostic test results showed that presepsin had the highest AUC on the first day (AUC 0.536, sensitivity 80%, specificity 61.5%, accuracy 70.75%). However, the

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kappa test ($p > 0.05$) showed that presepsin was not significant and inaccurate as a predictor of AKI severity. Urine KIM-1 and proenkephalin showed lower AUC, with non-significant p values, so they also cannot be used as predictors of AKI severity.

These findings are in line with earlier research, including Shimoyama, which demonstrated variations in presepsin threshold values for identifying sepsis and organ dysfunction associated with sepsis. The requirement for a comprehensive clinical evaluation in the diagnosis of sepsis is indicated by the overlap of presepsin cutoff values, which renders it insufficiently accurate to predict single organ dysfunction [32]. Given the presence of intricate pathophysiological pathways in addition to inflammation, more investigation is required to comprehend the predictive mechanism of presepsin in relation to the severity of AKI in sepsis.

The accuracy of Urine KIM-1 is low in predicting AKI in sepsis and is also ineffective in assessing the severity of AKI. KIM-1 is increased during renal repair and regeneration, which makes it difficult to differentiate between acute injury and recovery. This explains why

KIM-1 cannot be used as a predictor of AKI severity [27]. Proenkephalin showed a strong association with glomerular filtration rate in other studies, but was not shown to be accurate in this study in predicting AKI severity, which requires further research to explain this difference [31, 32].

5. Conclusion

Urine KIM-1, proenkephalin, and presepsin have not been proven to be accurate and and more studies needed to determine diagnostic predictors and severity of SA-AKI.

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Ethical Approval
This study was approved by the Ethics Committee of Soetomo General Academic Hospital (approval number:0874/KEPK/I/2024). Informed consent was obtained for each subject. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Conflicts of Interest:
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Transparency:
The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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