Pak. j. life soc. Sci. (2024), 22(2): 15379-15397 E-ISSN: 2221-7630;P-ISSN: 1727-4915

Pakistan Journal of Life and Social Sciences
www.pjlss.edu.pk

https://doi.org/10.57239/PJLSS-2024-22.2.001114

**RESEARCH ARTICLE**

# Analysis of Kidney Injury Molecule-1 of Urine and Serum Lactate as Predictors of Acute Kidney Injury in Critical Patients

Kashi Ameta Resijiadi Juwono[1]*, Prananda Surya Airlangga[2], Bambang Pujo Semedi[3]

[1,2,3] Clinical Medicine Study Program, Master's Degree, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

***ARTICLE INFO***

Received: Sep 18, 2024

Accepted: Nov 23, 2024

***Keywords***

uKIM-1
Serum Lactate
Acute Renal Injury
Critical Patient

***Corresponding Author**

kashiameta@gmail.com

**ABSTRACT**

About 30% to 60% of critical patients have acute kidney injury. ICU patients have shown a significant rise in mortality rates exceeding 50% due to the combination of acute kidney injury and multiorgan failure. Detecting and intervening in acute kidney injury early is essential for improving patients' outcomes. The current method of diagnosing acute kidney injury relies on elevated serum creatinine levels and reduced urine output, which have limited accuracy. Alternative biomarkers, such as urinary Kidney Injury Molecule-1 (uKIM-1) and serum lactate, show potential for identifying acute kidney injury sooner. The aim of this study was to evaluate the efficiency of using uKIM-1 biomarker in the early detection of acute kidney injury in critically ill patients in the intensive care unit, instead of depending on serum lactate levels. Observational analytical studies with analytical research design with cross-sectional design were conducted to evaluate the potential for early diagnosis of acute kidney injury using the biomarker uKIM-1, compared to serum lactate levels, in critical patients in the ICU. Difference test using Mann-Whitney and correlation test using Spearman test. Analysis of uKIM-1 against creatinine delta was associated ($r=0.433$; $p=0.002$). Analysis of lactate levels against delta creatinine was associated ($r = 0.676$; $p<0.001$). The examination of the difference in mean between uKIM-1 and the occurrence of AKI showed a significant variation ($p = 0.004$). Analysis of the average difference test between lactate levels and AKI events was significantly different ($p< 0.001$). In the ROC test, lactate levels were found to have an AUC of 0.875 with a sensitivity of 93.9% and specificity of 82.4%, and uKIM-1 had an AUC of 0.756 with a sensitivity of 72.7% and specificity of 70.6%. In critical patients in the ICU, the levels of uKIM-1 and lactate can serve as useful tools for the initial diagnosis of AKI. These results are expected to be used as a reference to provide early intervention for AKI patients in the ICU.

## INTRODUCTION

Acute kidney injury (AKI) is a prevalent and severe health issue in critically ill patients, often leading to higher rates of illness and death (Hoste et al., 2018). Approximately 30% to 60% of critical patients have acute kidney injury. The combination of acute kidney injury and multiorgan failure is linked to a mortality rate of over 50% in patients admitted to the ICU (Mohsenin, 2017). Prompt identification and prompt treatment of acute kidney injury is crucial in improving patient results and reducing mortality rates.

So far, the accepted method for diagnosing acute kidney injury has been through high levels of serum creatinine and reduced urine production. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO)

issued guidelines that align with these standards (Ostermann et al., 2020). Both tests have limited accuracy in detecting acute kidney injury and might not provide a precise indication of the immediate deterioration in kidney function (Ricci & Romagnoli, 2018). There is a pressing need for improved diagnostic tools, like biomarkers, to detect acute kidney injury earlier. By identifying kidney damage sooner, interventions can be implemented promptly to halt the advancement of kidney damage and decrease the risks of morbidity and mortality for patients (Wai et al., 2013; Xiao et al., 2022).

Some promising biomarkers for early diagnosis of acute kidney injury are urinary Kidney Injury Molecule-1 (uKIM-1) and serum lactate (Xiao et al., 2022). A number of researches have pinpointed uKIM-1 as a biomarker that is better at predicting and detecting acute kidney injury in its early stages, both in experimental models and human kidney disease (Bonventre, 2008; Huang & Craig Don-Wauchope, 2011; Waanders et al., 2010). One key benefit of uKIM-1 is that it shows high levels during the initial phases of acute kidney injury, enabling prompt action in treating acute kidney injury, sometimes even before serum creatinine levels increase (Kashani et al., 2017; Parikh et al., 2006)

Hemodynamic instability in critically ill patients can trigger anaerobic metabolism, resulting in lactic acidosis and hyperlactatemia, so serum lactate levels are a commonly used marker to assess tissue hypoperfusion (Gutiérrez et al., 2020; Yan et al., 2021). In individuals experiencing serious illnesses, high levels of lactate can be a useful predictor of outcomes, as research has indicated a higher likelihood of severe sickness in those with elevated lactate levels. Nevertheless, there is a lack of research on how serum lactate levels correlate with acute kidney damage in critically ill patients (Junior et al., 2016; Nasu et al., 2021; Radovic et al., 2019; Yan et al., 2021). Data regarding the use of uKIM-1 and serum lactate levels as early diagnostic markers for acute kidney injury is currently inadequate. There have been no studies done to assess how well the biomarker uKIM-1 compares to serum lactate levels in diagnosing acute kidney injury in critical patients. This study aims to investigate the effectiveness of uKIM-1 in early detection of acute kidney injury in ICU patients in contrast to relying on serum lactate levels. The primary objective of this research was to evaluate the accuracy and efficiency of the biomarkers uKIM-1 and serum lactate in predicting acute kidney injury in critically ill patients.

## LITERATURE REVIEW

### Acute Kidney Injury in Critical Patients

In clinical and epidemiologic studies, the criteria for defining acute kidney injury have changed over time. The most up-to-date and preferred definition and scoring system comes from the Kidney Disease: Improving Global Outcomes (KDIGO) organization. (Kellum et al., 2012). Other factors to consider include Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) as well as a revised edition developed by the Acute Kidney Injury Network (AKIN) and various other organizations (Chawla et al., 2017; Kellum et al., 2012; Mehta et al., 2007). The gold standard definition according to the KDIGO criteria emphasizes the importance of kidney function over kidney damage. This means that there may be "false positives," where acute kidney injury is detected despite only mild or "subclinical" damage, and "false negatives." Prerenal acute kidney injury refers to a situation where a temporary decrease in kidney function occurs, usually as a result of low blood pressure, without the detection of acute kidney injury.

### Kidney Injury Molecule-1 (KIM-1)

### KIM-1 Biology

KIM-1 is a protein present in the kidney that has a significant impact on both the damage and healing processes of the kidney (Bailly et al., 2002). Typically, KIM-1 levels are minimal in both the kidney and other body organs. Nevertheless, in instances of kidney damage, specifically following ischemia-reperfusion injury, there is a notable surge in KIM-1 expression (Ichimura et al., 1998). Proximal tubule cells in the kidney are the primary location where KIM-1 is upregulated (Won K Han et al., 2002).

**Role of urinary KIM-1 in acute kidney injury**

Studies investigating the effectiveness of KIM-1 as a biomarker have generated contradictory results. KIM-1 has shown to be a dependable marker for detecting acute kidney injury in patients suffering from congestive heart failure. Individuals with high levels of uKIM-1 are more likely to experience death or require hospitalization, regardless of their kidney function estimates (Ghatanatti et al., 2014). A research study focused on identifying indicators of sudden kidney damage in urine following heart surgery found that the combination of KIM-1 and IL-18 had an AUC of 0.92, outperforming other markers (Hall et al., 2011). Hazle and colleagues' research showed that KIM-1 was not effective as a prognostic marker for children, in contrast to what previous studies found. It was discovered that urinary KIM-1 was not effective in differentiating between patients who experienced positive outcomes and those who had negative outcomes, resulting in its exclusion from additional examination (Hazle et al., 2013).

**Serum Lactate**

Utilizing serum lactate as a diagnostic tool can help identify issues with tissue perfusion and organ function. Elevated levels of lactate can result from an increase in production and a decrease in consumption, leading to hyperlactasemia. Elevated lactate levels indicate an oxygen imbalance between supply and demand, making it a reliable marker for overall and localized perfusion issues (Zhu et al., 2021). A high lactate level on admission indicates tissue hypoxia due to hemodynamic disturbances and thus may be a sign of inadequate renal perfusion (Bakker et al., 2020). Nevertheless, the levels of lactate in the arteries after therapy and the rate at which lactate is cleared from the body may indicate how the patient's circulation is improving.

**Conceptual Framework**

An abrupt decline in kidney function that occurs within a week is referred to as acute kidney injury. The onset of this condition can be influenced by various elements, including individual characteristics like age and existing medical issues, environmental exposures such as sepsis, shock, contrast agents, cardiac surgery, and nephrotoxic drugs, as well as medical interventions such as early diagnosis, drug dose adjustment, hemodynamic support, and avoidance of nephrotoxic drugs. In literature, acute kidney injury is often categorized into three main groups known as prerenal, intrinsic, and postrenal causes.

Acute kidney injury is a process that develops gradually and can be divided into different stages of severity. This process begins with ischemia, an increased risk of cell damage (injury) mainly to the renal tubules, followed by a decline in Glomerular Filtration Rate (GFR), elevated levels of serum creatinine, and decreased output of urine. However, the injury actually begins before the loss of excretory function or decrease in GFR, and this can be detected through the measurement of biomarkers, such as uKIM-1 and serum lactate.

uKIM-1 is a biomarker of KIM-1 that is excreted in the urine. uKIM-1 is mainly found in the inner lining of proximal tubules that have lost differentiation, especially in areas with fibrosis and inflammation. Once injury occurs, KIM-1 may appear in the urine immediately. uKIM-1 could be used as a biomarker for the early detection of CGA, suggesting its potential in this area.

Acute kidney injury occurs when there is a decrease in the amount of blood reaching the kidney, leading to a deprivation of oxygen to the cells (Christin et al., 2023). Hypoxia during this condition inhibits oxygen supply to Krebs cycle reactions, reduces ATP production, and increases glycolysis. This ultimately impairs the ability of the liver and kidneys to excrete waste, thus causing lactate buildup in the bloodstream. Lactate is a universal indicator of inflammatory processes. Surprisingly, before acute kidney injury develops, this phenomenon occurs and indicates that serum lactate may be a useful marker for identifying the condition in its initial phases. People who experience abrupt kidney failure are at a higher risk of

developing chronic kidney issues in the future, which could potentially advance to End-Stage Renal Disease (ESRD) and potentially lead to fatality due to related health issues.

### Research Hypotheses

1. There is an association between urinary KIM-1 and acute kidney injury in critical patients.

2. There is a relationship between serum lactate and acute kidney injury in critical patients.

3. There is a difference in diagnostic value between uKIM-1 and serum lactate in critical patients with acute kidney injury.

## RESEARCH METHOD

This research involved observing and analyzing data, utilizing a research design focused on analysis and cross-sectional observations. The study concentrated on seriously ill individuals who were hospitalized in the intensive care unit at Dr. Soetomo Hospital. The participants were those in the study who satisfied the criteria for inclusion and did not meet the exclusion criteria. The sample size in this study was determined based on the minimum sample size formula Sensitivity and specificity relationship (Buderer, 1996). In previous research, the occurrence rate of sudden kidney damage was recorded at 60% (Mohsenin, 2017). The discovery of uKIM-1 showed that it is 74% sensitive and 85% specific in identifying acute kidney injury (Geng et al., 2021). The alpha value was set at 0.05 and beta at 10%. The minimum sample size for uKIM-1 sensitivity (N1) was 54 samples and uKIM-1 specificity (N2) were 55 samples, with a total of 10% of dropouts being 5, so 50 samples were required. The research sampling method involved selecting participants continuously, with all individuals meeting the criteria being included until the desired number of subjects was reached.

This study included critical patients aged 18-65 years who had been admitted to the ICU for 12 hours or less. Patients were excluded if they had a history of chronic kidney disease, use of nephrotoxic drugs, kidney malignancy, or obstructive uropathy. Subjects were dropped from the study if they voluntarily withdrew, died within 12 hours of ICU treatment, or died before the collection of uKIM-1, serum lactate, and serum creatinine samples. The independent variables in this study were uKIM-1 and serum lactate. In this research, acute kidney injury is the main focus. Factors that could potentially impact the results include age, existing health conditions, when the acute kidney injury began, and the initial treatment received during the first 12 hours in the ICU.

In a span of 12 hours, samples meeting the study's criteria were collected for analysis of uKIM-1 and serum lactate. The information gathered will be documented and organized. In this research, data analysis was carried out using SPSS 17.0. Demographic details such as age, gender, and comorbidities will be analyzed using descriptive statistics. If the data follows a normal distribution, measurement results will be displayed as mean ± standard deviation. Comparing quantitative data within a single group using unpaired t-tests involves presenting non-normally distributed data as a median (range) and analyzing data using the Mann-Whitney test. A p-value lower than 0.05 suggests a notable outcome. Receiver Operating Characteristic (ROC) curves were used to analyze the diagnostic test results for uKIM-1 and serum lactate. From the ROC curve results, Area Under the Curve (AUC) data was obtained. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and accuracy were also correlated using the Youden Index method.

## RESULT AND DISCUSSION

### Characteristics of Research Subjects

The demographic characteristics of the subjects in this study were gender, age, BMI, comorbidities, MAP, LOS, SOFA, Blood Pressure, Hb, WBC, PLT, Bilirubin, Vasopressors and 28-day Mortality. The following table 1 shows the demographic characteristics' findings are displayed using frequency, percentage, and mean with standard deviation.

**Table 1. Demographic characteristics**

| Demography | N (%) | Range | Mean±SD | Normality p-value |
|---|---|---|---|---|
| **Gender** | | | | |
| Male | 32 (64,0%) | - | - | - |
| Female | 18 (36,0%) | - | - | |
| **Age** | 50 (100%) | 24 - 64 | 50,28 ± 11,95 | 0,001 |
| **BMI** | 50 (100%) | 17,78 - 43,09 | 24,17 ± 3,92 | 0,001 |
| **Comorbid** | | | | |
| Exists | 24 (48,0%) | - | - | - |
| Does not exist | 26 (52,0%) | - | - | |
| **HT** | 18 (36,0%) | - | - | - |
| **DM** | 9 (18,0%) | - | - | - |
| **Obesity** | 2 (4,0%) | - | - | - |
| **MAP** | 50 (100%) | 57 – 115 | 91,5 ± 12,41 | 0,160 |
| **LOS** | 50 (100%) | 3 – 34 | 9,88 ± 7,08 | 0,000 |
| **SOFA** | 50 (100%) | 1 – 12 | 6,00 ± 3,18 | 0,004 |
| **TD Systole** | 50 (100%) | 100 - 172 | 130,8 ± 18,53 | 0,200 |
| **TD Diastole** | 50 (100%) | 48 – 92 | 72,98 ± 11,44 | 0,200 |
| **Hb** | 50 (100%) | 6,4 - 16,4 | 11,5 ± 2,37 | 0,200 |
| **WBC** | 50 (100%) | 5590 - 41990 | 16566,2 ± 6748,24 | 0,018 |
| **PLT** | 50 (100%) | 88000 - 572000 | 276480 ± 111211,6 | 0,023 |
| **Bilirubin** | 50 (100%) | 0,1 – 4 | 0,85 ± 0,72 | 0,000 |
| **Vasopressor** | | | | |
| Exists | 23 (46,0%) | - | - | - |
| Does not exist | 27 (54,0%) | - | - | |
| **28 Days Mortality** | | | | |
| Exists | 19 (38,0%) | - | - | - |
| Does not exist | 31 (62,0%) | - | - | |

* Normal if the p value of normality > 0.05

According to the findings in table 1, the spread of general characteristics for gender characteristics of the 50 samples obtained for males as many as 32 (64.0%) while for females as many as 18 (36.0%). For age characteristics of 50 samples the age range is 24 to 64 years with a mean and standard deviation of age 50.28 ± 11.95. For BMI characteristics of 50 samples the age range is 17.78 to 43.09 with a mean and standard deviation of BMI 24.17 ± 3.92.

Table 1 data shows that out of 50 samples with comorbidities, 24 cases (48.0%) had additional clinical characteristics allocated while there were no comorbidities as many as 26 (52.0%), based on the type of comorbidities obtained for HT comorbidities as many as 18 (36.0%), DM as many as 9 (18.0%) and for Obesity as many as 2 (4.0%) samples. In this case, mean arterial pressure (MAP) values ranged from 57 to 115 (mean ± SD: 91.5 ± 12.41), length of stay (LOS) extended from 3 to 34 days (mean ± SD: 9.88 ± 7.08), Sequential Organ Failure Assessment (SOFA) scores varied from 1 to 12 (mean ± SD: 6.00 ± 3.18), systolic blood pressure spanned from 100 to 172 (mean ± SD: 130.8 ± 18.53), and diastolic blood pressure ranged from 48 to 92 (mean ± SD: 72.98 ± 11.44). Laboratory parameters revealed hemoglobin (Hb) values from 6.4 to 16.4 (mean ± SD: 11.5 ± 2.37), white blood cell (WBC) counts from 5,590 to 41,990 (mean ± SD:

16,566.2 ± 6,748.24), platelet (PLT) counts from 88,000 to 572,000 (mean ± SD: 276,480 ± 111,211.6), and bilirubin levels from 0.1 to 4 (mean ± SD: 0.85 ± 0.72).

**Overview of Lactate Levels**

Lactate level values are obtained through serum lactate taken from blood samples of critical patients in the ICU who are treated ≤ 12 hours, to determine whether the lactate level data is normally distributed, a normality test is needed due to its presentation in ratio form. The Kolmogorov-Smirnov test is being used because there are 50 data points in the sample. By conducting a normality test, the researchers can determine the appropriate type of test to use next - if the data follows a normal distribution, parametric methods will be applied; otherwise, non-parametric methods will be used. The descriptive summary of lactate levels and the outcomes of the normality test are presented in Table 2.

**Table 2. Lactate Level Descriptive and Normality Tests**

| | N | Range | Mean±SD | Normality p-value |
|---|---|---|---|---|
| Lactate Levels | 50 | 0,12 – 5,10 | 1,84 ± 1,29 | 0,200 |

*Normal if the p value of normality > 0.05

Based on the results of Table 2 for Lactate levels of 50 samples are in the range of 0.12 to 5.10 with an average or mean value and standard deviation of 1.84 ± 1.29. According to the findings of the normality test using Kolmogorov-Smirnov, the p value is 0.200 where the value is > 0.05, meaning that the distribution of Lactate levels is declared normally distributed.

**Overview of uKIM-1**

The uKIM-1 value is obtained through uKIM-1 taken from urine samples of critical patients in the ICU who are treated ≤12 hours. Due to the fact that the uKIM-1 data is presented as a ratio, it is important to conduct a normality test in order to assess whether the distribution of the uKIM-1 data follows a normal distribution pattern. The normality test chosen for this purpose is the Kolmogorov-Smirnov test, which is suitable for analyzing 50 samples. The normality test assists in determining the appropriate type of test to be conducted next; if the data is deemed to be normally distributed, parametric methods will be utilized for the subsequent test, whereas non-parametric methods will be employed if the data does not exhibit a normal distribution. The following table 3 is a descriptive table of uKIM-1 and the results of the normality test.

**Table 3. uKIM-1 Descriptive and Normality Tests**

| | N | Range | Mean±SD | Normality p-value |
|---|---|---|---|---|
| uKIM-1 | 50 | 0,585 – 1,839 | 1,164 ± 0,299 | 0,200 |

*Normal if the p value of normality > 0.05

Based on the results of table 5.3 for uKIM-1 from 50 samples in the range of 0.585 to 1.839 with an average or mean value and standard deviation of 1.164 ± 0.299. As per the findings of the study the normality test using Kolmogorov- Smirnov, the p value is 0.200 where the value is> 0.05, meaning that the distribution of uKIM-1 is declared normally distributed.

**Delta creatinine overview**

Delta creatinine value is the value of the change in initial creatinine with day 2 creatinine. Since the Delta creatinine data is presented as a ratio, it is crucial to conduct a test for normality in order to ascertain

whether the distribution of this data follows a normal distribution or not. The Kolmogorov-Smirnov test is employed for this purpose due to the sample size of 50 data points. The normality test plays a key role in guiding the selection of the appropriate testing method for the next stage; if the data conforms to a normal distribution, parametric methods will be used, whereas if it does not, non-parametric methods will be applied. The following table 4 is a descriptive table of Delta creatinine and normality test results.

**Table 4. Delta creatinine descriptive and normality test**

| | N | Range | Mean±SD | Normality p-value |
|---|---|---|---|---|
| Delta creatinine | 50 | -0,30 – 2,90 | 0,768 ± 0,683 | 0,000 |

*Normal if the p value of normality > 0.05

Based on the results of table 4 for Delta creatinine from 50 samples in the range of -0.30 to 2.90 where the negative Delta creatinine value means a decrease in creatinine from baseline to day 2 while the positive Delta creatinine value means an increase in creatinine from baseline to day 2, the mean or mean and standard deviation of Delta creatinine is 0.768 ± 0.683. According to the findings of the study, the normality test using Kolmogorov-Smirnov, the p value is 0.000 where the value is <0.05, meaning that the distribution of Delta creatinine is not normally distributed.

**Overview of Acute Kidney Injury (AKI)**

The research identified acute kidney injury (AKI) according to the KDIGO (2012) standards, which involve a rise in serum creatinine levels of over 0.3 mg/dL in 48 hours and a serum creatinine increase of more than 1.5 times the baseline level, believed to have occurred within the past week. The baseline serum creatinine signifies the level of serum creatinine upon admission to the ICU. Table 5 below provides a descriptive overview of AKI in this study.

**Table 5. Descriptive of acute kidney injury (AKI)**

| Acute Kidney Injury (AKI) | N (%) |
|---|---|
| Yes | 33 (66,0%) |
| No | 17 (34,0%) |

In the results of table 5 for the description of the distribution of the incidence of acute kidney injury (AKI) of 50 samples obtained who experienced acute kidney injury (AKI) as many as 33 samples with a percentage of 66.0%, and who did not experience acute kidney injury (AKI) as many as 17 samples with a percentage of 34.0%.

**Demographic Test with Acute Kidney Injury (AKI)**

The study also examines the demographic traits, including both general and clinical factors, to determine whether they are linked to the occurrence of acute kidney injury (AKI). The following table 6 shows the descriptive results and tests of demographic characteristics with acute kidney injury (AKI).

**Table 6. Descriptive and test of demographic characteristics with acute kidney injury (AKI)**

| Demography | n | Acute Kidney Injury (AKI) | | p value |
|---|---|---|---|---|
| | | Yes | No | |
| **Gender** | | | | |
| Male | 32 | 23 (71,9%) | 9 (28,1%) | 0,391 |
| Female | 18 | 10 (55,6%) | 8 (44,4%) | |
| **Age** | 50 | 50,79 ± 12,60 | 49,29 ± 10,88 | 0,400 |

| | | | | |
|---|---|---|---|---|
| **BMI** | 50 | 24,83 ± 4,39 | 22,90 ± 2,43 | 0,095 |
| **Comorbid** | | | | |
| Exists | 24 | 16 (66,7%) | 8 (33,3%) | 1,000 |
| Does not exist | 26 | 17 (65,4%) | 9 (34,6%) | |
| **MAP** | 50 | 91,82 ± 11,84 | 90,88 ± 13,82 | 0,804 |
| **LOS** | 50 | 9,21 ± 6,39 | 11,18 ± 8,33 | 0,338 |
| **SOFA** | 50 | 6,88 ± 3,19 | 4,29 ± 2,42 | 0,007 |
| **TD Systole** | 50 | 130,88 ± 18,59 | 130,65 ± 18,97 | 0,967 |
| **TD Diastole** | 50 | 73,18 ± 11,06 | 72,59 ± 12,48 | 0,864 |
| **Hb** | 50 | 11,19 ± 2,47 | 12,09 ± 2,10 | 0,211 |
| **WBC** | 50 | 18350,91 ± 7094,86 | 13101,76 ± 4412,06 | 0,011 |
| **PLT** | 50 | 272787,88 ± 116196,97 | 283647,06 ± 103879,10 | 0,580 |
| **Bilirubin** | 50 | 0,964 ± 0,824 | 0,616 ± 0,406 | 0,048 |
| **Vasopressor** | | | | |
| Exists | 23 | 19 (82,6%) | 4 (17,4%) | 0,047 |
| Does not exist | 27 | 14 (51,9%) | 13 (48,1%) | |
| **28 Days Mortality** | | | | |
| Exists | 19 | 16 (84,2%) | 3 (15,8%) | 0,069 |
| Does not exist | 31 | 17 (54,8%) | 14 (45,2%) | |

*Significant if p value <0.05

After analyzing the data in Table 6, the test results indicate a correlation between general demographic characteristics and the occurrence of acute kidney injury (AKI), the p value for gender p=0.391, age p=0.400 and BMI p=0.095 where the value is> 0.05 which means that there is no relationship between general demographic characteristics of gender, over and BMI with acute kidney injury (AKI).

As seen in the findings from the analysis presented in Table 6, there was an examination of the relationship between clinical demographic characteristics and acute kidney injury (AKI), the p value for comorbid p = 0.000, MAP p = 0.804, LOS p = 0.338, BP systole p = 0.967, BP diastole p = 0.864, Hb p = 0.211, PLT p = 0,580 and 28-day mortality p=0.067 where the value > 0.05 which means that there is no relationship between clinical demographic characteristics of comorbid, MAP, LOS, Blood pressure, Hb, PLT, and clinical 28-day mortality with acute kidney injury (AKI).

Based on the findings in table 6, there was an examination of the clinical demographic traits associated with the occurrence of acute kidney injury (AKI), the p value for SOFA p=0.007, WBC p=0.011, Bilirubin p=0.048, and Vasopressors p=0.047 where the value is <0.05 which means that there is an association between clinical demographic characteristics of SOFA, WBC, Bilirubin. Based on the descriptive mean value of SOFA, WBC, Bilirubin obtained in subjects with acute kidney injury (AKI), the worth is higher for individuals with acute kidney injury (AKI) than for those without, whereas Vasopressors were most commonly used by individuals with AKI based on the percentage achieved.

**Analysis of the Relationship Test of Lactate and uKIM-1 with Delta Creatinine**

Test the relationship between lactate and uKIM-1 levels with delta creatinine using the Spearman test because the data on delta creatinine levels were declared abnormal during the data normality test. Table 7 displays the findings of the examination on the link between lactate levels and uKIM-1 with delta creatinine.

**Table 7. Relationship test of lactate and uKIM-1 levels with delta creatinine**

| | N | r | p value | Description |
|---|---|---|---|---|
| Lactate with Delta creatinine | 50 | 0,676 | 0,000 | Related |
| uKIM-1 with Delta creatinine | 50 | 0,433 | 0,002 | Related |

*Related if the p value <0.05

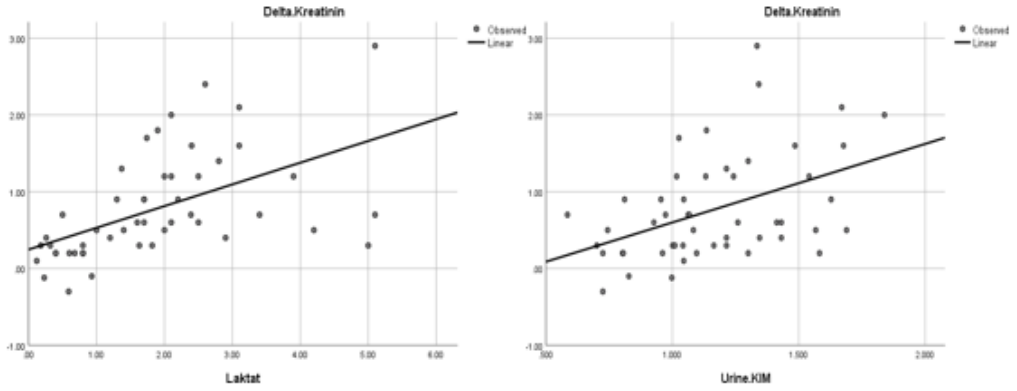


**Figure 1. Scatterplot lactate and uKIM-1 levels with delta creatinine**

According to the findings shown in Table 7, the test results indicate a correlation between lactate and uKIM-1 levels with delta creatinine when using the Spearman test, the p value is 0.000 and 0.002 where the value is <0.05, which means that the connection between lactate and uKIM-1 levels and Delta creatinine is important and notable. Based on the test results, the correlation coefficient or r value is 0.676 and 0.433 where the value is positive, which means that the relationship between lactate and uKIM-1 levels with delta creatinine is unidirectional, which means that when lactate and uKIM-1 levels are high, the initial creatinine change to day 2 will also increase and vice versa. The correlation coefficient, also known as the r value, indicates the strength of the connection between lactate levels and uKIM-1 with delta creatinine. The findings suggest a strong relationship with values of 0.676 and 0.433, equivalent to 67.6% and 43.3%. This implies that the association between the variables falls into the strong category for lactate levels and delta creatinine, while it is categorized as moderate for uKIM-1 with Delta creatinine.

**Comparative Test Analysis of Lactate and uKIM-1 based on Acute Kidney Injury (AKI)**

Comparative test of lactate and uKIM-1 levels based on acute kidney injury (AKI) using the T Test because the data on lactate and uKIM-1 levels were declared normal during the data normality test. Comparison test of lactate and uKIM-1 levels based on AKI to see if the value of lactate and uKIM-1 levels in subjects with AKI is different from subjects without AKI by statistical test. The following table 8 shows the results of the Lactate and uKIM-1 comparison test based on acute kidney injury (AKI).

**Table 8. Comparison test of lactate and uKIM-1 based on acute kidney injury (AKI)**

| | n | Acute Kidney Injury (AKI) | | p-value | Description |
|---|---|---|---|---|---|
| | | Yes (*Mean* ± SD) | No (*Mean ± SD*) | | |
| **Lactate** | 50 | 2,299 ± 1,125 | 0,947 ± 1,141 | 0,000 | Significantly Different |
| **uKIM-1** | 50 | 1,248 ± 0,297 | 1,000 ± 0,232 | 0,004 | Significantly Different |

*Different if p value <0.05

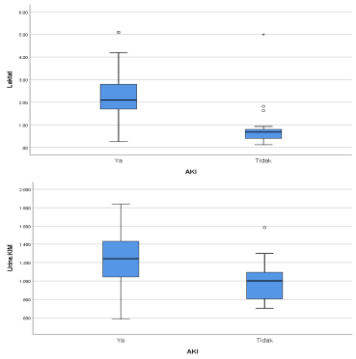


**Figure 2. Lactate and uKIM-1 levels based on acute kidney injury (AKI)**

According to table 8, the comparison test between lactate levels and uKIM-1 for acute kidney injury (AKI) yielded p values of 0.000 and 0.002 through the T test, both of which are less than 0.05 which means there is a significant / meaningful difference in lactate levels and uKIM-1 based on acute kidney injury (AKI), Based on the results for lactate levels, the mean value and standard deviation in subjects with acute kidney injury (AKI) was 2.299 ± 1.125, while those without acute kidney injury (AKI) was 0.947 ± 1.141 which can be concluded that lactate levels in patients with acute kidney injury (AKI) will be higher when compared to those without acute kidney injury (AKI). Likewise, for uKIM-1, the mean and standard deviation values were obtained in subjects with acute kidney injury (AKI) 1.248 ± 0.297, while those without acute kidney injury (AKI) 1.000 ± 0.232, which can be concluded that uKIM-1 in patients with acute kidney injury (AKI) will be higher when compared to those without acute kidney injury (AKI).

**Analysis of Lactate and uKIM-1 Diagnostic Test based on Acute Kidney Injury (AKI)**

The diagnostic test of lactate and uKIM-1 levels based on acute kidney injury (AKI) uses the ROC Curve test where the diagnostic test can determine the AUC value, cut off, sensitivity, specificity and OR value at Lactate and uKIM-1 levels based on the incidence of AKI. Table 9 below displays the findings from the comparison study analyzing levels of lactate and uKIM-1 in relation to acute kidney injury (AKI).

**Table 9. Diagnostic Test of Lactate and uKIM-1 based on acute kidney injury (AKI)**

| | N | p-value | AUC | Cut Off | Sensitivity | Specificity | OR (C195%) |
|---|---|---|---|---|---|---|---|
| Lactate | 50 | 0,000 | 0,875 | >0,93 | 93,9% | 82,4% | 72,333 (10,849 – 482,281) |
| uKIM-1 | 50 | 0,000 | 0,756 | >1,045 | 72,7% | 70,6% | 6400 (1,754 – 23,351) |

*Significant if p value <0.05

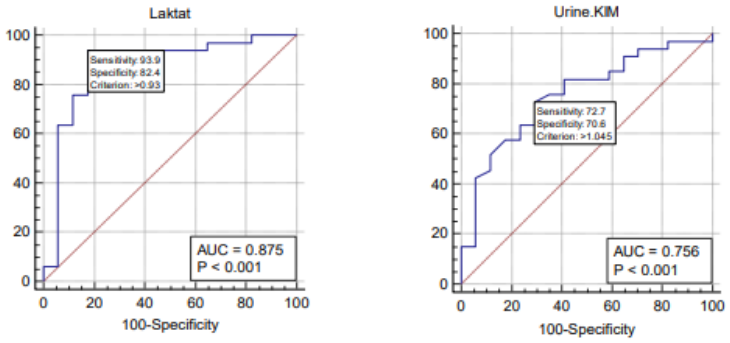


**Figure 3. lactate and uKIM-1 levels based on acute kidney injury (AKI)**

Based on Table 9, the diagnostic test results of lactate levels for acute kidney injury (AKI) using ROC Curve analysis showed a p-value of 0.000, which is < 0.05, indicating statistical significance. The diagnostic test yielded an AUC value of 0.875, suggesting that lactate levels have an 87.5% strength in predicting AKI. The ROC test determined a lactate level cut-off point for AKI of > 0.93, with a sensitivity of 93.9% and specificity of 82.4%, leading to an OR of 72.333 (95% CI: 10.849 - 482.281).

Based on Table 9, the diagnostic test results of uKIM-1 for AKI with ROC Curve analysis showed a p-value of 0.000, which is < 0.05, indicating statistical significance. The diagnostic test yielded an AUC value of 0.756, suggesting that uKIM-1 has a 75.6% strength in predicting acute kidney injury (AKI). The ROC test determined a uKIM-1 cut-off point for AKI of > 1.045, with a sensitivity of 72.7% and specificity of 70.6%, leading to an OR of 6.400 (95% CI: 1.754 - 23.351).

## DISCUSSION

### Demographic Characteristics of Acute Kidney Injury

The study aimed to investigate the relationship between uKIM-1 and serum lactate levels in individuals experiencing severe acute kidney injury. Analysis of demographic information revealed no significant correlation between age, gender, BMI, and the likelihood of experiencing acute kidney injury. In a study conducted by Shi and colleagues last year, it was indicated that people with BMI levels outside the normal range of 18.5 to 24.0 had an increased likelihood of developing AKI. The risk of AKI was 1.68 times greater for those with a BMI below 18.5 and 1.43 times higher for individuals with a BMI of 28.0 or higher (Shi et al., 2020). The idea of the "obesity paradox" refers to the phenomenon where critically ill obese patients have survival rates that are as good as or even better than non-obese patients. One possible reason for this occurrence is that overweight individuals might possess metabolic or nutritional resources that enhance their ability to endure sickness, leading to higher chances of survival (Tobias & Hu, 2013). Research involving 940 participants from various medical facilities revealed no connection between obesity (BMI > 30 kg/m2) and an increased risk of major complications during transcatheter aortic valve procedure. However, individuals who were obese had a higher incidence of CS-AKI (stage I). A different research project with 13,637 participants from different hospitals demonstrated that a higher body mass index (BMI) was linked to an increased likelihood of experiencing major complications following surgery, especially acute kidney failure and pneumonia (Ghanta et al., 2017).

In their study conducted in 2023, Privratsky et al. found that out of 390,382 patients, 25,809 individuals (6.6%) experienced postoperative AKI. This included 2,190 of 58,585 women aged 50 years or younger (3.7%), 9,320 of 144,047 women older than 50 years (6.5%), 3,289 out of 55,503 men aged 50 years or younger (5.9%), and 11,010 of 132,447 men older than 50 years (8.3%). After adjusting for risk factors for AKI, women over 50 had a higher likelihood of developing AKI compared to younger women (odds ratio, 1.51; 95% CI, 1.43-1.59). Meanwhile, men under 50 had a higher odds ratio of 1.90 (95% CI, 1.79-2.01) and men over 50 had the highest odds ratio of 2.06 (95% CI, 1.96-2.17). In younger women, the chances of MMR decreased, while they increased as women grew older (Privratsky et al., 2023). The literature varies from the findings of this study because the sample sizes and comorbid conditions of the patients are different.

The correlation between the onset of acute kidney damage and specific elements like vasopressors, SOFA score, and bilirubin levels has been widely recognized. Studies have conflicting opinions on whether norepinephrine, a common treatment for septic shock in AKI patients, may have negative effects on kidney function. In sepsis, vasopressin depletion occurs so that vasopressin administration is one of the options in increasing blood pressure in sepsis shock, especially for AKI patients (Gunardi, 2013). Lauzier et al, in their study using creatinine clearance as a measure of kidney function, discovered that vasopressin had a notable impact on creatinine clearance within the initial 24-hour period. This increase in creatinine clearance was not found with norepinephrine (Lauzier et al., 2006). Gordon and colleagues discovered that the application of vasopressin had a notable impact on slowing down the advancement of renal failure

when compared to norepinephrine (Gordon et al., 2010). In risk category AKI patients, the use of vasopressin significantly reduced serum creatinine compared to norepinephrine. Vasopressin is better at improving renal function than norepinephrine, especially in risk category AKI patients. Vasopressin causes constriction of the arterioles that carry blood away from the kidneys, leading to an increase in the rate at which the kidneys filter blood. This increase can be measured by higher levels of creatinine being cleared from the body. Vasopressin can also activate oxytocin receptors and release atrial natriuretic peptide resulting in natriuresis.3 Improved renal function is also associated with lower SOFA scores in patients given vasopressin compared to norepinephrine. Improvement in SOFA score reduced mortality more in patients receiving vasopressin than norepinephrine (Gunardi, 2013).

**Effect of uKIM-1 on Delta Creatinine and AKI**

The Spearman correlation test was carried out on the uKIM-1 and delta creatinine variables and the results were found to be significantly related. The connection between uKIM-1 and delta creatinine only goes in one direction - when uKIM-1 levels are elevated, there will be an increase in creatinine levels from baseline to day 2. The mean difference test also found significant results between uKIM-1 in patients with AKI and those without. uKIM-1 was found to be higher in the group with AKI.

Geng and colleagues, in their 2021 study, discovered a similar finding from a compilation of 14 studies involving 3300 patients. In the study, it was discovered that urinary KIM-1 (uKIM-1) showed a sensitivity of 0.74 (95% CrI 0.62-0.84) and a specificity of 0.84 (95% CrI, 0.76-0.90) when diagnosing AKI. The combined diagnostic odds ratio (DOR) was calculated to be 15.22 (95% CrI, 6.74-42.20), with a RD of 0.55 (95% CrI 0.43-0.70) and an AUC of 0.62 (95% CrI 0.41-0.76) for uKIM-1 in diagnosing AKI. Results from subgroup analysis highlighted the influence of various factors on the diagnosis. uKIM-1 in adult patients shows promising results as a dependable indicator for AKI detection, boasting high sensitivity and specificity (Geng et al., 2021).

Kim-1, a protein found in the kidneys, plays a crucial role in the progression of kidney injury and recovery (Bailly et al., 2002). Typically, the levels of KIM-1 are minimal in the kidney and various organs. Nevertheless, in instances of kidney damage, particularly following ischemia-reperfusion injury, there is a notable rise in KIM-1 expression (Ichimura et al., 1998). The primary site of upregulation of KIM-1 is in the cells of the proximal tubule of the kidney (Won K Han et al., 2002).

Studies conducted in the adult population have revealed that evaluating KIM-1 levels in urine may provide advantages in differentiating individuals with acute tubular necrosis, a particular type of kidney injury, from those without this condition (Liangos et al., 2007; van Timmeren et al., 2007). Moreover, increased concentrations of KIM-1 found in urine have been associated with negative outcomes in medical situations, such as the necessity for dialysis and greater rates of mortality (W K Han et al., 2008). KIM-1 has demonstrated promise as an indicator for identifying nephrotoxicity in early stage clinical trials 1 and 2, as well as in pre-clinical studies (Dieterle et al., 2010; Vaidya et al., 2010). KIM-1 has been authorized by the FDA as a marker for pre-clinical drug development due to its ability to signal kidney injury in the early stages (Dieterle et al., 2010). An additional method has been created to test for KIM-1 using a dipstick, offering a quick and easy way to measure its levels in urine. This test gives approximate results in a short amount of time, making it a convenient option for detecting kidney damage in a medical environment (Fuchs et al., 2012; Vaidya et al., 2010).

The uKIM-1 variable was subjected to the ROC test to assess its effectiveness in diagnosing AKI. The test showed an AUC of 0.756, indicating moderate accuracy. The sensitivity was calculated to be 72.7%, while the specificity was 70.6%. The results indicate that the uKIM-1 variable could be a valuable predictor for the occurrence of AKI among critically ill patients. This study's results support the findings of Shao et al, which proposed the use of urine KIM-1 for the detection of AKI, showing a sensitivity of 0.74 and specificity of 0.86. Shao et al's study involved patients of various ages. Moreover, the combined DOR was 15.22 (95% CrI, 6.74-42.20), indicating that uKIM-1 is highly effective in diagnosing AKI (Shao et al., 2014). A higher

diagnostic odds ratio suggests better test performance when the diagnostic odds ratio is larger than 1 (Shao et al., 2014). The marked intersection points show variations in the accuracy and effectiveness among the research papers analyzed, with some studies presenting slightly different outcomes.

Research has revealed that uKIM-1 is highly effective in detecting acute kidney injury. The FDA has approved KIM-1 as a dependable indicator for acute kidney injury when trials for new medications begin (Dieterle et al., 2010). Using uKIM-1 has the benefit of detecting acute kidney injury in its early stages, prior to any noticeable changes in serum creatinine levels, enabling prompt intervention (Kashani et al., 2017). Many research studies suggest that uKIM-1 could be used as a reliable indicator of acute kidney damage and an effective predictor of patient prognosis (Bonventre, 2008). Research on KIM-1 as an indicator has produced varied outcomes. KIM-1 has been found to be a dependable indicator for detecting instances of acute kidney injury in patients with congestive heart failure (Damman et al., 2011). Elevated levels of uKIM-1 have also been linked to an increased likelihood of mortality or need for hospitalization among these individuals, irrespective of their predicted kidney function (Ghatanatti et al., 2014). A research investigating 32 indicators of kidney damage in urine following heart surgery found that when KIM-1 and IL-18 were combined, they had an AUC of 0.92, surpassing the effectiveness of other markers (Hall et al., 2011). Hazle and colleagues' research diverged from earlier studies by concluding that KIM-1 was not an effective prognostic indicator for children. Urinary KIM-1 was found to be inadequate in differentiating between patients with positive or negative outcomes, leading to its exclusion from further examination (Hazle et al., 2013).

There is not enough evidence to fully comprehend the function of KIM-1 in critically ill patients suffering from acute kidney injury. Research on the potential of new markers like KIM-1 in this patient population is scarce. However, the small number of studies conducted so far do indicate that KIM-1 levels might have predictive value for determining the necessity for Renal Replacement Therapy (RRT) and predicting 7-day mortality in critically ill patients with acute kidney injury (Gonzalez & Vincent, 2012). A recent investigation in pediatrics examined 252 patients in the emergency department, revealing that monitoring KIM-1 levels could help predict the development of acute kidney injury (Abdallah et al., 2013). The significance of KIM-1 in various phases of kidney disease holds importance for individuals in emergency and critical care situations, with several research studies indicating that KIM-1 has the capability to differentiate between patients with varying forms of acute tubular necrosis as opposed to those without AKI (Medić et al., 2015). Thus far, there hasn't been a single biomarker that has been adopted across the board for everyday clinical use, as each biomarker comes with its own set of strengths and weaknesses (Pickkers et al., 2021). An expanding group of researchers have proposed a set of kidney-specific markers that can reveal both functional and structural harm as well as healing potential (Yerramilli et al., 2016).

**Effect of Lactate on Delta creatinine and AKI**

Spearman correlation test was conducted on lactate and delta creatinine variables and the results were found to be significantly related. The connection between lactate and delta creatinine is one way, indicating that an elevation in lactate levels will result in an increase in creatinine levels between baseline and day 2. The mean difference test also found significant results between lactate in patients with AKI and those without. Lactate was found to be higher in the group with AKI. In accordance with research carried out by Wang et al in 2022, it was discovered that those in the acute kidney injury group showed higher levels of age ($p = 0.016$), serum creatinine ($p < 0.001$), and lactate ($p < 0.001$) in comparison to individuals in the non-AKI group. TBI patients show a correlation between AKI and serum lactate levels in the early stages of their condition. Physicians have the ability to determine the risk of AKI in TBI patients by monitoring their lactate levels (Wang et al., 2022). Recognized as a sign of decreased blood flow in the body, levels of serum lactate often rise in critically ill individuals with different conditions. Numerous research studies have noted a surge in serum lactate levels following traumatic brain injury (TBI) and have investigated the link between high lactate levels and the outlook for patients with TBI (Dübendorfer et al., 2013; Fu et al., 2019; Wettervik et al., 2020).

Hidayatullah and his colleagues made a groundbreaking discovery in 2022 when they found a connection between higher levels of serum lactate and the onset of AKI. They concluded that the likelihood of AKI occurring is directly related to the fluctuations in serum lactate levels. A higher concentration of serum lactate has been linked to an increased likelihood of developing AKI (Hidayatullah et al., 2022). Radovic and colleagues observed an increase in serum lactate levels in patients with AKI after undergoing significant surgical procedures. Their research also indicated that the actual levels of lactate could serve as a reliable indicator for AKI in cardiac surgery patients with a low risk of developing AKI, showing an odds ratio of 2.7 [1.4-4.9] 24 hours after CPB. When the concentration of serum lactate reaches 4 mmol/L, there is a significant increase in the risk of AKI, with an odds ratio of 6.3 [1.9-20.5] (Radovic et al., 2019). In the same way, Wang and his team found a connection between elevated serum lactate levels in the initial period and the chances of developing AKI in severe traumatic brain injury patients (Wang et al., 2022).

Serum lactate is a valuable indicator for detecting insufficient blood flow to tissues and dysfunction in organs. Hyperlactasemia is a result of increased production and reduced consumption of lactate. Elevated levels of lactate indicate an oxygen imbalance between supply and demand, making it a reliable biomarker for overall and localized inadequate blood flow (Zhu et al., 2021). An elevated lactate level suggests that there may be tissue hypoxia resulting from disruptions in blood flow, potentially signaling insufficient blood supply to the kidneys (Bakker et al., 2020). Nonetheless, the levels of lactate in the arteries after treatment and the rate at which lactate is cleared from the body may show changes in blood flow in patients. Elevated lactate levels could also signal a reaction to stress, with the heightened activity of the sympathetic nervous system contributing to the onset of sudden kidney damage (Garcia-Alvarez et al., 2014). Stimulation of β2 receptors leads to a surge in adrenaline production, triggering higher pyruvate levels that overwhelm the enzyme pyruvate dehydrogenase, leading to a metabolic shift and elevated lactate levels. Patients suffering from acute kidney injury tend to have elevated glucose levels upon admission, which further rise in stressful situations. According to a study by Jorge and his colleagues, elevated levels of lactate and glucose may indicate potential kidney damage in critically ill patients (Freire Jorge et al., 2017).

The ROC examination was carried out on the lactate indicator to detect AKI, yielding an AUC of 0.875, a sensitivity of 93.9%, and a specificity of 82.4%. These findings are robust in anticipating the emergence of AKI in critically ill individuals. This outcome aligns with research performed by Yu et al in 2023, revealing an AUC of 0.756 for the forecast of off-pump CABG-related AKI utilizing 12-hour postoperative arterial lactate, with a threshold of 1.85. The forecast model containing various risk factors demonstrated strong predictive performance with an AUC of 0.846. An established prognostic indicator for AKI related to off-pump CABG is the 12-hour post-surgery arterial lactate level (Yu et al., 2023). Arterial lactate serves as a quick and easily obtainable measure. Deficiencies in blood volume and issues with tiny blood vessels can result in reduced blood flow to tissues, causing low oxygen levels and elevated lactate levels. Prolonged elevation in lactate levels is strongly linked to organ dysfunction (Jansen et al., 2009). Furthermore, AKI could lead to increased levels of lactate. According to Legouis and his team, alterations in renal gluconeogenesis in the presence of AKI could potentially impact overall metabolism and worsen mortality rates (Legouis et al., 2020). A recent investigation discovered a notable rise in blood lactate levels and a decrease in lactate clearance rate in rats experiencing renal ischemia-reperfusion injury. Those who have AKI are at a higher risk for metabolic imbalances, such as low to normal glucose levels or elevated lactate, which can lead to higher mortality rates. Additionally, the research suggests that vitamin supplements may lower mortality rates in AKI patients by improving both lactate clearance and glucose production. Lactate serves as a crucial indicator for assessing tissue perfusion in patients who are critically ill. Elevated levels of arterial lactate may indicate a disarray in tissue oxygen metabolism, leading to the onset of AKI. According to the research conducted by Lopez-Delgado and team, arterial lactate levels measured 24 hours after surgery independently influenced the risk of CSA-AKI (Lopez-Delgado et al., 2013). Zhang and his team discovered that the standardized lactate burden was linked to CSA-AKI on its own (Zhang & Ni, 2015). A study with 100 patients at low risk found that measuring lactate levels after surgery can accurately predict the likelihood of developing CSA-AKI (Radovic et al., 2019).

## CONCLUSION

The findings of the research that has been carried out lead to the following conclusions in this study:

1. In critical patients, there is a notable correlation between uKIM-1 levels and the development of acute kidney injury.

2. In critically ill patients, there is a notable correlation between serum lactate levels and the onset of acute kidney injury.

3. Serum lactate is more effective for diagnosis in critically ill patients with acute kidney injury compared to uKIM-1.

### Suggestion

For future similar studies, researchers are expected to use more time and coverage of a larger amount of data and involve more confounding variables in analyzing the correlation between variables, it is also hoped that this study can be used by other researchers as a reference and information.

## REFERENCES

Abdallah, E., Waked, E., Al-Helal, B., Asad, R., Nabil, M., & Harba, T. (2013). Novel troponin-like biomarkers of acute kidney injury. *Saudi Journal of Kidney Diseases and Transplantation*, *24*(6), 1111–1124. https://doi.org/10.4103/1319-2442.121267

Bailly, V., Zhang, Z., Meier, W., Cate, R., Sanicola, M., & Bonventre, J. V. (2002). Shedding of kidney injury molecule-1, a putative adhesion protein involved in renal regeneration. *Journal of Biological Chemistry*, *277*(42), 39739–39748. https://doi.org/10.1074/jbc.M200562200

Bakker, J., Postelnicu, R., & Mukherjee, V. (2020). Lactate: where are we now? *Critical Care Clinics*, *36*(1), 115–124. https://doi.org/10.1016/j.ccc.2019.08.009

Bonventre, J. V. (2008). Kidney Injury Molecule-1 (KIM-1): a specific and sensitive biomarker of kidney injury. *Scandinavian Journal of Clinical and Laboratory Investigation*, *68*(sup241), 78–83. https://doi.org/10.1080/00365510802145059

Buderer, N. M. F. (1996). Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. *Academic Emergency Medicine*, *3*(9), 895–900. https://doi.org/10.1111/j.1553- 2712.1996.tb03538.x

Chawla, L. S., Bellomo, R., Bihorac, A., Goldstein, S. L., Siew, E. D., Bagshaw, S. M., Bittleman, D., Cruz, D., Endre, Z., & Fitzgerald, R. L. (2017). Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nature Reviews Nephrology*, *13*(4), 241–257. https://doi.org/10.1038/nrneph.2017.2

Christin, T., Ali, Z., Legiran, L., & Ferawaty, F. (2023). Overview Of Peripheral Neuropathy In Chronic Kidney Disease Patients Undergoing Hemodialysis At Dr. Mohammad Hoesin Hospital Palembang. *Pharmacology, Medical Reports, Orthopedic, And Illness Details (COMORBID)*, *2*(3), 1–18. https://doi.org/10.55047/comorbid.v2i3.890

Damman, K., Masson, S., Hillege, H. L., Maggioni, A. P., Voors, A. A., Opasich, C., van Veldhuisen, D. J., Montagna, L., Cosmi, F., & Tognoni, G. (2011). Clinical outcome of renal tubular damage in chronic heart failure. *European Heart Journal*, *32*(21), 2705–2712. https://doi.org/10.1093/eurheartj/ehr190

Dieterle, F., Perentes, E., Cordier, A., Roth, D. R., Verdes, P., Grenet, O., Pantano, S., Moulin, P., Wahl, D., & Mahl, A. (2010). Urinary clusterin, cystatin C, β2-microglobulin and total protein as markers to detect drug-induced kidney injury. *Nature Biotechnology*, *28*(5), 463–469. https://doi.org/10.1038/nbt.1622

Dübendorfer, C., Billeter, A. T., Seifert, B., Keel, M., & Turina, M. (2013). Serial lactate and admission SOFA scores in trauma: an analysis of predictive value in 724 patients with and without traumatic brain

injury. *European Journal of Trauma and Emergency Surgery*, *39*, 25–34. https://doi.org/10.1007/s00068-012-0212-z

Freire Jorge, P., Wieringa, N., de Felice, E., van der Horst, I. C. C., Oude Lansink, A., & Nijsten, M. W. (2017). The association of early combined lactate and glucose levels with subsequent renal and liver dysfunction and hospital mortality in critically ill patients. *Critical Care*, *21*, 1–11. https://doi.org/10.1186/s13054-017-1785-z

Fu, Y., Bai, K., & Liu, C. (2019). The impact of admission serum lactate on children with moderate to severe traumatic brain injury. *PloS One*, *14*(9), e0222591. https://doi.org/10.1371/journal.pone.0222591

Fuchs, T. C., Frick, K., Emde, B., Czasch, S., Landenberg, F. von, & Hewitt, P. (2012). Evaluation of novel acute urinary rat kidney toxicity biomarker for subacute toxicity studies in preclinical trials. *Toxicologic Pathology*, *40*(7), 1031–1048. https://doi.org/10.1177/0192623312444618

Garcia-Alvarez, M., Marik, P., & Bellomo, R. (2014). Stress hyperlactataemia: present understanding and controversy. *The Lancet Diabetes & Endocrinology*, *2*(4), 339–347. https://doi.org/10.1016/S2213-8587(13)70154-2

Geng, J., Qiu, Y., Qin, Z., & Su, B. (2021). The value of kidney injury molecule 1 in predicting acute kidney injury in adult patients: a systematic review and Bayesian meta-analysis. *Journal of Translational Medicine*, *19*, 1–13. https://doi.org/10.1186/s12967-021-02776-8

Ghanta, R. K., LaPar, D. J., Zhang, Q., Devarkonda, V., Isbell, J. M., Yarboro, L. T., Kern, J. A., Kron, I. L., Speir, A. M., & Fonner, C. E. (2017). Obesity increases risk-adjusted morbidity, mortality, and cost following cardiac surgery. *Journal of the American Heart Association*, *6*(3), e003831. https://doi.org/10.1161/JAHA.116.003831

Ghatanatti, R., Teli, A., Tirkey, S. S., Bhattacharya, S., Sengupta, G., & Mondal, A. (2014). Role of renal biomarkers as predictors of acute kidney injury in cardiac surgery. *Asian Cardiovascular and Thoracic Annals*, *22*(2), 234–241. https://doi.org/10.1177/0218492313502028

Gonzalez, F., & Vincent, F. (2012). Biomarkers for acute kidney injury in critically ill patients. *Minerva Anestesiologica*, *78*(12), 1394–1403.

Gordon, A. C., Russell, J. A., Walley, K. R., Singer, J., Ayers, D., Storms, M. M., Holmes, C. L., Hébert, P. C., Cooper, D. J., & Mehta, S. (2010). The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Medicine*, *36*, 83–91. https://doi.org/10.1007/s00134-009-1687-x

Gunardi, H. (2013). Efektivitas Vasopresin dan Norepinefrin dalam Memperbaiki Fungsi Ginjal pada Pasien Syok Sepsis yang Disertai Acute Kidney Injury. *EJournal Kedokteran Indonesia*, *1*(3), 59478. https://doi.org/10.23886/ejki.1.3006

Gutiérrez, H. B., Concepción, Y. A., Pérez, J. S., Lara, Y. D., López, F. M. R., & Contreras, P. R. (2020). Prognostic value of serum lactate levels in critically ill patients in an intensive care unit. *The Journal of Critical Care Medicine*, *6*(1), 59–64. https://doi.org/10.2478/jccm-2020-0005

Hall, I. E., Coca, S. G., Perazella, M. A., Eko, U. U., Luciano, R. L., Peter, P. R., Han, W. K., & Parikh, C. R. (2011). Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. *Clinical Journal of the American Society of Nephrology*, *6*(12), 2740–2749. https://doi.org/10.2215/CJN.04960511

Han, W K, Waikar, S. S., Johnson, A., Betensky, R. A., Dent, C. L., Devarajan, P., & Bonventre, J. V. (2008). Urinary biomarkers in the early diagnosis of acute kidney injury. *Kidney International*, *73*(7), 863–869. https://doi.org/10.1038/sj.k10.1038/sj.ki.5002715i.5002715

Han, Won K, Bailly, V., Abichandani, R., Thadhani, R., & Bonventre, J. V. (2002). Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney International*, *62*(1), 237–244. https://doi.org/10.1046/j.1523-1755.2002.00433.x

Hazle, M. A., Gajarski, R. J., Aiyagari, R., Yu, S., Abraham, A., Donohue, J., & Blatt, N. B. (2013). Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. *The Journal of Thoracic and Cardiovascular Surgery*, *146*(4), 861–867.

Hidayatullah, R. M., Waloejo, C. S., & Semedi, B. P. (2022). Differences in Serum Lactate Levels, AKI Incidence, and Intraoperative Fluid Therapy Based on GDFT and Standards in Major Laparotomy

Surgery Patients. *International Journal of Health Sciences*, *6*(S6), 5058–5075. https://doi.org/10.53730/ijhs.v6nS6.10726

Hoste, E. A. J., Kellum, J. A., Selby, N. M., Zarbock, A., Palevsky, P. M., Bagshaw, S. M., Goldstein, S. L., Cerdá, J., & Chawla, L. S. (2018). Global epidemiology and outcomes of acute kidney injury. *Nature Reviews Nephrology*, *14*(10), 607–625. https://doi.org/10.1038/s41581-018-0052-0

Huang, Y., & Craig Don-Wauchope, A. (2011). The clinical utility of kidney injury molecule 1 in the prediction, diagnosis and prognosis of acute kidney injury: a systematic review. *Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy)(Discontinued)*, *10*(4), 260–271. https://doi.org/10.2174/187152811796117735

Ichimura, T., Bonventre, J. V, Bailly, V., Wei, H., Hession, C. A., Cate, R. L., & Sanicola, M. (1998). Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. *Journal of Biological Chemistry*, *273*(7), 4135–4142. https://doi.org/10.1074/jbc.273.7.4135

Jansen, T., J, van B., R, W., PG, M., & J, B. (2009). Association between blood lactate levels, sequential organ failure assessment subscores, and 28- day mortality during early and late intensive care unit stay: a retrospective observational study. *Crit Care Med*, *37*(8), 2369–74. https://doi.org/10.1097/CCM.0b013e3181a0f919

Junior, G. B. S., Daher, E. F., Barreto, A. G. C., & Pereira, E. D. B. (2016). Acute kidney injury after liver transplantation is associated with viral hepatitis, prolonged warm ischemia, serum lactate and higher mortality. *Annals of Hepatology*, *14*(6), 939–940. https://doi.org/10.5604/16652681.1171790

Kashani, K., Cheungpasitporn, W., & Ronco, C. (2017). Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. *Clinical Chemistry and Laboratory Medicine (CCLM)*, *55*(8), 1074–1089. https://doi.org/10.1515/cclm- 2016-0973

Kellum, J. A., Lameire, N., Aspelin, P., Barsoum, R. S., Burdmann, E. A., Goldstein, S. L., Herzog, C. A., Joannidis, M., Kribben, A., & Levey, A. S. (2012). Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplements*, *2*(1), 1–138.

Lauzier, F., Lévy, B., Lamarre, P., & Lesur, O. (2006). Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Medicine*, *32*, 1782–1789. https://doi.org/10.1007/s00134-006-0378-0

Legouis, D., Ricksten, S.-E., Faivre, A., Verissimo, T., Gariani, K., Verney, C., Galichon, P., Berchtold, L., Feraille, E., & Fernandez, M. (2020). Altered proximal tubular cell glucose metabolism during acute kidney injury is associated with mortality. *Nature Metabolism*, *2*(8), 732–743. https://doi.org/10.1038/s42255-020- 0238-1

Liangos, O., Perianayagam, M. C., Vaidya, V. S., Han, W. K., Wald, R., Tighiouart, H., MacKinnon, R. W., Li, L., Balakrishnan, V. S., & Pereira, B. J. G. (2007). Urinary N-acetyl-β-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. *Journal of the American Society of Nephrology*, *18*(3), 904–912. https://doi.org/10.1681/ASN.2006030221

Lopez-Delgado, J. C., Esteve, F., Torrado, H., Rodríguez-Castro, D., Carrio, M. L., Farrero, E., Javierre, C., Ventura, J. L., & Manez, R. (2013). Influence of acute kidney injury on short-and long-term outcomes in patients undergoing cardiac surgery: risk factors and prognostic value of a modified RIFLE classification. *Critical Care*, *17*(6), 1–12. https://doi.org/10.1186/cc13159

Medić, B., Rovčanin, B., Basta Jovanović, G., Radojević-Škodrić, S., & Prostran, M. (2015). Kidney injury molecule-1 and cardiovascular diseases: from basic science to clinical practice. *BioMed Research International*, *2015*(1), 854070. https://doi.org/10.1155/2015/854070

Mehta, R. L., Kellum, J. A., Shah, S. V, Molitoris, B. A., Ronco, C., Warnock, D. G., Levin, A., & Network, A. K. I. (2007). Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Critical Care*, *11*, 1–8. https://doi.org/10.1186/cc5713

Mohsenin, V. (2017). Practical approach to detection and management of acute kidney injury in critically ill patient. *Journal of Intensive Care*, *5*, 1–8. https://doi.org/10.1186/s40560-017-0251-y.

Nasu, T., Ueda, K., Kawashima, S., Okishio, Y., Kunitatsu, K., Iwasaki, Y., & Kato, S. (2021). Prehospital blood

pressure and lactate are early predictors of acute kidney injury after trauma. *Journal of Surgical Research*, *265*, 180–186. https://doi.org/10.1016/j.jss.2021.03.037

Ostermann, M., Bellomo, R., Burdmann, E. A., Doi, K., Endre, Z. H., Goldstein, S. L., Kane-Gill, S. L., Liu, K. D., Prowle, J. R., & Shaw, A. D. (2020). Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney International*, *98*(2), 294–309. https://doi.org/10.1016/j.kint.2020.04.020

Parikh, S. M., Mammoto, T., Schultz, A., Yuan, H.-T., Christiani, D., Karumanchi, S. A., & Sukhatme, V. P. (2006). Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. *PLoS Medicine*, *3*(3), e46. https://doi.org/10.1371/journal.pmed.0030046

Pickkers, P., Darmon, M., Hoste, E., Joannidis, M., Legrand, M., Ostermann, M., Prowle, J. R., Schneider, A., & Schetz, M. (2021). Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Medicine*, *47*(8), 835–850. https://doi.org/10.1007/s00134-021-06454-7

Privratsky, J. R., Fuller, M., Raghunathan, K., Ohnuma, T., Bartz, R. R., Schroeder, R., Price, T. M., Martinez, M. R., Sigurdsson, M. I., & Mathis, M. R. (2023). Postoperative acute kidney injury by age and sex: a retrospective cohort association study. *Anesthesiology*, *138*(2), 184–194. https://doi.org/10.1097/ALN.0000000000004436

Radovic, M., Bojic, S., Kotur-Stevuljevic, J., Lezaic, V., Milicic, B., Velinovic, M., Karan, R., & Simic-Ogrizovic, S. (2019). Serum lactate as reliable biomarker of acute kidney injury in low-risk cardiac surgery patients. *Journal of Medical Biochemistry*, *38*(2), 118. https://doi.org/10.2478/jomb-2018-0018

Ricci, Z., & Romagnoli, S. (2018). Acute kidney injury: diagnosis and classification in adults and children. *Acute Kidney Injury-Basic Research and Clinical Practice*, *193*, 1–12. https://doi.org/10.1159/000484956

Shao, X., Tian, L., Xu, W., Zhang, Z., Wang, C., Qi, C., Ni, Z., & Mou, S. (2014). Diagnostic value of urinary kidney injury molecule 1 for acute kidney injury: a meta-analysis. *PloS One*, *9*(1), e84131.

Shi, N., Liu, K., Fan, Y., Yang, L., Zhang, S., Li, X., Wu, H., Li, M., Mao, H., & Xu, X. (2020). The association between obesity and risk of acute kidney injury after cardiac surgery. *Frontiers in Endocrinology*, *11*, 534294. https://doi.org/10.1016/j.jcrc.2020.08.014

Tobias, D. K., & Hu, F. B. (2013). Does being overweight really reduce mortality? *Obesity (Silver Spring, Md.)*, *21*(9), 1746. https://doi.org/10.1002/oby.20602

Vaidya, V. S., Ozer, J. S., Dieterle, F., Collings, F. B., Ramirez, V., Troth, S., Muniappa, N., Thudium, D., Gerhold, D., & Holder, D. J. (2010). Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. *Nature Biotechnology*, *28*(5), 478–485. https://doi.org/10.1038/nbt.1623

van Timmeren, M. M., van den Heuvel, M. C., Bailly, V., Bakker, S. J. L., van Goor, H., & Stegeman, C. A. (2007). Tubular kidney injury molecule-1 (KIM-1) in human renal disease. *The Journal of Pathology*, *212*(2), 209–217. https://doi.org/10.1002/path.2175

Waanders, F., van Timmeren, M. M., Stegeman, C. A., Bakker, S. J. L., & van Goor, H. (2010). Kidney injury molecule-1 in renal disease. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*, *220*(1), 7–16. https://doi.org/10.1002/path.2642

Wai, K., Soler-García, Á. A., Perazzo, S., Mattison, P., & Ray, P. E. (2013). A pilot study of urinary fibroblast growth factor-2 and epithelial growth factor as potential biomarkers of acute kidney injury in critically ill children. *Pediatric Nephrology*, *28*, 2189–2198. https://doi.org/10.1007/s00467-013-2543-3

Wang, R., Wang, S., Zhang, J., He, M., & Xu, J. (2022). Serum lactate level in early stage is associated with acute kidney injury in traumatic brain injury patients. *Frontiers in Surgery*, *8*, 761166. https://doi.org/10.3389/fsurg.2021.761166

Wettervik, T. S., Engquist, H., Howells, T., Rostami, E., Hillered, L., Enblad, P., & Lewén, A. (2020). Arterial lactate in traumatic brain injury–relation to intracranial pressure dynamics, cerebral energy metabolism and clinical outcome. *Journal of Critical Care*, *60*, 218–225. https://doi.org/10.1016/j.jcrc.2020.08.014

Xiao, Z., Huang, Q., Yang, Y., Liu, M., Chen, Q., Huang, J., Xiang, Y., Long, X., Zhao, T., & Wang, X. (2022).

Emerging early diagnostic methods for acute kidney injury. *Theranostics*, *12*(6), 2963. https://doi.org/10.7150/thno.71064

Yan, G., Wang, D., Tang, C., & Ma, G. (2021). The association of serum lactate level with the occurrence of contrast-induced acute kidney injury and long-term prognosis in patients undergoing emergency percutaneous coronary intervention. *International Journal of General Medicine*, 3087–3097. https://doi.org/10.2147/IJGM.S316036

Yerramilli, M., Farace, G., Quinn, J., & Yerramilli, M. (2016). Kidney disease and the nexus of chronic kidney disease and acute kidney injury: the role of novel biomarkers as early and accurate diagnostics. *Veterinary Clinics: Small Animal Practice*, *46*(6), 961–993.

Zhang, Z., & Ni, H. (2015). Normalized lactate load is associated with development of acute kidney injury in patients who underwent cardiopulmonary bypass surgery. *PloS One*, *10*(3), e0120466. https://doi.org/10.1371/journal.pone.0120466

Zhu, X., Xue, J., Liu, Z., Dai, W., Xu, H., Zhou, Q., Zhao, S., Zhou, Q., & Chen, W. (2021). The lactate/albumin ratio Predicts Mortality in critically ill patients with acute kidney injury: An observational multicenter study on the eICU database. *International Journal of General Medicine*, 10511–10525. https://doi.org/10.2147/IJGM.S339767