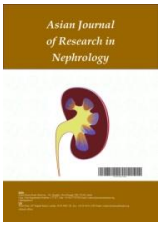

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Assessment of Urinary Kidney Injury Molecule-1 in the Early Post-Burn Period to Predict Acute Kidney Injury for Various Degrees of Burn

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background*:* Acute kidney injury *(*AKI*)* is defined as a sudden and rapid decline in renal excretory function within hours to days, accompanied by an accumulation of nitrogenous waste products such as creatinine, urea, and other clinically unmeasured products*.* Historically acute kidney injury has carried a bad prognosis in the burn population*.*

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Objective: To evaluate urinary kidney injury molecule-1 in the early post-burn period to predict acute kidney injury for various degrees of burn.

Methods: This prospective observational study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, over one year from July 2016 to June 2017. 43 burn patients were enrolled in this study. Serum creatinine, BUN, and KIM-1 were measured on admission and within 48 hours of admission. SPSS 22.0 was used to analyze data. Kappa statistics were done, and AUC was calculated for KIM-1 to predict AKI.

Results In this study, most of the burn patients were below 35 years old. The mean age of the burn patients was 31.39±10.69 years. Males were predominant in burn patients. Maximum burns were due to flame (67.9%), and seven were from scald (13.2%). Mean TBSA was 30.62±14.89%. TBSA, serum creatinine, KIM-1 were significantly high in severe burn patients comparing mild and moderate burn patients. In this study, AKI was developed among 12 (27.9%) burn patients. TBSA was significantly high in AKI patients. Within 2 hours of admission, serum creatinine and BUN were normal in AKI and non-AKI patients, but the KIM-1 level was increased in AKI patients. By 48 hours of admission, urinary KIM-1, serum creatinine, and blood urea nitrogen were significantly higher in AKI patients comparing non-AKI patients.

Conclusion: Urinary KIM-1 is a valuable biomarker in predicting early AKI in burn patients. Our study suggests that urinary KIM-1 may be used as early, sensitive indicators of AKI in patients with burns of varying degrees and provide clinical clues for early AKI prevention.

Keywords: AKI; burn patients; KIM-1; creatinine; kidney.

1. INTRODUCTION

Acute kidney injury (AKI) is defined as a sudden and rapid decline in renal excretory function within hours to days, accompanied by an accumulation of clinically unmeasured products and nitrogenous waste products such as creatinine and urea [1] In routine clinical practice, serum creatinine is used to estimate renal function and thus as a marker for the diagnosis and staging of AKI [2]. The RIFLE (risk, injury, failure, loss of function, end-stage renal disease) and Acute Kidney Injury Network criteria have become the standard diagnostic criteria of AKI [3]. Although serum creatinine is regarded as a traditional biomarker for AKI, it is essentially a renal performance indicator rather than a pathology indicator because its level changes only when renal function is reduced by about 50% [4]. Besides, it varies with muscle size, chronologic age, gender, drugs, and state of hydration [5]. An elevation in serum creatinine may not evidence a sudden reduction in renal function until after 24 to 48 hrs [6]. For alternative biomarkers, these limitations have led to the search; secondly, it provides the nature of the renal injury, is less accurate for patients with small muscle mass, and unusual diets, and scanty information about the underlying cause. Unfortunately, reliable biomarkers would better identify individuals at high risk for developing AKI. Identify AKI early enough, identify those patients at higher risk for poor outcomes, monitor its progression, and the patient's recovery is not yet available in renal care. Investigations have focused on several new biomarkers, some of which could provide this information in the future. Proteomic biomarkers hold prospects by enabling more accurate and earlier detection of renal disease than is possible with currently available biomarkers such as serum creatinine and urinary albumin for improving the management of patients with kidney diseases [7]. Biomarkers under investigation include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and cystatin C [8,9]. Burn is a complex injury and may involve any organ, but the skin is affected first as it serves as a fence between the environment and the human body. In burn patients, systemic capillary leakage occurs, and multiple organs may be involved due to endothelial dysfunction and inflammatory and hypermetabolic activities. Acute kidney injury (AKI) is a common and serious complication of large-area burns, and it is a critical condition clinically characterized by oliguria and elevated serum creatinine [10]. Associated with the size and severity of the burn, the incidence of AKI is 45.5%; severe AKI occurs in 0.5 to 30% of burn patients. [11]. Patients with AKI tend to have higher mortality than those without AKI; in particular, the mortality associated with burns and severe AKI is greater than 80.0% [12]. Therefore, early diagnosis of AKI is important to undertaking effective treatment [13]. Depending on the time of onset, two types of burn-related kidney injury have been developed. Within the

first five days of burn, early onset of AKI has been developed, mainly due to intravascular hypovolemia, systemic vasoconstriction, and myoglobinuria [14]. Late-onset AKI is a multifactorial problem usually associated with sepsis and nephrotoxic drugs and occurs after five post-burn days [14]. According to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 AKI guidelines, AKI is defined as an increase in Serum creatinine to ≥26.5 μmol/L within 48 h, or to ≥1.5 times the baseline value within seven days [14]. However, the guidelines use urine output and serum creatinine (Serum creatinine) values as staging criteria. Moreover, because Serum creatinine is affected by many factors and has low sensitivity and specificity for an association with AKI. It is essential to determine other sensitive, specific, and reliable biomarkers of early kidney injury. Numerous studies have indicated that factors such as kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), N-acetyl-β-glucosidase (NAG), and neutrophil gelatinase-associated lipocalin (NGAL) increase in the early stages of AKI and can therefore be used as markers for early AKI diagnosis [15,16]. Because burn patients with AKI have higher mortality, rapid diagnosis and early treatment of AKI are necessary [17]. Few studies have demonstrated the ability of NGAL to reflect the severity of the renal injury or to be used as an indicator of inflammation in burn patients even though plasma and urinary NGAL levels within 48 h after admission have been independently associated with AKI development and mortality [18]. For early diagnosis of AKI, urinary KIM-1 may be one of the most stable, reliable, sensitive, and specific indicators. KIM-1, a type I transmembrane protein, was identified in a study of ischemia-reperfusion in rat kidney cells using representational difference analysis. Han et al. [19-21] were the first to detect the significant expression of KIM-1 in humans using renal biopsy specimens of patients with acute tubular necrosis. Urinary KIM-1 showed a progressive increase within 12 h following early acute renal ischemia, their study revealed. Other studies have shown that the detection of KIM-1 in kidney tissue and urine facilitates the early diagnosis of AKI and is a better indicator than Serum creatinine or serum BUN [22,23]. Studies have demonstrated that urinary KIM-1 and IL-18 are potential biomarkers of early-stage AKI caused by contrast-induced nephrotoxicity, cardiac surgery, and preeclampsia and can reveal AKI much earlier than can Serum creatinine [24]. However, changes in urinary KIM-1 and IL-18 levels are unclear in patients with burns. Decreasing urinary output (UO) may help diagnose AKI because of reduced glomerular filtration; however, neurohormonal and functional changes influence diuresis, and thus urine output may be normal despite ongoing renal injury [25]. Because of these inadequacies of Serum creatinine and urine output, more reliable biomarkers are needed for the early diagnosis of AKI. A standard biomarker should be noninvasive, detectable at very early stages of acute damage, specific for cellular damage, and prognostically pertinent.

2. OBJECTIVES

2.1 General Objective

To evaluate urinary kidney injury molecule-1 in the early post-burn period to predict acute kidney injury for various degrees of burn.

2.2 Specific objectives

- Measurement of urinary KIM-1 and evaluate the relationship with serum creatinine in the early post-burn period.
- To determine the relationships between urinary KIM-1 and severity of the burn, which are known prognostic factors for the burn.

3. MATERIALS AND METHODS

A prospective observational study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, from July 2016 to June 2017 for one year. Total 43 patients aged 18 years and above who were admitted to the burn unit of Dhaka Medical College Hospital of both sex were recruited as the study population. Purposive sampling techniques were followed for sample selection. Patients with known cardiac disease, first degree or superficial burn, chemical burn, concomitant trauma, chronic kidney, liver, rheumatoid arthritis & rheumatoid arthritis disease, and receiving nephrotoxic drugs patients were excluded in this study. All patients were categorized into Group I (AKI patients) and group II (non-AKI patients). The differences between the two groups were assessed using t-test or Mann–Whitney U test, as appropriate. After enrollment, serum creatinine, blood urea nitrogen, and urinary KIM-1 measurements were done within 2 hours of admission and 48 hours of admission. History of a prior kidney transplant, end-stage kidney disease, pre-injury renal

disease was made through interrogation of the patient's past medical history. A non-survivable burn injury was determined at the time of admission by the attending burn surgeon. Patients were divided into mild, moderate, and severe burn groups based on total body surface area (TBSA), burn depth and complications. Mild burn group those with a second degree or partial thickness burn involving TBSA ≤15%, moderate burn group those with second-degree burn involving TBSA of approximately 16 to 30% or third-degree or full-thickness burn involving TBSA <10%, severe burn group those with second-degree burn involving TBSA is exceeding 31% or third-degree burn involving TBSA >10% or whose second or third-degree TBSA not yet reached the previously defined percentages but who will be in shock or other complications, including inhalation burns or severe combined injuries. Clinical data, including age, sex, second-degree or third-degree burn area, and presence of inhalation injury on admission, were collected from all patients. A patient was diagnosed with AKI. Suppose S creatinine was increased (≥26.5 μmol/L or 0.3 mg/dl) to meet the AKI criteria according to KDIGO guidelines by 48 hours after admission. Clean-catch mid-stream urine specimens were collected from patients in each group after admission and within 48 hours of admission. Patients with compromised mental status were given an indwelling catheter to obtain clean urine. Urinary KIM-1 was measured by enzyme-linked immunosorbent assay (ELISA). Blood samples were collected after admission and within 48 hours to determine serum creatinine and blood urea nitrogen (BUN). Statistical analysis was done by using SPSS version 22.0 for Windows. Assumptions of normality and homogeneity of variance were initially checked. Data were presented as median and ranges when distribution was asymmetric and meant and SD when distribution was normal. Categorical variables were expressed as proportions and were compared using the Chi-square test. A receiver operating characteristic (ROC) curve was constructed to determine the area under the curve (AUC) to measure the efficacy level of on admission urinary KIM-1, serum creatinine level for the diagnosis of AKI. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of KIM-1 were measured for the diagnosis of AKI with a 95% confidence interval. A value of $p<0.05$ was considered statistically significant for all tests.

4. RESULTS

Table 1 shows the demographic profile of the patients. The mean age of the burn patients was 31.39 ± 10.69 years. Males were predominant. The male-female ratio was 1.68:1.

Table 2 shows type of burn and TBSA of the burn patients. Maximum burns were due to flame (67.9%) and were from scald (13.2%). Maximum patients (22.6%) had TBSA 30%-39% followed by 11 (20.8%), 10 (18.9%), 5 (9.4%) and 5 (9.4%) had TBSA 20%-29%, <20%, ≥50% and 40%-49% respectively.

Table 3 shows a comparison of urinary KIM-1 with total body surface area (TBSA). KIM-1 was significantly high in severe burn patients comparing mild and moderate burn patients.

Table 4 compares age and TBSA between Group I **(**AKI patients**)** and Group II **(**non**-**AKI patients**).** TBSA was significantly high in Group I patients **(**AKI**).**

Table 1. Demographic profile of the patients (**N=43**)

Age (**years**)	**Frequency** (**n**)	**Percentage** (%)
18 – 24	13	30.2
25 – 34	13	30.2
35 – 44	11	25.6
≥45	6	14.0
Total	43	100.0
Mean ± SD	31.39±10.69	
Range (Min-max)	18 - 65	
Sex		
Male	27	62.8
Female	16	37.2

The urine KIM-1 concentration of healthy humans is less than 1 ng/ml. [*Hy Test* (*2012*)]

Table 2. Type of burn and%TBSA of the burn patients (N=43)

Type of burn	Frequency (n)	Percentage (%)
Scald	7	16.2
Flame	30	69.9
TBSA (%)≥45	6	13.9
Mean ± SD	31.39±10.69	
Range (Min-max)	18 - 65	
Sex		
Male	27	62.8
Female	16	37.2

Table 3. Comparison of urinary KIM-1 with a degree of burn and total body surface area involved (TBSA) (N=43)

	Mild burn (n=8)	Moderate burn (n=16)	Severe burn (n=19)	p- Value
TBSA (%)	14.63 ± 0.74	23.56 ± 4.16	43.32 ± 13.23	<0.001[s]
KIM-1	0.33 ± 0.26	0.53 ± 0.46	0.91 ± 0.66	0.027[s]

Mann-Whitney U test was done to measure the level of significance

Table 4. Comparison of age and TBSA between Group I and Group II patients (N=43)

	Group I	Group II	p-Value
Patients (n)	12 (27.9)	31 (72.1)	
Age (years)	38.25 ± 9.21	28.68 ± 10.23	0.007[s]
TBSA (%)	44.92 ± 18.01	25.10 ± 8.86	<0.001[s]

Table 5. Comparison of urinary KIM-1, serum creatinine, and blood urea nitrogen between Group I (AKI) and Group II (non-AKI) patients (N=43)

	Group I (n=12)	Group II (n=31)	p- Value
KIM-1 (ng/ml)			
Within 2 hours of admission	1.46 ± 0.29	0.30 ± 0.21	<0.001[s]
Within 48 hours of admission	3.76 ± 0.77	0.49 ± 0.24	<0.001[s]
S. creatinine (µmol/L)			
Within 2 hours of admission	87.89 ± 8.90	81.65 ± 11.22	0.094
Within 48 hours of admission	165.34 ± 39.74	82.75 ± 25.30	<0.001[s]
Blood urea nitrogen (mmol/L)			
Within 2 hours of admission	6.15 ± 0.68	5.60 ± 0.90	0.062
Within 48 hours of admission	11.61 ± 1.13	6.37 ± 1.38	<0.001[s]

Table 6. Distribution of patients by urinary KIM-1 level within 2 hours of admission (N=43)

Urinary KIM-1	Test of reference		Total
	Group I	Group II	
Raised level	11 [TP]	2 [FP]	13
Normal level	1 [FN]	29 [TN]	30
Total	12	31	43
Statistics	Value	Low 95% CI	High 95% CI
Kappa	0.831	0.600	0.904
Accuracy	0.930	0.791	0.974
Sensitivity	0.917	0.666	0.995
Specificity	0.935	0.839	0.966
Positive Predictive Value (PPV)	0.846	0.615	0.919
Negative Predictive Value (NPV)	0.967	0.867	0.998

Table 5 compares urinary KIM-1, serum creatinine, and blood urea nitrogen between Group I and Group II patients. Within 2 hours of admission, serum creatinine and BUN were normal, but KIM-1 was significantly high in Group I patients. Within 48 hours of admission, urinary KIM-1, serum creatinine, and blood urea nitrogen were significantly high in Group I patients comparing Group II patients.

Table 6 shows the distribution of patients by urinary KIM-1 level within 2 hours of admission. Urinary KIM-1 showed excellent agreement in the diagnosis of AKI, according to Kappa statistics. Urinary KIM-1 (within 2 hours of admission) in AKI diagnosis showed accuracy, sensitivity, specificity, PPV, and NPV were 0.930, 0.917, 0.935, 0.846, and 0.967, respectively.

Table 7 shows the distribution of patients by urinary KIM-1 level within 48 hours of admission. Urinary KIM-1 showed excellent agreement in the diagnosis of AKI, according to Kappa statistics. Urinary KIM-1 (within 48 hours of admission) in AKI diagnosis showed accuracy, sensitivity, specificity, PPV, and NPV were 0.953, 0.917, 0.968, 0.917, and 0.968, respectively.

The area under the curve (AUC) for urinary KIM-1 within 2 hour's admission was 0.989 (CI, 0.967-1.000), and the area under the curve (AUC) for serum creatinine within 2 hours of admission was 0.677 (CI, 0.513-0.842).

The area under the curve (AUC) for urinary KIM-1 within 48 hours of admission was 0.995 (CI, 0.980-1.000), and the area under the curve (AUC) for serum creatinine within 48 hours of admission was 0.935 (CI, 0.854-1.000).

Table 7. Distribution of patients by urinary KIM-1 level within 48 hours of admission (N=43)

Urinary KIM-1	Test of reference		Total
	Group I	Group II	
Raised level	11 [TP]	1 [FP]	13
Normal level	1 [FN]	30 [TN]	30
Total	12	31	43
Statistics	Value	Low 95% CI	High 95% CI
Kappa	0.944	0.810	0.987
Accuracy	0.953	0.819	0.996
Sensitivity	0.917	0.676	0.933
Specificity	0.968	0.875	0.997
Positive Predictive Value (PPV)	0.917	0.676	0.933
Negative Predictive Value (NPV)	0.968	0.875	0.997

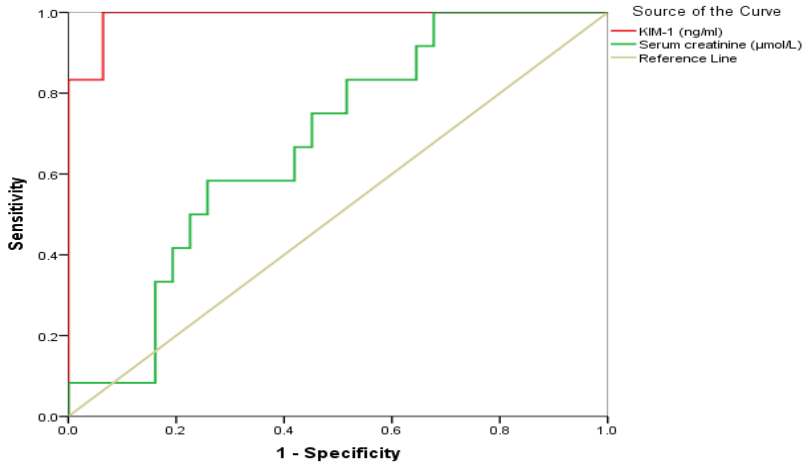

Fig. 1. ROC for accuracy to predict AKI within 2 hours of admission

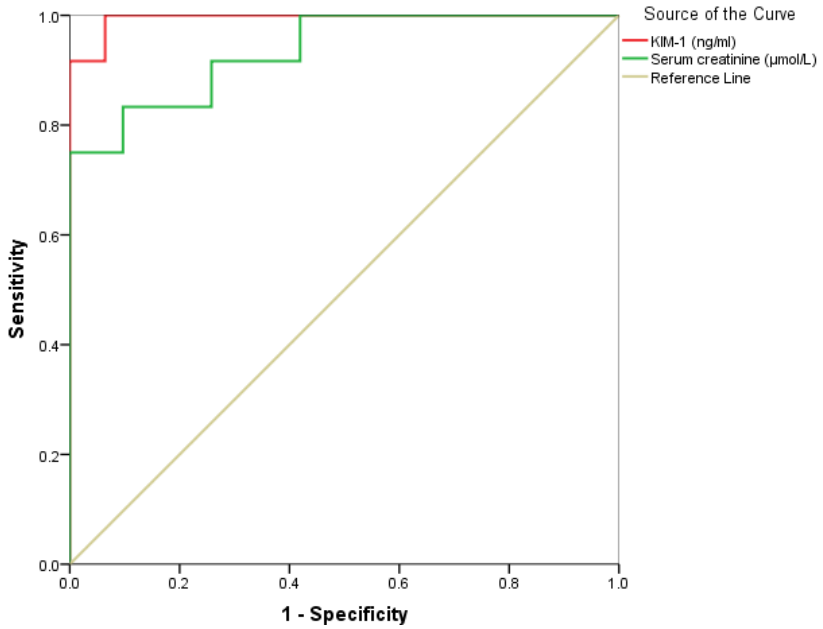

Fig. 2. ROC for accuracy to predict AKI a within 48 hours of admission

5. DISCUSSION

This study evaluated KIM-1 to predict AKI in the early post-burn period from July 2016 to June 2017 in the Department of Nephrology, Dhaka Medical College Hospital. In this study, most of the burn patients were below 35 years old. The mean age of the burn patients was 31.39±10.69 years. The mean age of the burn patients was 38.01 years in the study of Ren et al. [8]. Males were predominant in burn patients. The male-female ratio was 1.68:1. Males were predominant in the study of Ren et al., Yang et al. and Palmieri et al. [8,18,10]. Maximum burns were due to flame (67.9%) and 7 (13.2%) were from scald. Mean TBSA was 30.62±14.89%, within the range from 13-75. Maximum patients (22.6%) had TBSA 30%-39% followed by 11 (20.8%), 10 (18.9%), 5 (9.4%) and 5 (9.4%) had TBSA 20%-29%, <20%, ≥50% and 40%-49% respectively. The mean%TBSA was 34.31% [8]. TBSA and KIM-1 were significantly high in severe burn patients comparing mild and moderate burn patients. Similarly, in the study of Ren et al. [8], it was seen that TBSA and KIM-1 were significantly higher in server burn patients comparing mild and moderate burn patients. In this study, AKI was developed in 12 (27.9%) burn patients. The reported incidence rates of acute kidney injury (AKI) among burn patients range from <1 to 36%, depending on the population studied and the classification criteria used [26] found 47% among burn patients and Palmieri et al. [10] found 53.3% AKI among severe burns patients. TBSA was significantly high in AKI patients. In a study by Kuo et al. [27] similar results were revealed. In this study, within 2 hours of admission, serum creatinine and BUN were at normal levels, but urinary KIM-1 level was significantly increased in AKI patients than non-AKI patients. But in the study of Ren et al. [8] found a significant increase in BUN and serum creatinine at the time of admission, which was not consistent with our result. At the time of admission, Ren et al. [8] found a significant increment of KIM-1, which was consistent with our result. Within 48 hours of admission, urinary KIM-1, serum creatinine, and blood urea nitrogen were significantly higher in AKI patients comparing non-AKI patients. The reason can be renal failure, which is characterized by elevated levels of BUN and creatinine. The ratio of BUN and creatinine can exceed in conditions that favour enhanced urea reabsorption, such as volume contraction. In the study of Ren et al. [8] serum creatinine, BUN, and urinary KIM-1 were significantly higher in AKI patients than non-AKI patients by 48 hours of admission, consistent with our result. In this study, within 2 hours of admission, urinary KIM-1 showed excellent agreement in AKI diagnosis according to Kappa statistics. Urinary KIM-1 (within 2 hours of admission) in AKI diagnosis showed accuracy, sensitivity, specificity, PPV, and NPV were 0.930,

0.917, 0.935, 0.846, and 0.967, respectively. Ren et al. [8] showed sensitivity and specificity were 0.727 and 0.869, which were not the same as our result but almost similar. According to Kappa statistics, within 48 hours of admission, urinary KIM-1 showed excellent agreement in AKI diagnosis. Urinary KIM-1 (within 48 hours of admission) in AKI diagnosis showed accuracy, sensitivity, specificity, PPV, and NPV were 0.953, 0.917, 0.968, 0.917, and 0.968, respectively. The area under the curve (AUC) for urinary KIM-1 within 2 hour's admission was 0.989 (CI, 0.967-1.000), and the area under the curve (AUC) for serum creatinine within 2 hours of admission was 0.677 (CI, 0.513-0.842). The AUC for urinary KIM-1 on admission was 0.846 [8], almost similar to our result. In a study by Han et al. [28] they used urinary KIM-1 to detect postoperative AKI in a prospective study of 90 adults undergoing cardiac surgery. The AUCs for urinary KIM-1 to predict AKI immediately and 3 hours after cardiac surgery were 0.68 and 0.65. The accuracy of KIM-1 was poor in the early detection of postoperative AKI in cardiac surgery patients in their study. Our study result was not consistent with this result; in our study, AUCs for urinary KIM-1 to predict AKI after 2 hours of admission was 0.989. Naggar et al. [29] conducted a study to investigate the role of urinary KIM-1 as an early marker for AKI in critically ill patients. Their result shown that urinary KIM-1 was significantly elevated on admission (7.88 ±1.72 ng/mL) as compared with elevation of serum creatinine (0.895 ± 0.173 mg/dL), blood urea (37.4±14.53 mg/dL) and reduction in estimated glomerular filtration rate (eGFR) (85.2+21.02 mL/minute/1.73 m²). Similarly, urinary KIM-1 was elevated in our study, but serum creatinine remains the same within 2 hours of admission. The area under the curve (AUC) for urinary KIM-1 within 48 hours of admission was 0.995 (CI, 0.980-1.000), and the area under the curve (AUC) for serum creatinine within 48 hours of admission was 0.935 (CI, 0.854-1.000).

6. LIMITATIONS

There are some limitations to this study. It was a single-centered study. The sample size was not reflecting the whole country scenario. KMI-1 was not compared with any other biomarker.

7. CONCLUSION AND RECOMMENDATION

Urinary KIM-1 is a valuable biomarker in predicting early AKI in burn patients. Our study suggests that urinary KIM-1 may be used as early, sensitive indicators of AKI in patients with burns of varying degrees and provide clinical clues for early AKI prevention. The further large-scale study should be carried out. KIM-1 should be compared with other biomarkers.

DISCLAIMER

The products used for this research are commonly and predominantly used in our research area and country**.** There is no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for litigation but the advancement of knowledge**.** Also, the research was not funded by the producing company**.** Instead, it was funded by personal efforts of the authors**.**

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline Patient's consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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