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Original Research Article

Assessment of urinary interleukin-18 in the early post-burn period to predict acute kidney injury of various degrees of burn patients

Sharif Qamar Uddin[1]*, M. Nazrul Islam[2], M. Nizamuddin Chowdhury[3], Nizam Uddin Ahmed Chowdhury[4], Mohammad Zahir Uddin[5], Maksuda Begum Mony[6]

[1]Dhaka University Medical Center and Hospital, Dhaka, Bangladesh
[2]Department of Nephrology, Dhaka Medical College Hospital Dhaka, Bangladesh
[3]Department of Nephrology, BRB Hospital Limited, Dhaka, Bangladesh
[4]Department of Nephrology, Sheikh Fazilatunnessa Mujib Memorial KPJ Specialized Hospital, Gazipur, Bangladesh
[5]Department of Nephrology, Cumilla Medical College Hospital, Cumilla, Bangladesh
[6]Department of Nephrology, Universal Medical College, Dhaka, Bangladesh

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***Correspondence:**
Dr. Sharif Qamar Uddin,
E-mail: publicationhub098@gmail.com

ABSTRACT

Background: Early detection of acute kidney injury (AKI) in burn-injured patients can help modify the treatment to prevent progression of acute renal failure and reduce the need for renal replacement therapy. The aim of the study was to evaluate urinary interleukin-18 in the early post-burn period to predict the AKI for the various degrees of burn patients.
Methods: This prospective observational study was conducted in the department of nephrology, Dhaka medical college in collaboration with burn and plastic surgery unit of the same medical college hospital, from July 2017 to June 2018 for a period of one year. The 48 burn patients (Age>18 years) who attended in the burn unit of Dhaka medical college, Dhaka of both sexes were enrolled in this study. Data were analyzed by using SPSS 22.0. A value of $p<0.05$ was considered statistically significant for all tests.
Results: In this study, mean age of the burn patients was 32.41±10.59 years. Male female ratio was 3.36:1. Urinary IL-18 in diagnosis of AKI showed accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 93.8%, 91.7%, 94.4%, 84.6% and 97.1% respectively. AUC for urinary IL-18 at admission was 0.968 (CI, 0.921-1.000) and AUC for serum creatinine at admission was 0.937 (CI, 0.871-1.000).
Conclusions: According to Kappa value, AUC and sensitivity and specificity urinary IL-18 is a good biomarker in predicting of early AKI in burn patients.

Keyword: Burn patients, Study, Admission, Urinary, AKI, Urinary IL18, Early

INTRODUCTION

Acute kidney injury (AKI) is a syndrome characterized by the rapid loss of the kidney's excretory function, decreased urine output and is typically diagnosed by the accumulation of end products of nitrogen metabolism or both. It is the clinical manifestation of several disorders which acutely affect the kidney.[1] AKI is diagnosed with progressive rise in serum creatinine over several days, which may or may not be accompanied with oliguria. Due to lacking signs of renal function deteriorations, clinical diagnosis is often delayed. However, Serum creatinine changes can differ from actual GFR changes. For early diagnosis of AKI, the detection of a reliable biomarker would be very helpful in facilitating early intervention, evaluating the effectiveness of the therapeutic

intervention, and guiding pharmaceutical development.[2,3] Recent studies reported that routine renal function test based on serum creatinine, blood urea nitrogen and urine production were outdated because they failed to identify early stages of renal dysfunction and structural injury.[4] Unlike serum troponin in myocardial infarction, increase of serum creatinine is not directly correlated with tubular disturbances in AKI but it is correlated with filtration function. Creatinine changes are not specific because it can also occur as a result to non-renal etiologies, such as muscle mass and nutrition intake.[5] AKI is defined as an increase in Scr to ≥26.5 μmol/L within 48 h, or to ≥1.5 times the baseline value within 7 days, according to the kidney disease improving global outcomes (KDIGO) 2012 AKI guidelines. However, it uses urine output and Scr values as staging criteria. Moreover, due to Scr is affected by many factors and has low sensitivity and specificity for an association with AKI. It is particularly important to determine other biomarkers of early kidney injury that are sensitive, specific, and reliable. Numerous recent years studies 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 be used as markers for early AKI diagnosis.[6-8] Burns can cause injuries that are amongst the most physiologically demanding to treat. The cost to both the individual and to the medical system can be enormous. Burn can be classified according to severity as mild, moderate and severe burn. Mild burn: PT10% tBSA involving EEHFP, inhalation.[9] Burn is a complex injury and may involve in any organ. The incidence of AKI is 26.6% with burns on 10% or greater total-body surface area.[10] Patients with AKI tend to have higher mortality than those without AKI; in particular, the mortality associated with burns and severe AKI is 73.0%.[10] Therefore, early diagnosis of AKI is important to undertaking effective treatment. Interleukin-18, is an 18-kDa pro-inflammatory cytokine that is induced in the proximal tubule after AKI, and released into urine after cleavage by caspase-1.[11-13] Following cleavage by active caspase-1 mature IL-18 is secreted from the cells although over 80% precursor remains unprocessed inside the cells, uIL-18 is induces in the proximal tubule after AKI and released in urine after cleavage.[14] Urinary IL-18 levels were significantly increased in patients with AKI compared with non-AKI. UIL-18 had sensitivity of 81.9% for diagnosis of AKI in burn patients.[15] To predict AKI for various degrees of burn thus the purpose of the present study was to assess urinary IL-18 in the early post-burn period.

Objectives

General objective

The general objective of the study was to evaluate urinary Interleukin-18 in the early post-burn period to predict the acute kidney injury for the various degrees of burn patients.

Specific objectives

The objective was to measure urinary IL-18 in burn patients at admission and within 48 hours of admission and to measure the relationship between S. creatinine, blood urea nitrogen (BUN) and IL-18 in the development of AKI.

METHODS

It was a prospective observational study, was conducted in the department of nephrology and burn and plastic surgery unit of Dhaka medical college hospital from July 2017 to June 2018. All burn patients who attended in the burn unit of Dhaka medical college, of both sexes and age ≥18 years within 12 hours of injury were recruited as study population. Purposive sampling technique was followed as per inclusion and exclusion criteria. Patients with known chronic disease like-CKD, CLD, COPD, and RA, first degree or superficial burn, receiving nephrotoxic drugs prior to admission and chemical burn were excluded from this study. Prior to commencement of this study, the research protocol was approved by the ethical committee of DMCH, Dhaka. After enrollment, serial S. creatinine, blood uren nitrogen and urinary IL-18 was measured at admission and within 48 hours of admission. Serum creatinine was also measured after 5 days of admission. AKI was diagnosed based on renal RIFLE criteria.[16] Statistical analysis was done by using SPSS version 21.0 for Windows. All patients were categorized into two groups, AKI group and no AKI group. Categorical variables were expressed as proportions and were compared with using Chi square test. A receiver operating characteristic (ROC) curve was constructed to determine the area under curve (AUC) to measure the efficacy level of on admission urinary IL-18, serum creatinine level and urine output for the diagnosis of AKI. Sensitivity, specificity, PPV, NPV, and accuracy of IL-18 was measured for the diagnosis of AKI with 95% confidence interval. P<0.05 was considered statistically significant for all tests.

RESULTS

Table 1 showed demographic profile of the patients. Mean age of the burn patients was 32.41±10.59 years. Males were predominant. Male female ratio was 3.36:1.

Table 1: Demographic profile of the patients (n=48).

Age (years)	Frequency	Percentage (%)
18-20	6	12.5
21-30	22	45.8
31-40	11	22.9
41-50	7	14.6
51-60	2	4.2
Mean ± SD	32.41±10.59	
Range (Min-max)	18-60	

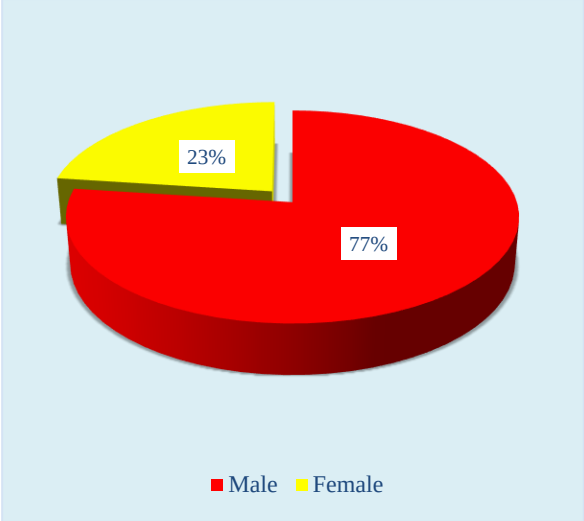

Figure 1: Patient's gender wise distribution.

Table 2: Type of burn and TBSA of the burn patients, (n=48).

Type of burn	Frequency	Percentage (%)
Type of burn injury		
Flame burn	32	66.7
Electric burn	9	18.7
Scald	7	14.6
TBSA (%)		
<20	10	20.8
20-29	15	31.3
30-39	11	22.9
40-49	7	14.6
≥50	1	10.4
Mean ± SD	31.17±14.54	
Min-max	(10-70)	

Table 2 shows type of burn and TBSA of the burn patients. Maximum burns were due to flame burn (67.9%) followed by electric burn (18.8%) and scald (14.7%). Maximum patients 15 (31.3%) had TBSA 20%-29% followed by 11 (22.9%), 10 (20.8%), 7 (14.6%) and 5 (10.5%) had TBSA% 30%-39%, <20%, 40%-49% and ≥50% respectively.

Table 3: Comparison of urinary interleukin-18 with degree of burn and total body surface area involved (TBSA%), (n=48).

Variables	Mild burn, (n=8)	Moderate burn, (n=18)	Severe burn (n=22)	P value
TBSA (%)	13.2± 1.67	23.39± 3.48	44.05± 10.72	<0.001
Urinary interleukin-18	5.9± 0.14	6.62± 2.13	7.45± 2.12	0.134

ANOVA test was done to measure the level of significance

Table 3 showed comparison of urinary Interleukin-18 with total body surface area (TBSA%). Urinary interleukin-18 was high in severe burn patients comparing mild and moderate burn patients but not statistically significant.

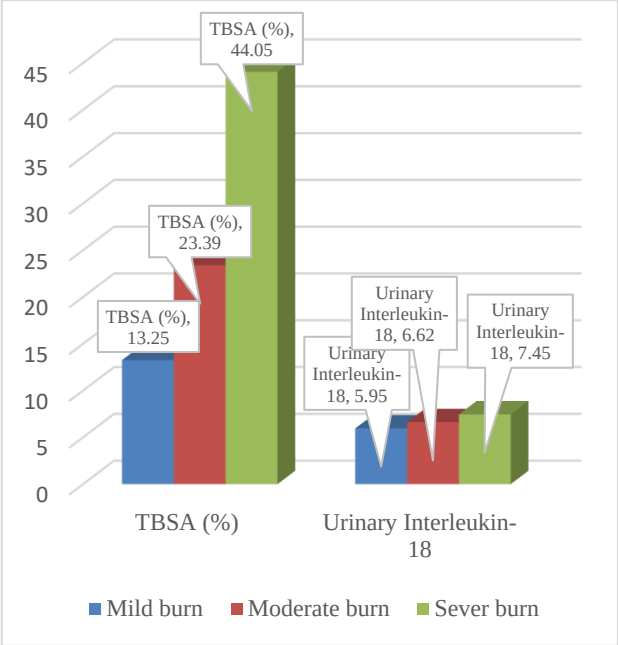

Figure 2: Comparison of urinary interleukin-18 with TBSA %.

Table 4: Comparison of urinary IL-18, serum creatinine and blood urea nitrogen between group I (AKI) and group II (non-AKI) patients (n=48).

Variables	Group I, (n=12)	Group II, (n=36)	P value
Urinary IL-18 (pg/ml)			
At admission	9.55±1.11	6.00±1.25	<0.001
Within 48 h	10.60±1.10	6.42±1.17	<0.001
S. creatinine (µmol/L)			
At admission	100.78±9.20	80.18±11.07	<0.001
Within 48 h	187.03±14.35	93.43±21.61	<0.001
At day 5	209.42±14.64	98.12±27.08	<0.001
Blood urea nitrogen (mmol/L)			
At admission	6.96±0.71	5.96±0.83	<0.001
Within 48 h	12.36±1.36	7.10±1.16	<0.001

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

Table 4 showed comparison of urinary interleukin-18, serum creatinine and blood urea nitrogen between group I and group II patients. Within 2 hours of admission and after 48 hours of admission, urinary interleukin-18, serum creatinine and BUN were significantly high in group I patients.

Table 5: Sensitivity and specificity of urinary IL-18 (at admission) at different cut off value in diagnosis of post burn AKI, (n=48).

Urinary IL-18	Sensitivity	Specificity
7.43	91.7	88.9
7.71	91.7	91.7
7.92	91.7	94.4
8.37	83.3	94.4
8.72	75.0	94.4
8.95	66.7	97.2

Table 6: Distribution of patients by urinary interleukin-18 level at admission, (n=48).

Urinary IL-18	Test of reference		Total
	Group I	Group II	
Raised level (>7.92)	11 [TP]	2 [FP]	13
Normal level (≤7.92)	1 [FN]	34 [TN]	35
Total	12	36	48

TP: True positive; FP: False positive; FN: False negative; TN: True negative

Table 6 showed distribution of patients by urinary IL-18 level at admission. Urinary IL-18 showed very good agreement in diagnosis of AKI according to Kappa statistics. Urinary IL-18 (at admission) in diagnosis of AKI showed accuracy, sensitivity, specificity, PPV and NPV were 93.8, 91.7, 94.4, 84.6 and 97.1 respectively.

Table 7: Distribution of patients by urinary IL-18 level within 48 hours of admission, (n=48).

Urinary IL-18	Test of reference		Total
	Group I	Group II	
Raised level (>7.92)	11 [TP]	1 [FP]	13
Normal level (≤7.92)	1 [FN]	35 [TN]	35
Total	12	36	48

DISCUSSION

Early detection of AKI in burn-injured patients can help alter treatment to prevent progression to acute failure and reduce the need for renal replacement therapy. Recently, the serum cystatin C and serum and urinary IL-18 levels have been introduced as early biomarkers for AKI; the levels of these biomarkers are known to increase 24 to 48 hours before the serum creatinine levels increase. In this study, we aimed to estimate the diagnostic utility of urinary IL-18 level in the early post-burn period as biomarkers for predicting AKI. In this study, almost half of the patients were 21-30 years of age group. Mean age of the burn patients was 32.41±10.59 years. Males were predominant. Male to female ratio was 3.36:1. Males were predominant in the study of Yang et al and Palmieri et al.[17,18] Maximum burns were due to flame (66.7%), 9 (18.8%) were from electric burn and 7 (14.6%) were from scald in this study. Mean %TBSA was 31.17±14.54% within the range from 10-70. Maximum patients (31.3%) had TBSA 20%-29% followed by 11 (22.9%), 10 (20.8%), 7 (14.6%) and 5 (10.5%) had TBSA 30%-39%, 10-19%, 40%-49% and ≥50% respectively in this study. AKI was developed in 25.0% of the patients in this study. In a study of Sen et al AKI was developed 47% of their patients.[19] AKI was diagnosed in 52 (35.8%) burn patients in the study of Kuo et al.[20] In this study, %TBSA was significantly higher in severe burn patients comparing mild and moderate burn patients. In this study %TBSA was significantly higher in AKI patients (44.83±16.27 vs 26.61±10.74). At the time of admission Ren et al found significant increment of urinary IL-18 which was consistent with this study result.[15] Within 48 hours of admission, urinary IL-18, serum creatinine and blood urea nitrogen (BUN) was significantly higher in AKI patients comparing non-AKI patients in this study. In the study of Ren et al serum creatinine, BUN and urinary IL-18 were significantly higher in AKI patients than non-AKI patients within 48 hours of admission which was consistent with this study result.[15] In this study, at admission, urinary IL-18 showed very good agreement in diagnosis of AKI according to Kappa statistics. Urinary IL-18 (at admission) in diagnosis of AKI showed accuracy, sensitivity, specificity, PPV and NPV were 93.8%, 91.7%, 94.4%, 84.6% and 97.1% respectively. Ren et al showed sensitivity and specificity were 72.7 and 86.9 which were not exactly same to our result but almost similar.[15] Within 48 hours of admission, urinary IL-18 showed excellent agreement in diagnosis of AKI according to Kappa statistics. Urinary IL-18 (within 48 hours of admission) in diagnosis of AKI showed accuracy, sensitivity, specificity, PPV and NPV were 95.8%, 91.7%, 97.2%, 91.7% and 97.2% respectively. Area under curve (AUC) for urinary IL-18 at admission was 0.968 (CI, 0.921-1.000) and area under curve (AUC) for serum creatinine at admission was 0.937 (CI, 0.871-1.000). The AUC for urinary IL-18 on admission was 0.846 Ren et al which is almost similar to our result.[15] In a study of Washburn et al they used urinary IL-18 for the early detection of AKI in critically ill children.[21] Urinary IL-18 concentration ≥100 pg/ml had specificity and NPV of 81% and 83% to predict AKI development within 24 hour. Urinary IL-18 ≥200 pg/ml collected within 24 h of day 0 had a specificity and PPV of 93% and 88% respectively to predict the AKI duration ≥48 hour.

Limitations

It was a single centered study. Sample size was not reflecting the whole country scenario. Urinary IL-18 was not compared with any other bio marker. Anuric patients developing AKI could not be included in the study.

CONCLUSION

According to this study findings it can be concluded that urinary IL-18 is a good bio marker in predicting AKI in burn patients. Further large-scale study should be carried out. Urinary IL-18 should be compared with another bio marker.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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