

# COMPARISON OF URINARY INTERLEUKIN-18 AS A BIOMARKER OF ACUTE KIDNEY INJURY WITH ROUTINE MARKERS IN INTENSIVE CARE UNITS OF TERTIARY CARE HOSPITALS OF PESHAWAR

Mahum Farooq<sup>1</sup>, Mohsin Shafi<sup>2,3</sup>, Ahmad Rafiq<sup>3</sup>, Ihsan Ullah<sup>4</sup>, Naumana Rehman<sup>5</sup>, Safia Rahman<sup>3</sup>

<sup>1</sup> Department of Pathology, Combined Military Hospital, Peshawar - Pakistan

<sup>2</sup> Department of Pathology, Rehman Medical Institute, Peshawar - Pakistan

<sup>3</sup> Department of Pathology, Khyber Medical College, Peshawar - Pakistan

<sup>4</sup> Institute of Pathology and Diagnostic Medicine, Khyber Medical University, Peshawar - Pakistan

<sup>5</sup> Town Children Hospital, Peshawar - Pakistan

## ABSTRACT

**Objective:** This study aims to determine the diagnostic utility of IL-18 for early diagnosis of AKI by comparing it with the routinely used marker serum creatinine.

**Material and Methods:** This validation study was carried out in the Department of Pathology, Khyber Medical College, Peshawar from September 2021 to February 2022. A total of 156 patients with Acute Kidney Injury were recruited from the intensive care units of three Peshawar tertiary care hospitals. Serum and urinary samples were taken at the time of admission and 48 hours after admission to estimate Serum creatinine level and urinary IL-18. Comparisons were made between the diagnostic utility of Urinary IL-18, and serum creatinine using the paired t-test. Sensitivity, specificity, positive predictive value, and negative predictive values were calculated.

**Results:** This study included 156 acute kidney injury (AKI) patients. The mean creatinine level on admission was  $0.90 \pm 0.26$  mg/dl; after 48 hours of admission, it was  $1.38 \pm 0.70$  mg/dl. Similarly, IL-18 on admission was  $130.14 \pm 61.31$  pg/ml while after 48 hours it was  $290.32 \pm 136.50$  pg/ml. IL-18 levels of  $\geq 75$  pg/ml with a positive predictive value of 100% and a negative predictive value of 29% can be used as a cutoff in the diagnosis of AKI in patients after 48 hours of admission.

**Conclusion:** Due to high sensitivity and specificity, Urinary IL-18 can predict AKI 24-48 hours before the onset of renal injury and can be used as an early marker for this purpose.

**KEYWORDS:** Acute kidney injury, IL 18, Urine, creatinine

**This article may be cited as:** Farooq M, Shafi M, Rafiq A, Ullah I, Rehman N, Rahman S. Comparison Of Urinary Interleukin-18 As A Biomarker Of Acute Kidney Injury With Routine Markers In Intensive Care Units Of Tertiary Care Hospitals Of Peshawar. J Med Sci 2024 April-June;32(2):180-184

## INTRODUCTION

A quick decline in function including both structural damage and loss of function is known as Acute Kidney Injury (AKI).<sup>1</sup> Possible causes of AKI include acute tubular necrosis, hypovolemia (because of hemorrhage, burns, sepsis, etc), urinary tract blockage, direct kidney injury and certain drugs.<sup>2</sup>

Correspondence

**Dr. Mohsin Shafi**

Resident Chemical Pathology, Rehman Medical Institute, Peshawar and Associate Professor, Department of Pathology, Khyber Medical College, Peshawar - Pakistan

**Cell:** +92-321-9009689

**Email:** mohsinshafi@gmail.com

**Date Received:** 25-02-2024

**Date Revised:** 24-04-2024

**Date Accepted:** 07 -05-2024

Acute Kidney Injury is known for contributing significantly to increased morbidity and death, particularly in critically ill patients.<sup>3</sup> In routine, Serum Creatinine (SCr) and Urinary output are the two indicators used to detect a decline in renal function.<sup>4</sup> Reduction in glomerular filtration rate, declining acid-base, and electrolytes are also present.<sup>2</sup> Acute kidney injury per Kidney Disease Improving Global Outcome (KDIGO) is defined as an increase of SCr by 0.3mg/dl or more in 48 hours or an increase of SCr up to 1.5 times or more within the last 7 days.

SCr often predicts a poorer outcome, and the diagnosis of AKI may be overlooked if urine output is not measured.<sup>4</sup> However, it is known that they have limitations. SCr detects deterioration in renal function when it

has already deteriorated by 50 percent; it is only applicable when the human body is in a steady state (and not when renal function is declining) which can take a significant amount of time, particularly when a patient is in the ICU.<sup>5</sup> In addition, it does not correlate perfectly with GFR. It is affected by factors outside of renal function, such as the individual's muscle mass, drugs containing salicylates, and nutrition.<sup>6</sup> Also, SCr is a functional measure of kidney function and not a kidney damage marker.<sup>7</sup> In contrast, the urinary output is also influenced by extrarenal variables such as water intake and vigorous activity.<sup>3</sup>

When biological and molecular alterations lead to cell destruction, kidney disease ensues.<sup>8</sup> It is of the utmost significance to detect AKI early and accurately to provide rapid therapy and enhance the clinical outcome. Numerous developments have been made towards this end. Biomarkers can be used to detect the early onset of AKI and to plan its recovery. Urinary Interleukin-18 is one of these emerging biomarkers that can detect early deterioration in Kidney Function and avoid problems, therefore preventing a lifetime of dialysis or renal replacement therapy.<sup>6</sup>

Interleukin-18 (IL-18) is a cytokine belonging to the IL-1 cytokine family. Various cells, including monocytes, macrophages, and proximal tubular epithelial cells, produce it. Initially generated as an inactive precursor of 23 kDa, it is converted to an active cytokine of 18.3 kDa by caspase 1.<sup>9, 10</sup> Intercalated cells in the distal convoluted tubule, connecting tubule, and collecting duct of the kidneys produce this cytokine. Post-injury, IL-18 begins to rise six hours after the damage and reaches its peak of around 25 times the normal value twelve hours later.<sup>11</sup> The significant diagnostic function of IL-18 as a predictor of severe AKI was identified for the first time in animal experiments.<sup>12</sup>

AKI is among the top causes of death in intensive care units. To limit the problems associated with it, early detection and appropriate care are required, which is not attainable with our current biomarkers. This study aims to compare the use of urine IL-18 in the early diagnosis of AKI as compared to the gold standard SCr.

## MATERIAL AND METHODS

This validation study was carried out at the Chemical Pathology Department of the Khyber Medical College, Peshawar from September'2021 to February'2022. Patients were recruited from the intensive care units of three Peshawar tertiary care hospitals: Lady Reading Hospital,

Khyber Teaching Hospital, and Hayatabad Medical Complex, Peshawar. Using the WHO sample size calculator, the sample size was calculated to be 156. Non-probability sampling techniques were utilized.

After receiving approval from the Advance Study Review Board of Khyber Medical University, Peshawar, and Ethical approval from Khyber Medical College, Peshawar, the study was commenced. First, consent was taken followed by a detailed history from the patient along with general physical and systematic examination. Patients over the age of 18 who were critically ill, exhibiting AKI symptoms, and admitted to the ICU for fewer than four hours were included, while all the patients with a history of end-stage renal disease or chronic dialysis, post-kidney transplantation, end-stage liver disease or terminal cancer, patients on steroids and post-cardiopulmonary resuscitation were excluded from the study.

A detailed proforma containing the demographic information and symptoms of the patients was filled out. Blood and urine samples were collected at admission and 48 hours later. The blood sample was extracted aseptically from a vein, placed in a gel tube, centrifuged to separate serum, and kept between 2-8 C. SCr was estimated on a fully automated chemical pathology analyzer (Cobas 6000). The urinary IL-18 levels were tested at Khyber Medical University using an Enzyme-Linked Immunosorbent Assay (ELISA) kit that detects IL-18 in urine on an ELISA Plate Reader.

The data was analyzed on Statistical Package for the Social Sciences (SPSS) 26. For numerical data mean and standard deviation were calculated. Comparisons were made between the diagnostic utility of Urinary IL-18, and serum creatinine using the paired t-test. Consideration of a P-value of less than 0.05 was statistically significant. The sensitivity, specificity, positive predictive value, and negative predictive values were calculated. The area under the curve (AUC) was calculated from the receiver operating curve (ROC).

## RESULTS

In this validation study, 156 acute kidney failure (AKI) patients were included. Table 1 shows the demographic characteristics of the participants.

Regarding comorbidities, 101 (64.74%) had no associated comorbidities, 22 (14.10%) had diabetes mellitus, 11 (7.05%) had hypertension, while 21 (13.46%) had both hypertension and diabetes mellitus and 1 (0.64%) had cardiovascular disease.

Mean values of serum creatinine and urinary interleukin-18 levels on admission and after 48 hours are shown in Table 2.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IL-18 at the time of admission and after 48 hours are shown in Tables 3 and 4.

By applying paired t-test, it was noted that on ad-

**Table No 1. Demographic characteristics of the participants. n=156**

Variable	Frequency	Percentage
Gender		
Male	94	60.3%
Female	62	39.7%
Age group		
18-25 years	38	24.4%
26-35 years	38	24.4%
36-45 years	30	19.2%
46-55 years	21	13.5%
>55 years	29	18.6%
Marital status		
Married	125	80.1%
Unmarried	31	19.9%
Education status		
Primary school	36	23.1%
Middle school	22	14.1%
High school	2	1.3%
College	18	11.5%
University	25	16.0%
Illiterate	53	34.0%

**Table No 2: Mean creatinine and IL 18 level on admission and after 48 hours. (n=156)**

	Serum Creatinine(mg/dl) on admission (n=156)	Serum Creatinine (mg/dl) after 48 hours (n=142)	IL18 (pg/ml) on admission	IL18 (pg/ml) after 48 hours
Mean	0.90	1.38	130.14	290.32
Std. Deviation	0.26	0.70	61.31	136.50

**Table No 3: Predict AKI on admission: AUC=0.911 (0.844-0.977)**

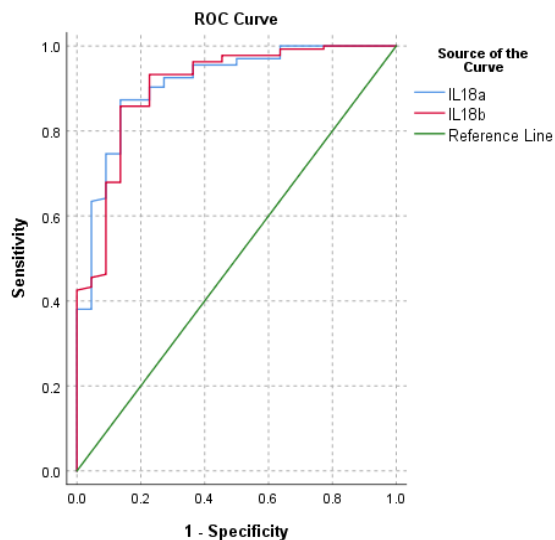
IL-18(pg/ml)	Sensitivity	Specificity	PPV	NPV
>50	83.33	12.50	86	27
>75	83.33	18.71	85	27
>100	58.33	29.86	83	22
>200	8.33	77.08	81	21

**Table No 4 Predict AKI after 48 hours: Area under curve (AUC): 0.904 (0.831-0.977)**

IL-18(pg/ml)	Sensitivity	Specificity	PPV	NPV
>50	100	2.78	100	34
>75	100	3.47	100	29
>100	83.33	10.42	81.25	27
>200	75.0	77.08	76.24	22

**Table No 5: Paired t-test of serum creatinine and IL 18, on admission and after 48 hours. n=156 (Value < 0.001 is significant)**

		Mean	Std. Deviation	P-Value
On admission	Serum Creatinine (mg/dl)	0.90	0.26313	0.000
	IL18 (pg/ml)	130.14	61.31245	
After 48 Hours	Serum Creatinine (mg/dl)	1.21	0.28540	0.000
	IL18 (pg/ml)	290.32	136.49869	



**Fig 1: ROC curve showing sensitivity and specificity of IL18 on admission and after 48 hours.**

mission the creatinine – IL-18 pair was statistically significant with a p-value of <0.001, similarly after 48 hours creatinine and IL-18 were significant with a p-value of <0.001. (Table 5)

Figure 1 shows ROC showing sensitivity and specificity of IL18 on admission and after 48 hours. Our study showed an Area under the curve (AUC) of 0.91 at admission and 0.90 after 48 hours.

## DISCUSSION

AKI is one of the most important causes of death in ICU setups all around the world. To reduce the complications arising from it, early detection and prompt management are necessary which is not possible with the biomarkers that are currently in use in our setups. The current study presents the role of urinary IL-18 as a potential biomarker in early detection of AKI in patients from ICU setups and the role of IL-18 is compared with other routine biomarkers (SCr) in early detection of AKI.

We report an excellent AUC of 0.91 at admission and 0.90 after 48 hours for the prediction of AKI. This is nearly identical to a study carried out in intensive care units in Saudi Arabia which reported an AUC of 0.946 for IL-18 in predicting AKI.<sup>13</sup> In contrast, the largest research with IL-18 in an ICU population (528 patients) yielded an AUC of 0.55 despite observing the onset of AKI for 7 days.<sup>14</sup> A meta-analysis revealed that the pooled AUC for IL-18 in predicting AKI in all groups was 0.70, and 0.66 in intensive care settings which was also in contradiction to our study.<sup>15</sup> The discrepancy in results is most probably because these studies were carried out in different races of people as compared to ours. The ability of IL-18 to predict AKI was superior in our study (AUC:0.9).

The degree to which biomarker levels alter over time is critical. Various studies have reported that after cardiopulmonary bypass, or any other sudden injury the level of urine IL-18 increases rapidly at 4-6 hours, peaks at 12 hours, and remains elevated for up to 48 hours with a stable condition afterward.<sup>16,17</sup> In our study we only determined urinary IL-18 levels at the time of admission and after 48 hours while serial measurements were not taken. Another study has a good correlation to our findings urinary IL-18 showed greater than 90% sensitivity and specificity for early prediction of AKI.<sup>18</sup>

It is critical to define the cutoff value for developing a diagnostic biomarker. Different cutoff values have been reported in the literature. Our study has also set a cutoff value for different periods. We exposed the diagnostic value of IL-18 in AKI patients from admission time to predict severe AKI. We obtained the best cutoff level for urine IL-18 to be  $\geq 75$  pg/ml during the admission time and after 48 hours as the most accurate for early diagnosis of AKI.

One of the limitations of our study is that it signifies the outcomes from a comparatively limited number of patients, although we have obtained data from three separate tertiary care facilities. Although our findings are clinically and statistically significant, they will need to be confirmed in a larger sample. Furthermore, the current cohort of patients was homogeneous, with no substantial AKI-related comorbidities. The findings of this study will need to be replicated in additional AKI scenarios where the etiology of AKI is complex, such as in individuals with diabetes and CVDs.

## CONCLUSION

Our study suggests that IL-18 levels rise approximately 24-48 hours before full-blown AKI develops and can be rapidly measured. We obtained the best cutoff level for urine IL-18 at the time of admission and after 48 hours as the most accurate for early diagnosis of AKI. It is a helpful marker in Acute Kidney Injury and proves to be superior in earlier detection than Serum Creatinine as it may detect AKI a day or two earlier.

## REFERENCES

- Zdziechowska M, Gluba-Brzózka A, Poliwczyk AR, Franczyk B, Kidawa M, Zielinska M, et al. Serum NGAL, KIM-1, IL-18, L-FABP: new biomarkers in the diagnostics of acute kidney injury (AKI) following invasive cardiology procedures. *Int Urol Nephrol.* 2020; 52:2135-43. DOI: 10.1007/s11255-020-02530-x
- Ülger F, Pehlivanlar Küçük M, Küçük AO, İlkaya NK, Murat N, Bilgiç B, et al. Evaluation of acute kidney injury (AKI) with RIFLE, AKIN, CK, and KDIGO in critically ill trauma patients. *Eur J Trauma Emerg Surg.* 2018;44:597-605. DOI: 10.1007/s00068-017-0820-8
- Lin X, Yuan J, Zhao Y, Zha Y. Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. *J Nephrol.* 2015;28(1):7-16. DOI 10.1007/s40620-014-0113-9
- Goldstein SL. Urine Output Assessment in Acute Kidney Injury: The Cheapest and Most Impactful Biomarker. *Frontiers in pediatrics.* 2020;7:565. DOI: 10.3389/fped.2019.00565
- Andreucci M, Faga T, Pisani A, Perticone M, Michael A. The ischemic/nephrotoxic acute kidney injury and the use of renal biomarkers in clinical practice. *Eur J Intern Med.* 2017;39:1-8. DOI: 10.1016/j.ejim.2016.12.001
- Griffin BR, Faubel S, Edelstein CL. Biomarkers of Drug-Induced Kidney Toxicity. *Ther Drug Monit.* 2019;41(2):213-226. DOI: 10.1097/FTD.0000000000000589.
- Medić B, Rovcanin B, Vujovic KS, Obradovic D, Duric D, Prostran M. Evaluation of Novel Biomarkers of Acute Kidney Injury: The Possibilities and Limitations. *Curr Med Chem.* 2016;23(19):1981-1997.
- Beker BM, Corleto MG, Feiras C, Musso CG. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. *Int Urol Nephrol.* 2018;50:705-713. DOI: 10.1007/s11255-017-1781-x
- Yasuda K, Nakanishi K, Tsutsui H. Interleukin-18 in Health and Disease. *Int J Mol Sci.* 2019; 20 (3) : 649. DOI: 10.3390/ijms20030649
- Hirooka Y, Nozaki Y. Interleukin-18 in Inflammatory Kidney Disease. *Front Med (Lausanne).* 2021;8:639103. DOI: 10.3389/fmed.2021.639103.
- Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. *Clin Chem Lab Med.* 2017;55(8):1074-1089. DOI 10.1515/cclm-2016-0973
- Liu X, Guan Y, Xu S, Li Q, Sun Y, Han R, et al. Early Predictors of Acute Kidney Injury: A Narrative Review. *Kidney and Blood Pressure Research.* 2016;41(5):680-700.

DOI: 10.1159/000447937

13. Al-Saegh RMA, Mohanad MA, Khudhair NJ, Al-Mukhtar MAR. Using Urinary Interleukin-18 as a Potential Marker for Early Detection of Acute Kidney Injury in Intensive Care Unit. *Saudi Journal of Kidney Diseases and Transplantation*. 2021;32(2):341-347. DOI: 10.4103/1319-2442.335445
14. Endre ZH, Pickering JW, Walker RJ, Devarajan P, Edelstein CL, Bonventre JV, et al. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. 2011;79(10):1119-1130. DOI: 10.1038/ki.2010.555
15. Liu Y, Guo W, Zhang J, Xu C, Yu S, Mao Z, et al. Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. 2013;62(6):1058-1067. DOI: 10.1053/j.ajkd.2013.05.014
16. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, et al. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Kidney Int*. 2006;70(1):199-203. DOI: 10.1038/sj.ki.5001527
17. Krawczeski CD, Goldstein SL, Woo JG, Wang Y, Pi-yaphanee N, Ma Q, et al. Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. *J Am Coll Cardiol*. 2011;58(22):2301-2309. DOI:10.1016/j.jacc.2011.08.017
18. Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. *Am J Kidney Dis*. 2004;43(3):405-414. DOI: 10.1016/J.JACC.2011.08.017

**Authors Contribution:**

Following authors have made substantial contributions to the manuscript as under

Authors	Conceived & designed the analysis	Collected the data	Contributed data or analysis tools	Performed the analysis	Wrote the paper	Other contribution
Farooq M	x	✓	✓	✓	✓	x
Shafi M	✓	✓	✓	✓	x	x
Rafiq A	x	✓	x	✓	x	✓
Ullah I	x	x	✓	✓	✓	x
Rehman N	x	✓	x	✓	x	✓
Rahman S	x	x	✓	x	✓	✓

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Ethical Approval:**

**This Manuscript was approved by the Ethical Review Board of Khyber Medical College, Peshawar. Vide No. 274/PG/KMC.**

**Dated: 27 08 2020**



This work is Licensed under a Creative Commons Attribution-(CC BY 4.0)