Effectiveness of Urinary Kidney Injury Molecule-1 to diagnose Subclinical Acute Kidney Injury induced by Extracorporeal Shock Wave Lithotripsy

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Abstract

Objective: To find the effectiveness of Kidney Injury Molecule-1 (KIM-1) as biomarker in diagnosing Extracorporeal Shock Wave Lithotripsy (ESWL) induced renal damage by taking serum creatinine concentration as gold standard

Materials and Method: In this interventional study, a total of (80) diagnosed patients of nephrolithiasis undergoing ESWL of age ≥ (18) years were enrolled from the Outpatient Department of Mayo Hospital, Lahore. After informed consent, urine and whole blood samples were drawn pre and post ESWL. Samples after centrifugation were analyzed for urinary KIM-1 levels employing sandwich ELISA technique. While serum creatinine levels were measured by colorimetric photometry in the Advanced Research Lab of Biomedical Sciences, King Edward Medical University, Lahore.

Results: Of (80) patients, 53 (66.3%) of them were males and 27 (33.8%) were femaless. Serum creatinine levels were decreased by 0.15 times from the baseline after procedure of ESWL but remained within normal clinical range. Whereas urinary KIM-1 levels were raised 2.04 times than the baseline after ESWL ($p< 0.001$) depicting subclinical acute kidney injury. At a cut off value of >50.9pg/ml, urinary KIM-1 had a 71.25% sensitivity and 46.25% specificity with AUC of 0.699 ($p<0.001$) to predict acute kidney injury after ESWL. A strong positive correlation ($r= 0.62$, $p<0.001$) was found between pre and post ESWL values of KIM-1.

Conclusion: The noninvasive biomarker KIM-1 was observed more effective in our study for diagnosing ESWL–induced subclinical acute kidney injury than serum creatinine.

Keywords: Kidney injury molecule-1, KIM-1, biomarker, extracorporeal shock wave lithotripsy, ESWL, subclinical acute kidney injury, nephrolithiasis, urolithiasis

How to cite: Ahmed R, Choudhry N, Rathore M. Qureshi K, Awan AN, Gondal AJ. Effectiveness of Urinary Kidney Injury Molecule-1 to diagnose Subclinical Acute Kidney Injury induced by Extracorporeal Shock Wave Lithotripsy. Esculapio - JSIMS 2024;20(02):263-267

DOI: https://doi.org/10.51273/esc24.251320223

Introduction

Nephrolithiasis or urolithiasis is a common condition that affects people all over the world, with rates ranging from (7-13%) in North America, (5–9%) in Europe, and (1–5%) in Asia.[1] Stone management is associated with acute and chronic morbidity and is costly due to high recurrence.[2] Extracorporeal Shock Wave Lithotripsy (ESWL), a less invasive treatment modality is considered the best option for kidney stones smaller than 2.5cm.[3] ESWL carries a lot of hazards in addition to its many benefits. These include inflammation, cavitation, and renal ischemia reperfusion injury.[4] Acute kidney injury (AKI) induced by ESWL is usually measured by serum creatinine concentration but it is raised after few days and is unable to detect subclinical kidney injury.[5] Recently, researchers have investigated multiple ways to determine ESWL–induced subclinical kidney injury and various biomarkers are under investi-

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Submission Date: 12-04-2024
1st Revision Date: 27-04-2024
Acceptance Date: 09-06-2024

gation for this purpose. The most recent kidney damage indicator to emerge is Kidney Injury Molecule 1 (KIM-1). KIM-1 is a (38)-kilo Dalton (kDa) glycoprotein. KIM-1 is found in proximal tubular cells and is hypothesized to aid in the clearance of apoptotic and necrotic cells.[6] Due to its high sensitivity and specificity, it was approved for the detection of drug-induced nephrotoxicity in rats. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have now approved it for use in safety biomarker panels to help detect kidney tubular injury in phase 1 trials.[7]

Indonesian researchers conducted a systemic review in 2018 and concluded that KIM-1 is useful in determining ESWL induced renal damage. The pre and post value of this biomarker has been used in several studies to gauge the safe time between two lithotripsy sessions.[8] The notion to determine this biomarker's levels in relation to renal injury in our population was sparked by the paucity of data and inconsistent results of a few researches using it. In patients receiving ESWL, the current study intended to assess effectiveness of KIM-1 to diagnose subclinical acute kidney injury induced by ESWL by taking serum creatinine concentration as gold standard.

Materials and Method

In this pre and post interventional study, STARD guidelines were followed to report studies of diagnostic accuracy.[9] In this study 80 patients of age ≥ 18 years undergoing 1st session of ESWL were taken as study subjects from Urology Department of Mayo Hospital, Lahore. All patients had radiopaque unilateral stone(s) but had normal levels of serum creatinine before intervention. Ultrasound KUB was used to determine the size and site of the stone. Non-probability convenient sampling technique was used for sample selection of patients. Patients having history of using nephrotoxic drugs within four weeks before ESWL, hydronephrosis, glomerulonephritis, CKD diabetes mellitus, cardiac disorders, hypertension and inflammatory disorders were excluded from the study.

All guidelines for the use of human biological samples were followed in this research project. The study was approved by the institutional review board of King Edward Medical University (KEMU), Lahore vide letter no.43/RC/KEMU, Dated: 13/01/2020. The subjects gave written, informed consent at the time of recruitment. Demographic and clinical data of the patients were documented by taking the history and scrutiny of existing medical records. Following all aseptic measures two blood samples to measure serum creatinine levels were collected from every patient. 1st sample was drawn before the procedure and 2nd sample was drawn at the 3rd day of intervention. Blood samples were centrifuged at 1000rmp for 10 minutes to separate the serum which was stored at -80˚C until further use. Similarly, two urine samples were collected from every patient, 1st before the procedure and 2nd after 3 hours of ESWL. Urine samples were centrifuged using Labcon disposable 15mL urine centrifuge tubes and the superficial fractions were kept at -80°C until further use.

Creatinine levels in serum were measured by Jaffe's reaction colorimetric photometric method, using Human, creatinine liquicolor test kit having Catalog no: 10051, as it is less vulnerable to interference from Jaffe positive chemicals other than creatinine. The micro lab 300 automatically calculated the concentration of creatinine in a sample.

The levels of KIM-1 were determined in urine by sandwich enzyme-linked immunosorbent assay (ELISA) technique using Human KIM-1 ELISA Kit provided by ELABSCIENCE Biotechnology Inc (Houston, Texas, USA), having catalog no: E-EL-H6029. In the above-mentioned ELISA kit, the manufacturers protocol was followed. At a wavelength of 450 nm, standard curves were plotted on graphs automatically by Accu Skan FC micro-plate reader (Fisher Scientific, Pittsburgh, Pennsylvania, USA) for KIM-1, and results were read from the curves for each sample. Acute kidney injury was defined according to the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria according to which serum creatinine (SCr) ≥ 1.5, ≥ 2.0 and ≥ 3.0 from the baseline was considered as risk, injury, and failure, respectively.[10]

Data was analyzed using SPSS version 26.0 (SPSS, Chicago, Illinois, USA) and MedCalc Version 22.009 (MedCalc Software, Mariakerke, Belgium). Shapiro-Wilk and Kolmogorov-Smirnov tests were employed to verify that continuous data was normal. Association of levels of urinary KIM-1 and serum creatinine pre and post ESWL was calculated by applying Wilcoxon Signed Ranks Test. We evaluated the sensitivity and specificity for urinary KIM-1 and serum creatinine at various cut-off values. To measure the accuracy of urine KIM-1 and serum creatinine as a marker of subclinical AKI, a receiver operating characteristic (ROC) curve analysis was performed. Spearman correlation analysis was performed to check the relationship of KIM-1 and serum creatinine with each other. A p value of <0.05 was considered statistically significant.

Results

Among 80 patients of urolithiasis, males were (53) (66.3%) and females were (27) (33.8%). Mean age of patients who underwent ESWL was (36.04±11.81) years. Mean size of the stone was (1.37 ± 0.66) cm. In the patients of nephrolithiasis, serum creatinine levels were decreased by (0.15 times) after ESWL, while urinary KIM-1 levels were raised (2.04 times) from the baseline after ESWL. Pre and post ESWL concentrations of serum creatinine and urinary KIM-1 are given in **Table 1**. The ability of serum creatinine and urinary KIM-1 levels to diagnose sub clinical acute kidney injury was assessed using ROC curve analysis. The graphs showing area under the curve (AUC) are given in **Fig-1&2**. The values of the validation criteria for the respective cut-off values of serum creatinine and KIM-1 are given in **Table 2**. A correlation analysis was performed to find the relation-ship of kidney injury biomarkers with each other before and after ESWL. The values of correlation coefficients are given in Table 3. Urinary KIM-1 levels were strongly and positively correlated to each other before and after ESWL.

Table 1: *Levels of serum creatinine and urinary KIM-1 in the patients undergoing ESWL*

Variables	Before ESWL (n = 80)	After ESWL (n = 80)	Wilcoxon Signed Ranks Test
	Median (IQR)	Median (IQR)	p-value
Serum Creatinine (mg/dl)	0.80 (0.70-1.0)	0.70 (0.50-0.80)	<0.001**
Urinary KIM-1 (pg/ml)	78.25 (25.05-329.50)	262.50 (36.68-636.25)	<0.001**

***A p< .001 was considered as highly significant.*

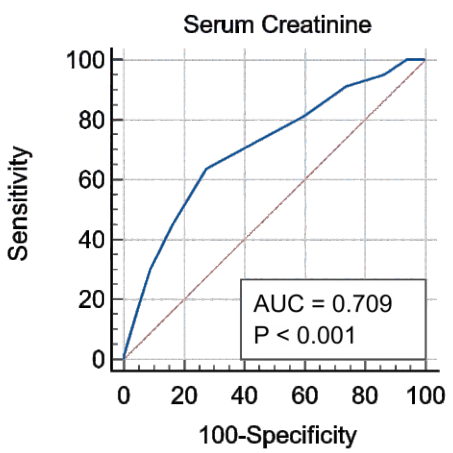

Fig-1. *ROC curve of serum creatinine*

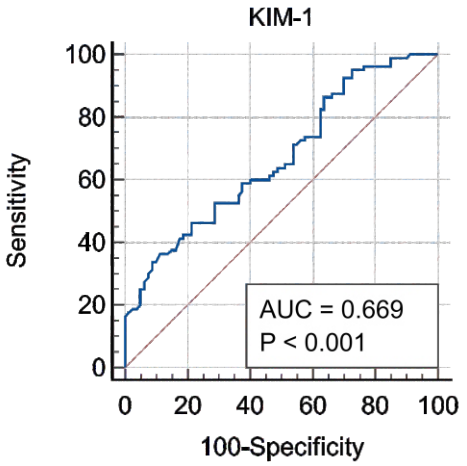

Fig-2: *ROC curve of urinary KIM-1*

Table 2: *Cut-off values and values of validation criteria for serum creatinine and urinary KIM-1*

Variables	Serum Creatinine	KIM-1
Cut-off value	≤0.70	>50.9
Sensitivity %	63.75	71.25
Specificity %	72.50	46.25
Positive Likelihood Ratio %	2.32	1.33
Negative Likelihood Ratio %	0.50	0.62
Positive Predictive Value %	10.9	6.5
Negative Predictive Value %	97.4	96.8

Table 3: *Correlation of kidney injury biomarkers*

	Pre ESWL sCr	Post ESWL sCr	Pre ESWL-KIM-1
Pre ESWL sCr	_____		
Post ESWL sCr	r= 0.23*	_____	
Pre ESWL-KIM-1	r= 0.00	r= 0.02	_____
Post ESWL KIM-1	r= -0.23*	r= 0.05	r= 0.62**

**p<0.05. **p<0.001*

Discussion

In Pakistan, ESWL was initially introduced in 1989 and now it is the most common type of lithotripsy performed for renal stones.[11] Its popularity grew rapidly, thanks in part to the notion that it was completely risk-free. After a decade of clinical ESWL, we now know that this is not the case. ESWL is quite successful at breaking kidney stones, but it can also produce significant renal damage, which can lead to long-term complications that are irreversible. Shock wave lithotripsy is associated with hemorrhage, reperfusion injury and in some cases scarring. All of these factors are responsible for chronic kidney damage.[12] According to a study, patients undergoing ESWL had dose-dependent kidney

fibrosis and this fibrosis was responsible for a partial or complete loss of function in the affected area. Moreover, 10% of ESWL patients may develop a urinary tract infection after treatment.[13] Acute kidney injury is diagnosed by RIFLE criteria according to which increased serum creatinine is used to define risk, injury, and failure of kidney.[10]

To determine the AKI induced by ESWL, we measured already established biomarker serum creatinine concentration. In our study the difference in the levels of creatinine pre and post ESWL was statically significant, but the levels were within normal range [0.70 (0.50-0.80)], which indicated that there was kidney injury but it was subclinical. Moreover, creatinine was decreased by 0.15 times after ESWL rather than increasing. Serum creatinine at a cut off value of ≤ 0.70mg/dl had a 63.75% sensitivity and 72.50% specificity with AUC of 0.709 ($p<0.001$) to predict acute kidney injury after ESWL. However, we classified the kidney injury as subclinical because sCr≤0.70 mg/dl was within the clinically normal range and did not predict any AKI if RIFLE criteria were followed.[10] This verified the fact that serum creatinine was not a good marker for the detection of ESWL-induced renal injury in our clinical setup.

This finding is in line with previous studies in which SCr was considered as a flawed biomarker. A recent review explained the discrepancy in criteria of acute renal damage on the basis of serum creatinine levels.[5] After a significant renal injury, the serum concentration of creatinine may take 24–36 hours to rise and remain normal in subclinical damage. It only increases abruptly if the kidney function decline under 50%. Moreover, the blood levels of sCr also rise nonspecifically in septic shock and muscular dystrophy and many laboratories use diverse methods to measure sCr levels in which there is considerable interference with other colored compounds.[5] Therefore, rather than serum creatinine levels, we pro-posed that urinary KIM-1 levels could be used as a reliable predictor of renal injury. KIM-1 is not present under normal conditions but becomes abundant in injured tubular membrane cells.[6] In our study urinary KIM-1 levels were raised 2.04 times from the baseline after ESWL. Similar results were concluded by a recent review conducted by Indo-nesian investigators., in which KIM-1 was raised by 0.2 times ($p=0.05$) after ESWL in the patients of nephrolithiasis.[8]

In our study, ROC curve analysis concluded that at a cut off value of >50.9pg/ml, urinary KIM-1 levels had a 71.25% sensitivity and 46.25% specificity with AUC of 0.699 ($p<0.001$) to predict acute kidney injury after ESWL. Our results as is comparable to the results of a meta-analysis of 11 studies having 2979 patients. According to which urinary KIM-1 had an estimated sensitivity of 74.0% and specificity of 86.0% to diagnosis AKI. Moreover, the summary receiver operating characteristic curves analysis of their study showed an area under the curve of 0.86(0.83–0.89) for KIM-1 to predict AKI which is in line with our results.[14]

Similar results were shown by a randomized clinical trial in which post ESWL values of KIM-1 were raised as compared to pre ESWL values ($p < 0.0001$). Additionally, after three days from the second session, this biomarker remained considerably higher ($p = 0.027$) and after seven days, it recovered to pre-ESWL values, suggesting that a seven-day gap was necessary between ESWL sessions in order to allow for full recovery of kidney functions.[15] In our study a strong positive correlation ($r= 0.62$, $p<0.001$) between pre and post ESWL values of KIM-1 indicated that urinary KIM-1 can be used to access renal injury after ESWL in place of serum creatinine which has a weak positive correlation ($r = 0.23$, $p<0.05$) before and after ESWL.

Conclusion

Hence, it is recommended that urinary KIM-1 may be used as promising noninvasive biomarker to assess kidney injury in post lithotripsy patients as it rise far before the level of serum creatinine which is used to diagnose kidney damage as of yet. KIM-1 might be used in future as a predictive marker for the detection of sub clinical renal damage at an early stage, before this damage become irreversible. Moreover, more studies with different variables like association of frequency of shock waves with renal damage and association of number of sessions of ESWL with renal damage could be done with the help of this marker. Urinary KIM-1 can be used to reduce morbidity and mortality due to hospital acquired kidney injury and as the rise in urinary KIM-1 concentration open new avenue for the clinicians to opt new interventions and strategies to prevent complications of this procedure.

Conflict of Interest None

Funding Source KEMU, Lahore

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Authors Contribution

RA: Conceptualization of Project
MR: Data Collection
NC, ANA: Literature Search
KQ, ANA: Statistical Analysis
MR, NC, AJG: Drafting, Revision
MR, RA: Writing of Manuscript