ORIGINAL PAPER

UROLITHIASIS

Urinary neutrophil gelatinase-associated lipocalin level as a biomarker of acute kidney injury following extracorporeal shock wave lithotripsy

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Introduction Although extracorporeal shock wave lithotripsy (ESWL) is minimally invasive and highly efficient for the management of kidney stones, adverse effects have been described. Available indicators of renal function exhibit insufficient sensitivity in acute renal injury (AKI). We aimed to evaluate the severity of the kidney tissue response to ESWL injury by measuring the urinary neutrophil gelatinase-associated lipocalin (uNGAL), which can indicate AKI in its early phase.

Material and methods The prospective, controlled study included 62 patients with nephrolithiasis undergoing single ESWL treatment. uNGAL level was measured before the procedure, and 6 h and 12 h after.

Results The median uNGAL level increased by 126.0%, 6 h after ESWL ($p < 0.001$). The growth rate continued and 12 h after was higher by 583.7%, compared to the pre-treatment level ($p < 0.001$). The median value of estimated glomerular filtration rate (eGFR) dropped by 15.3% 12 h after the treatment ($p < 0.001$). It increased by 5.0% in the period 7 days to 3 months after ($p < 0.001$) and after 3 months it was lower by 10.1% compared to pre-ESWL values ($p < 0.001$). uNGAL level after 12 h was significantly negatively associated with eGFR, 12 h, 7 days and 3 months after the ESWL. The sensitivity of uNGAL 12 h after ESWL was 60.6%; its specificity was 75.0%, with a positive predictive value of 74.0% and negative predictive value of 61.7%.

Conclusions uNGAL appears to be a useful biomarker for the assessment and prediction of AKI. It was noticed that uNGAL had the highest predictive value 12 h after the ESWL treatment.

Key Words: nephrolithiasis ‹› neutrophil gelatinase-associated lipocalin ‹› kidney injury ‹› biomarker ‹› extracorporeal shock wave lithotripsy ‹› lithotripsy

INTRODUCTION

Kidney stones are a common urological condition affecting health and quality of life, with a reported rate ranged from 0.1% to 14.8% in Western countries [1]. Since its introduction in the early 1980s, extracorporeal shock wave lithotripsy (ESWL) has proven to be a minimally invasive and highly efficient method for the management of kidney stones. It is more cost-effective than endoscopic interventions, which is the main reason for its introduction as a preferred treatment modality in all patients with renal stones <20 mm, even with lower polar stones of size 10–20 mm with favorable anatomy [2, 3, 4].

Numerous mechanisms have been proposed to explain how shock waves damage stones and tissue, although it is likely that direct stresses and cavitation are dominant in stone fragmentation, and that cavitation is dominant in tissue injury [5, 6]. The injury occurs first at the level of capillaries. Once vessels

have been ruptured, extravasation of blood occurs, followed by the ischemic change in tubular epithelium and infiltration by inflammatory cells. Subsequently, hematuria is observed in practically all patients after receiving at least 200 shock waves [5, 6, 7].

Despite its significant benefits, adverse effects of ESWL have been described. The injury is most often localized to the targeted region but can include the surrounding tissues [8]. Remarkable renal injury following ESWL can present as intraparenchymal and subcapsular hematomas, rupture of the renal pelvis, proliferative glomerulopathy, anti-glomerular basement membrane disease, diffuse fibrosis, papillary necrosis, and irreversible renal failure [8]. These effects originate from a direct effect of shock waves on the targeted tissue and secondly, from the passage of disintegrated stone fragments through the urinary tract [9]. Furthermore, lithotripsy can cause injury to the abdominal organs and blood vessels, resulting in severe bleeding. Also, it can lead to several long-term effects including new-onset hypertension, the exacerbation of lithiasis, and the development of diabetes [8, 9].

Well-known indicators of renal function are serum creatinine, urea, urinary albumin level, and estimated glomerular filtration rate (eGFR). However, they are useful only for the evaluation of chronic renal failure and exhibit insufficient sensitivity in acute renal injury (AKI) [9]. Therefore, more sensitive markers were introduced, such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and interleukin-18 (IL-18). The list of promising urinary markers is much longer and includes kidney injury molecule-1 (KIM-1), insulin-like growth factor binding protein 7 (IGFBP-7), liver-type fatty-acid-binding protein (L-FABP), tissue inhibitor of metalloproteinases-2 (TIMP-2), and many others [10]. These can indicate AKI in its early phase when the creatinine level is not increased.

Several experimental and clinical studies have shown that the expression of plasma/serum (pNGAL) and urinary NGAL (uNGAL) rises significantly in AKI. Specifically, uNGAL level is closely associated with the severity of AKI, and could be detected before other markers [11]. However, a wide range in its predictive value has been reported [12].

NGAL, also known as siderocalin or lipocalin 2, is a member of the lipocalin family of carrier proteins, produced by neutrophils, filtered in the glomeruli, and reabsorbed in the proximal tubules [13]. It is involved in immune response, bacterial growth limitation, cell proliferation, differentiation, and apoptosis [10]. It provides an anti-apoptotic effect and increases the proliferation of renal tubular cells [13]. NGAL is present in low concentrations in many tissues, but its level significantly increases a few hours after ischemic, septic, or toxic tubular injury.

In this study, we aimed to evaluate the severity of the kidney tissue response to ESWL injury by measuring the urinary excretion of NGAL and its potential as a biomarker of AKI.

MATERIAL AND METHODS

Study design

The study was designed as an observational, prospective, controlled study. Patients with nephrolithiasis undergoing single ESWL treatment at the Clinic of Urology Clinical Center University of Sarajevo were included in this phase II clinical trial (protocol number: 0207.52497). The effects of ESWL on the occurrence of early renal impairment have been examined by uNGAL measurement.

Patients

Primary selection of patients was performed based on anamnestic data and radiologically verified nephrolithiasis. A total of 386 patients who had undergone a single ESWL treatment were assessed for eligibility of participation in the study. After the exclusion of patients based on specific criteria, 112 patients were allocated to intervention (measuring the uNGAL level and eGFR). Subsequently, a cohort consisting of 78 patients were included in the follow-up. However, a total of 62 patients were enrolled in the final consideration (Figure 1). Patients were included in the study based on the specific criteria: unilateral radiopaque kidney stone with the position in the renal pelvis, upper or middle group of calyces, up to 20 mm in diameter. Furthermore, it included patients delegated to a single treatment, without previous kidney surgery, intravesical obstruction, or proven urinary tract infection. Patients had no history of use of anticoagulants, antihypertensives, or nephrotoxic drugs 4 weeks before and during treatment, and they signed informed consent to participate in the study.

Exclusion criteria were: patients younger than 18 and older than 60 years, body mass index (BMI) >30 kg/m^2, stone larger than 20 mm, the presence of radiolucent or bilateral kidney stones, ureteral stones, recent episodes of renal colic (less than 12 weeks), urinary tract infection or systemic inflammation, obstruction and malignancy, patients with identified hematoma after ESWL, or serum creatinine level >350 μmol/L in the last 12 weeks, patients with hypertension, diabetes mellitus, previous kidney surgery, those who consumed potentially neph-

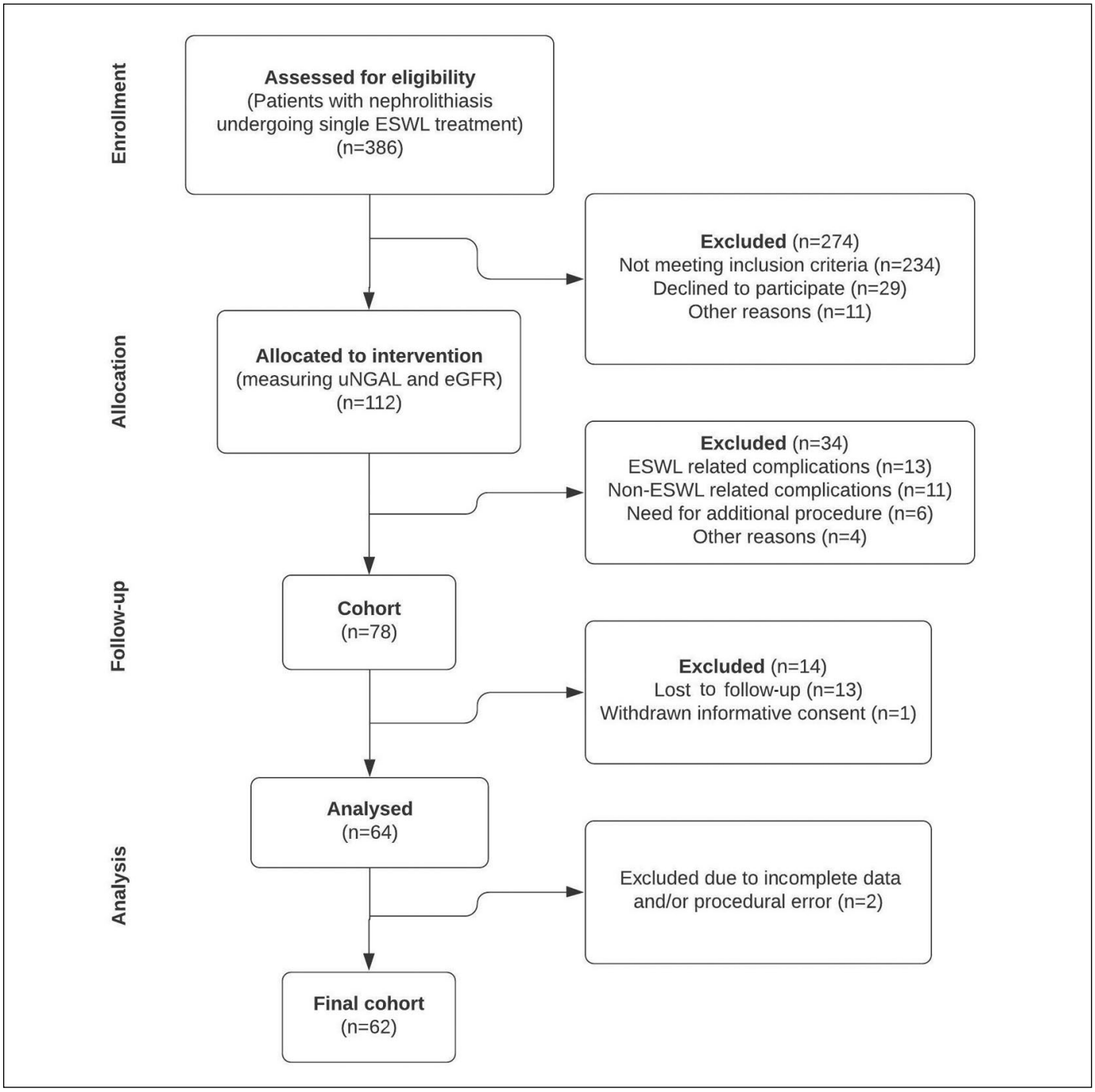

Figure 1. *Flow diagram of progress through the phases of present trial.*

ESWL – extracorporeal shock wave lithotripsy; uNGAL – urinary neutrophil gelatinase-associated lipocalin; eGFR – estimated glomerular filtration rate

rotoxic drugs within 4 weeks before the treatment, patients with unsigned informed consent. General exclusion criteria were considered - pregnancy, moderate and severely impaired renal function, patients with pronounced comorbidity (unstable cardiac status, aortic abdominal aneurysm, renal artery aneurysm, or stenosis). Also, patients with post-renal obstruction (steinstrasse) and the need for additional endourological procedures (placement of a JJ stent or percutaneous nephrostomy), were excluded.

During the follow-up period, 48 patients were excluded and 13 of them were due to the ESWL related complications (Figure 1). A complication directly related to incomplete fragmentation in the form of pileup of fragments, otherwise known as steinstrasse, appeared in 4 cases. Subcapsular hematoma

was recorded in 1 case, urinary infection in 7 patients, and sepsis in 1 case. However, an additional procedure was needed in 6 cases, due to obstruction and/or unfavorable localization of stone.

Methods and equipment

After the Ethics committee approved the study and informed consent was obtained, all patients were acquainted with the research plan. The preparation included anamnesis, objective physical examination, laboratory tests, and radiological examinations. All patients underwent a baseline radiographic evaluation of the kidneys, ureter, and bladder (KUB) and/or an abdominopelvic computed tomography (CT) (non-enhanced or enhanced) scan. The localization and maximum diameter of the stone were determined. However, average Hounsfield units (HU) were not evaluated. After the primary selection, a physical examination was performed and blood and urine samples were taken. Patients were then referred for ESWL treatment. The ESWL treatment was performed using a Siemens Multiline lithotripter, the device with an electromagnetic generation of high-energy shock waves, both X-ray and ultrasonic detection of stones. ESWL procedure was carried as an outpatient procedure, without anesthesia and with the application of standard analgesia.

Measurements

Morning blood samples were taken from the cubital vein according to the standard procedure, before, 12 hours, 7 days, and 3 months after treatment. Urine samples used to determine uNGAL levels were obtained immediately before treatment, 6 and 12 hours after treatment.
Serum creatinine levels were determined using standard methods of protein assay and nephelometric analyzer (BN II System, Siemens). uNGAL levels were determined using the advanced serological technique, Chemiluminescent Microparticle Immuno Assay (CMIA) (Architect 2000 SR, Abbott). The Modification of Diet in Renal Disease (MDRD) equation was used to assess the eGFR.

Statistical analysis

Data were provided as absolute (N) and relative (%) numbers, median and interquartile range, and standard deviation (SD). The Kolmogorov-Smirnov test and Shapiro-Wilk test were used for the data distribution analysis. A comparison was performed by the T-test for normal and the Mann-Whitney U test for not normally distributed data. For dependent variables that did not follow the normal distribution, the Wilcoxon test or the Friedman test depending on the number of repeated measurements was used.
The Chi-square test and Fisher's exact test were used in the analysis of the dependence between categorical variables. The correlation was assessed by Pearson or Spearman method. The specificity and sensitivity of uNGAL were examined by the ROC curve. Finally, appropriate regression analysis models were applied to determine the independent correlation of the variables.
P values <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS (Statistical Package for Social Sciences) ver. 23.0 statistical software system (IBM Corporation, Chicago, Illinois, USA).

RESULTS

The summary of patients' characteristics is shown in Table 1. Before ESWL treatment, 42 (67,74%) patients had completely preserved renal function, while it was slightly reduced in 20 (32.26%) patients. However, 12 hours after ESWL treatment, a minority of patients had normal renal function [29 (46.77%) vs 33 (53.2%)]. Recovery of renal function was observed 7 days and 3 months after the treatment, [32 (51.6%) vs 30 (48.4%), 37 (59.68%) vs 25 (40.32%), respectively] (Table 2).
The median value of eGFR before ESWL was 104.5 (83.0–126.0) mL/min/m^2, and it dropped significantly by 15.3% 12 h after the treatment [88.5 (72.5–109.8) mL/ min/m^2] ($p<0.001$). In the peri-

Table 1. *The summary of patients' characteristics*

Variable	Value
No. of patients	62
Age (years)	46.1 ±10.3 (18–59)
Sex	
Male	38 (61.29%)
Female	24 (38.71)
BMI (kg/m^2)	22.1 ±3.4 (17.4–30.0)
Stone size (mm)	9.3 ±3.1 (5.6–17.6)
Localization	
Upper pole	15 (24.19%)
Middle calyces	20 (32.26%)
Lower pole	4 (6.45%)
Renal pelvis	23 (37.10%)
Side	
Right	30 (48.39%)
Left	32 (51.61%)

Values are presented as absolute, relative numbers, and/or mean ±SD (range) appropriate
BMI – body mass index

Table 2. *Renal function of patients in the observed period after ESWL treatment*

	Renal function	
	Normal N (%)	Slightly reduced N (%)
Pre-treatment	42 (67.74%)	20 (32.26%)
12 hours after	29 (46.77%)	33 (53.23%)
7 days after	32 (51.61%)	30 (48.39%)
3 months after	37 (59.68%)	25 (40.32%)

Data are presented with absolute and relative numbers
ESWL – extracorporeal shock wave lithotripsy; N – number

od from 12 h to 7 days after ESWL, the median eGFR increased by 1.1% [89.5 (75.0–110.0) mL/min/m^2], without statistical significance (p=0.88). In the following period from 7 days to 3 months, eGFR increased statistically significantly by 5.0% [94.0 (79.0–121.3) mL/min/m^2] (p <0.001). eGFR 3 months after ESWL was statistically significantly lower by 10.1% compared to pre-ESWL measurement [94.0 (79.0–121.3) vs 104.5 (83.0–126.0) mL/min/m^2] (p <0.001) (Table 3).

The median value of uNGAL level in patients before ESWL was 19.6 (8.63–40.0) ng /mL, and increased significantly by 126.0%, 6 h after ESWL [44.3 (14.5–125.2) ng/mL] (p <0.001). In the period from 6 to 12 h after ESWL, the median level of uNGAL increased statistically significantly by 202.5% [134.0 (25.1–282.2) ng/mL], (p <0.001). A significant difference was found in uNGAL level 12 h after ESWL compared to the pre-treatment measurement, where the uNGAL level was higher by 583.7% [134.0 (25.1–282.2) vs 19.6 (8.63–40.0) ng/mL], (p <0.001) (Table 3). At 12 h after the procedure, uNGAL levels were significantly negatively associated with eGFR, 12 h, 7 days and 3 months after the ESWL [(Rho = -0.351; p = 0.001), (Rho = -0.397; p = 0.002), (Rho = -0.387; p = 0.003), respectively] (Table 3).

The sensitivity of uNGAL was 60.6%; its specificity was 75.0%, with a positive predictive value of 74.0%

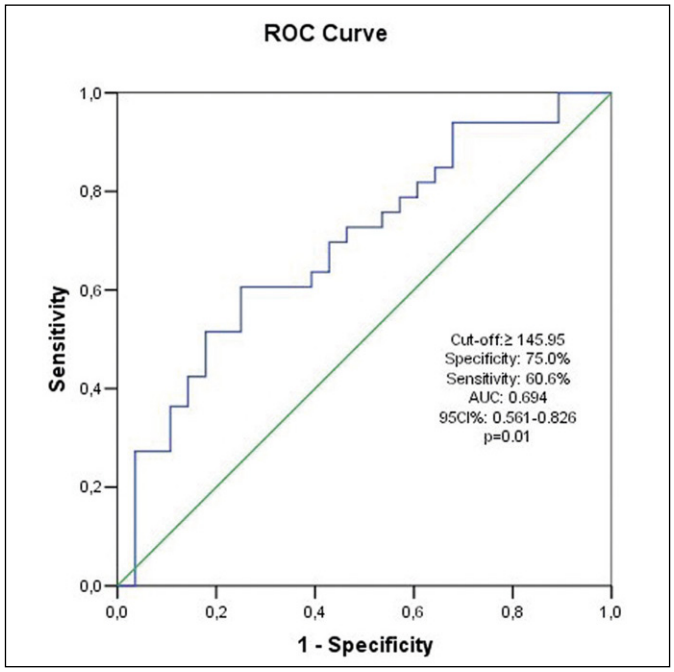

Figure 2. *Sensitivity and specificity of uNGAL measured 12 h after treatment.*

uNGAL – urinary neutrophil gelatinose-associated lipocalin; AUC – area under curve; ROC – receiver operating characteristic

and a negative predictive value of 61.7%. The area under the curve (AUC) for uNGAL was 0.694, and the cut-off value was 145.95 ng/mL (Figure 2).

DISCUSSION

ESWL represents an effective non-invasive method of treating urinary stones [2, 3, 4, 7]. For stones with a maximum diameter of 1.5–2.0 cm located in the renal calyces of the upper and middle groups, as well as stones of the proximal and middle third of the ureter, ESWL is the method of choice, with disintegration and complete elimination rate of 82–90%. For larger stones, the success rate drops to about 50%. For stones of the lower half of the kidney, and the

Table 3. *Change of eGFR and uNGAL level and their correlation after ESWL treatment*

	Pre-treatment	6 hours after	12 hours after	7 days after	3 months after
eGFR (mL/min/m^2)	104.5 (83.0–126.0)		88.5 (72.5–109.8) [-15.3%; p <0.001]	89.5 (75.0–110.0) [+1.1%; p = 0.88)]	94.0 (79.0–121.3)* [+5.0%; p <0.001]
uNGAL (ng/mL)	19.6 (8.63–40.0)	44.3 (14.5–125.2) [+126.0%; p <0.001]	134.0 (25.1–282.2)* [+202.5%; p <0.001]		
uNGAL 12 hours after treatment			Rho =-0.351 p = 0.001	Rho =-0.351 p = 0.001	Rho =-0.378 p = 0.003

eGFR – estimated glomerular filtration rate; uNGAL – urinary neutrophil gelatinose-associated lipocalin; ESWL – extracorporeal shock wave lithotripsy; *p <0,001 relative to pre-treatment values

distal third of the ureter, ESWL is the second treatment choice, with a success rate of 59% and 58–67%, respectively [14]. Better results are associated with stone attenuation less than 1000 HU and stone to skin distance (SSD) <10 cm [15].

Although ESWL is a popular method worldwide, adverse effects have been reported [5, 6, 8, 16]. The tissue injury caused by ESWL can lead to loss of renal mass and its functional impairment. The shock waves lead to a local increase in temperature and pressure due to the mechanism of cavitation, which is the most likely cause of kidney injury [5–8]. The tensile component of the wave can excite cavitation and form the bubbles in the urine surrounding the stone. When bubbles are collapsed by the compressive components of the wave, high-velocity microjets of liquid are formed which lead to stone damage [6]. These microjets and bubbles as well as the negative wave pressure, are capable of puncturing the wall of blood vessel.

AKI is a syndrome characterized by a sudden decline in renal function that leads to the accumulation of metabolic breakdown products, fluid retention, extracellular volume, and electrolyte imbalance, which ultimately lead to glomerular filtration disorders [17]. Today, acute renal impairment is defined according to established AKIN (Acute Kidney Injury Network) and RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria based on changes in serum creatinine levels and the amount of diuresis. The term includes a wide range, from minimal changes in renal function to the need for renal replacement therapy [18].

In clinical practice, impaired renal function is usually diagnosed by measuring serum creatinine which is an unreliable indicator of acute changes due to dependence on age, gender, BMI, medications, and hydration status. Its initial measurements do not reflect the extent of tissue damage, as an increase in creatinine always follows damage, and changes are registered only after a few days [19]. Serum creatinine value does not increase until more than 50% of the glomerular filtration rate is lost [20]. It usually leads to late detection of AKI and delayed initiation of therapy. Therefore, very promising newer biomarkers were introduced as 'kidney troponins' and hinted as indicators of early kidney damage [10].

Studies that followed the long-term effects of ESWL in a population of chronic kidney disease (CKD) patients with nephrolithiasis suggest its safety and efficacy. Yoo et al. showed that stone removal by ESWL is associated with delayed deterioration of renal function in CKD patients with nephrolithiasis. There was no difference in eGFR values during the first year of follow-up. However, eGFR decreased more slowly in the ESWL-treated group. In addition, among patients treated with ESWL, eGFR decreased more rapidly in patients with unsuccessful procedure [21].

Our results suggest that a certain degree of renal damage occurs following the ESWL. Almost a third of patients had slightly reduced function before ESWL which increased significantly 12 hours after. Recovery of renal function was observed 7 days to 3 months after the treatment. The median value of eGFR after 3 months was significantly lower by 10.1% compared to pre-treatment measurements.

Among more than 100 substances that have been identified as biomarkers of AKI, the two most often studied are cystatin C and NGAL. While cystatin C is a marker of kidney function, NGAL is a marker of kidney damage [10]. Under physiological conditions, small amounts of NGAL circulate in the bloodstream and are filtered by glomeruli. Normal reference interval for NGAL is 40–100 ng/ml [22, 23]. During AKI, NGAL rapidly accumulates in serum due to its increased nephron excretion, as well as a decrease in eGFR. This, combined with a short half-life (10 min), makes NGAL a potential early marker of AKI [22].

NGAL level significantly increases a few hours after exposure to ischemic or nephrotoxic agent, as a result of specific gene activation and affects new cell proliferation. It appears that it is correlated with serum creatinine but preceding its growth [24]. After AKI, pNGAL level increases tenfold and uNGAL level increases hundredfold [22, 25].

NGAL has been investigated in several studies on animal models in which the onset of AKI was induced, suggesting its role as a potential biomarker of renal impairment. Mesar et al. observed the gene expression in patients with ischemic-reperfusion renal injuries. pNGAL and uNGAL levels have been increased very soon after the onset of AKI [19]. Its increase was observed during cardiothoracic surgery, after radiological examinations as part of contrast nephropathy, and nephrotoxic effect of cytostatics. Elevated NGAL levels were shown as early as 2–4 hours after surgery [19, 24].

Some studies emphasize NGAL's ability to predict recovery of kidney function as well. A large study among patients with community-acquired pneumonia showed that pNGAL appears to be a useful biomarker for predicting renal recovery with high sensitivity and specificity for AKI. Moreover, NGAL was increased 48 hours before significant changes in creatinine and urea levels. In addition, NGAL improves the accuracy of predicting the onset of AKI and recovery, compared to creatinine alone. No difference in IL-6 levels during the recovery and poor

correlation between IL-6 and pNGAL, suggested that pNGAL is a unique marker of AKI [26].

In burn patients, NGAL is also an early predictive marker for AKI with a sensitivity of 87%, and specificity of 91% for a cut-off value of 125 ng/ml. In a study of 45 patients with burn injuries, NGAL levels on days 3 and 7 were found to be significantly higher in patients who developed AKI [27]. In addition, NGAL is an early independent predictor of AKI during acute resuscitation for severe burn injury [22, 28].

Our results showed that the median uNGAL level 6 h after ESWL increased significantly by 126.0%. The growth rate continued 12 h after and was significantly higher by 583.7% compared to the pretreatment level. These results are consistent with the results of Vittori et al. who observed an early increase in uNGAL after ESWL. The authors showed its increase 3 hours after treatment, although its levels returned to normal within a period of 1 to 30 days. The study also showed a significantly higher NGAL/creatinine ratio in urine measured 3 hours after ESWL [29]. Similar results were reported by Ng et al., showing a significant increase of uNGAL immediately after the treatment [30]. Another study showed that 30.4% of patients developed AKI with a significant increase of pNGAL and uNGA during a 12-month follow-up [31].

In the present study, ROC curve analysis revealed that uNGAL level 12 h after ESWL was a significant biomarker of AKI. eGFR was significantly negatively associated with uNGAL 12 hours after the treatment. This suggests that uNGAL level may be a predictor of kidney damage. Sensitivity and specificity 12 h after ESWL was 80.8% and 58.0%, respectively. He et al. showed that uNGAL level correlates with the degree of AKI [32]. uNGAL is a more sensitive marker of renal damage than KIM-1 and β2-microglobulin, and can be determined before an increase in serum creatinine. uNGAL is also associated with cystatin C level and significantly negatively associated with eGFR [33].

Bolignano et al. found that urinary and serum NGAL predicted the progression of chronic renal failure, independent of other potential predictors, including GFR and age [34]. Contrary to these results, Kardakos et al. and Zekey et al. did not establish a significant difference in uNGAL levels before and after ESWL treatment [35, 36].

A recent systematic review performed by Brewin et al. suggests that NGAL, as well as others novel biomarkers, could be used in the diagnosis, prognosis, and stone-treatment response in patients with kidney stones. However, they may not be reliable as the sole diagnostic or prognostic tool for these patients as they are readily confounded by other causes of kidney injury [37].

The main limitation of our study is the relatively small number of respondents included in the final cohort. The reason for this is the very rigorous inclusion and exclusion criteria, by which we sought to eliminate factors that could lead to renal injury and potentially raise uNGAL levels.

The ability to detect renal injury after ESWL in a reliable and noninvasive manner can be of great clinical benefit. Contrary to earlier assumptions that AKI generally has no long-term consequences, recent research shows that these impairments may increase the risk of developing chronic renal disease. Some studies have shown that the severity, duration, and frequency of AKI are predictors of poor treatment outcomes. Also, they suggest that reduction of renal tissue, vascular insufficiency, and cell disorders are modulators of progression in patients with and without coexistent renal impairment [38].

CONSLUSIONS

Our results suggest that a certain degree of renal damage occurs following ESWL treatment. uNGAL appears to be a useful biomarker for the assessment and prediction of renal impairment, with a significant increase as early as 6 hours after treatment. It achieved the peek value after 12 hours with the highest specificity and sensitivity. These levels were significantly negatively associated with the eGFR, suggesting that uNGAL may be a predictor of eGFR as a measure of renal impairment. However, further research involving studies with a larger pool of patients is needed.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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