Evaluation of the different ESWL session intervals on acute kidney injury using urinary NGAL and KIM-1

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ABSTRACT

Introduction: We aimed to compare two different extracorporeal shockwave lithotripsy (ESWL) session intervals in terms of morbidity, clinical outcomes, and procedural safety, based on biomarkers used to detect acute kidney injury (AKI).

Methods: Patients were randomized into two groups prior to ESWL. In group 1, ESWL sessions were performed on days 0, 4, and 8, whereas in group 2, sessions were performed on days 0, 7, and 14. Urine samples were collected using the midstream technique and centrifuged at 3500 rpm for four minutes on the same day, then stored at -80°C. Kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) levels were measured using the ELISA method from urine samples obtained before the procedure and after three ESWL sessions.

Results: A total of 51 patients were included (group 1: n=25; group 2: n=26), with a median age of 45 years; 64.7% were male. Baseline demographic characteristics, comorbidities, and stone-related parameters were comparable between the groups. Preprocedural GFR and KIM-1 levels were similar; however, baseline NGAL levels were significantly higher in group 1 (p=0.009). Postprocedural GFR, NGAL, and KIM-1 levels did not differ significantly

KEY MESSAGES

- Different ESWL session intervals did not result in significant differences in urinary NGAL and KIM-1 levels or GFR changes.
- Clinical outcomes, including complication rates and stone-free rates, were comparable between treatment schedules.
- Within the limitations of this study, shorter ESWL intervals were not associated with significantly increased AKI markers; however, larger studies are needed before definitive conclusions regarding equivalence between protocols can be drawn.

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between the groups. Likewise, the changes in biomarkers and GFR were comparable between groups. In addition, complications and stone-free rates were similar between the groups.
Conclusions: Shorter ESWL session intervals were not associated with increased AKI. These findings suggest that there is no difference in safety between shorter and longer treatment intervals, and that the choice should be determined by the clinician based on practicality and feasibility.

INTRODUCTION

The incidence of urinary system stone disease is influenced by many factors such as geographic region, socioeconomic status and dietary habits. The lifetime risk of developing urinary stones ranges between 1% and 15% [1]. In the treatment of urinary system stones, extracorporeal shock wave lithotripsy (ESWL), retrograde intrarenal procedures, percutaneous nephrolithotomy, laparoscopic and open surgical procedures may be preferred. Due to its effectiveness, minimally invasive nature, ease of application, low morbidity, and generally not requiring hospitalization, ESWL is often preferred as a first-line treatment for urinary system stone disease [2].ESWL refers to the fragmentation of stones by focusing shock waves generated from an external source onto the stone within the body. One of the most important advantages of this procedure is its very low complication rate [3].

Several biomarkers indicating acute kidney injury (AKI) have been reported in the literature. Among these, neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein consisting of a single polypeptide chain and is secreted by activated neutrophils [4]. NGAL was first identified in the granules of neutrophils during their maturation process in the bone marrow [5]. Its expression in human tissues is normally low, being present in the kidney, heart, liver, and lungs. In the kidney, NGAL is expressed by proximal and distal tubular epithelial cells [6]. Following renal injury, particularly tubular epithelial cells express NGAL at higher levels [7]. Due to its small molecular size, NGAL is freely filtered through the glomeruli and can be easily detected in urine. Therefore, urinary NGAL is a highly sensitive and early biomarker of AKI [8].

Kidney Injury Molecule-1 (KIM-1) is a transmembrane glycoprotein expressed by epithelial cells in the proximal tubule of the kidney and plays a role in cell-surface and cell-matrix interactions [9]. Studies have shown that KIM-1 is highly expressed during epithelial regeneration following proximal tubular injury and in the development of interstitial fibrosis [10, 11]. One of the most important features that make it an ideal biomarker for AKI is that, as a transmembrane protein extending into the lumen, it is rapidly shed into the tubular lumen and can be easily detected in urine [12].

To the best of our knowledge, prospective studies evaluating the impact of different ESWL application protocols on AKI are limited. The aim of our study was to compare two commonly used intervals between ESWL sessions with regard to morbidity, renal injury, and procedural safety.

METHODS

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This randomized prospective study was conducted in our tertiary centre. The study was approved by the Institutional Review Board (IRB) where the study took place with the protocol number of Local Ethics Committee (Protocol no: 2025.104557). The trial was prospectively registered in the ClinicalTrials.gov (NCT07341269). Informed consent was obtained by all patients.

Between March 2025 and June 2025, patients older than 18 years with renal stones, sterile urine culture and an indication for ESWL were included in the study. Patients were treated with ESWL modality in accordance with the recommendations of the EAU guidelines [13]. Patients with baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m², multiple stones, active urinary tract infection (UTI), those with nephrostomy or DJ stents, body mass index (BMI)> 30 kg/m^2, with stone diameter > 20 mm, bleeding disorders, presence of radiolucent or bilateral kidney stones, pregnancy, those receiving anticoagulant therapy, and those with a history of cardiac arrhythmia were excluded.

Before ESWL, patients were divided into two groups. Patients were randomly assigned in a 1:1 ratio to either Group 1 or Group 2 using a computer-generated randomization sequence created through randomizer.org. The allocation sequence was generated prior to patient enrolment, and group assignment was performed before the first ESWL session. In Group 1, ESWL sessions were scheduled on days 0, 4, and 8, whereas in Group 2, sessions were performed on days 0, 7, and 14. These procedure intervals were selected from the two most commonly used protocols, both in the literature and in routine clinical practice [14, 15].

The primary endpoint of this study was to evaluate the effect of different session intervals in a three-session ESWL treatment protocol, which has not been clearly defined in the literature to date. The assessment of acute kidney damage through changes in urinary biomarkers (such as NGAL and KIM-1) used to demonstrate AKI before and after ESWL, and the evaluation of stone free rate and the development of complications associated with different treatment intervals, are included among the secondary endpoints.

Post-procedural complications, including pain, fever, UTI, and haematuria, were clinically assessed within the first week after the final ESWL session. Stone-free status was determined one month after treatment using non-contrast computed tomography, which is considered the most sensitive modality for detecting residual fragments. Stones ≥4 mm were considered residual stones. [13].

The demographic characteristics of the patients included in the study were first compared according to the ESWL protocols applied, along with stone related parameters such as location, maximum diameter, volume, and stone density. Stone volumes were calculated manually using the ellipsoid formula [16]. Subsequently, pre- and post-ESWL GFR, NGAL, and KIM-1 values were compared between the groups. GFR was calculated using the modification of diet in renal disease (MDRD) formula [17]. In this study, CKD was defined as an estimated GFR <60 mL/min/1.73 m² at the 6-month follow-up visit [18].

ESWL procedures were carried out by a single experienced endourologist using an electromagnetic lithotripter (Elmed Lithoskop®). All patients received preprocedural antibiotic prophylaxis with ceftriaxone. Each session was performed using a standardised protocol. Treatment was terminated when sufficient stone fragmentation was achieved or

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when a maximum of 2,500 shock waves with a total energy of 80 J was reached. No patients underwent ureteral stent placement.

Biochemical analyses

Spot urine samples were collected prior to the procedure and at first hour post-procedure after the completion of three ESWL sessions under standardized conditions between 09:00 and 10:00 a.m. after at least 3 hours of fasting, with patients maintaining normal hydration, in order to minimize diurnal, dietary, and hydration-related variability. The collected urine samples were centrifuged at 3500 rpm for 4 minutes on the same day, after which 15 mL of the separated supernatant was obtained and stored at −80°C for up to one month until analysis. Urinary KIM-1 (SUNRED BIO, Cat. No: 201-12-1720) and NGAL (SUNRED BIO, Cat. No: 201-12-1100) levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions, as previously described for urinary AKI biomarker assessment [19, 20].

Statistical analysis

When calculating the sample size, the prospective study by Hughes et al. [21] examining the development of AKI following ESWL and changes in biomarkers was used as a reference study. A total of 29 were calculated to be required to achieve 95% power ($\alpha = 0.05$). Statistical analyses were carried out using IBM SPSS (Statistical Package for the Social Sciences) version 25.0. The Kolmogorov-Smirnov test was used for normality analysis. Non-parametric tests were used due to the non-normal distribution. Nominal data were presented as frequency and percentage values. Continuous variables are reported as median and interquartile range (IQR), whereas categorical variables were assessed using the Chi-square or Fisher's Exact test. Statistical significance was defined as a p value less than 0.05.

RESULTS

A total of 51 patients were included in the study, with 25 patients in Group 1 and 26 patients in Group 2. Of the patients included in the study, 33 (64.7%) were male and 18 (35.3%) were female. The median age was 45 (33-60) years.

The baseline demographic and clinical characteristics of the patients are presented in Table 1. There were no statistically significant differences between the groups in terms of age, sex distribution, BMI, and comorbidities including diabetes mellitus, hypertension, and coronary artery disease. Similarly, stone-related parameters, including stone side, location, diameter, volume, and density were comparable between the groups. Pre-procedural laboratory parameters were compared between the groups. Median baseline GFR and KIM-1 values were similar between groups. However, baseline NGAL levels were significantly higher in Group 1 compared to Group 2 ($p = 0.009$). Post-procedural measurements also showed no significant differences between the groups in terms of GFR, NGAL, or KIM-1 levels.

When the changes in biomarker levels were evaluated, the median ΔGFR values were −6 mL/min/1.73 m² in Group 1 and 0 mL/min/1.73 m² in Group 2, without a statistically significant difference. Similarly, ΔNGAL values were 151.39 ng/mL in Group 1 and 247.03 ng/mL in Group 2 ($p = 0.749$). The change in KIM-1 levels was also comparable between the

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groups. Overall, although baseline NGAL levels were significantly higher in Group 1, no significant differences were observed between the groups regarding post-procedural biomarker levels or the magnitude of change in GFR, NGAL, and KIM-1 (Table 2).
Then, the complications and stone free rates occurring between the groups were compared. The rates of pain, fever, haematuria, and UTI were similar between Group 1 and Group 2, with no statistically significant differences observed. There was no statistically significant difference in stone-free status between the groups ($p = 0.918$). Complete stone-free status was achieved in 10 patients (40%) in Group 1 and 11 patients (42.3%) in Group 2. Residual fragments <4 mm were observed in 10 (40%) and 9 (34.6%) patients, while residual fragments ≥4 mm were present in 5 (20%) and 6 (23.1%) patients in Group 1 and Group 2, respectively (Table 3).

During long-term follow-up, CKD was observed in 6 (11.8%) patients. In these patients, eGFR values were slightly below 60 mL/min/1.73 m², and no additional treatment was required.

DISCUSSION

In this prospective study, we evaluated the effect of different ESWL session intervals on AKI using urinary NGAL and KIM-1 as biomarkers. Our findings demonstrated that although baseline NGAL levels were higher in Group 1, post-procedural biomarker levels and the magnitude of change in GFR, NGAL, and KIM-1 were comparable between the groups. Although no statistically significant differences in ΔGFR were observed between groups, a numerical trend toward variation was noted, which may become more evident in a larger cohort with greater statistical power. Therefore, the absence of significance should not be interpreted as definitive evidence of equivalence between groups. In addition, while urinary biomarkers such as NGAL and KIM-1 are widely used indicators of tubular injury, they may not fully reflect subtle or early functional renal changes, particularly in the context of repeated ESWL exposure. This raises the possibility that these biomarkers, although sensitive to overt tubular injury, may have limited resolution for detecting minor or subclinical alterations in renal function.

Moreover, complication rates and stone-free outcomes did not differ significantly between treatment protocols. These results suggest that different ESWL session intervals may not have a significant impact on short-term renal injury as assessed by these biomarkers. During long-term follow-up, CKD was observed in 11.8% of patients. However, the decline in renal function was generally mild, with eGFR values only slightly below the threshold of 60 mL/min/1.73 m², and none of the patients required nephrological intervention or additional treatment. Importantly, the causal relationship between ESWL exposure and CKD development cannot be definitively established in the absence of a non-treated control group.

In addition, urinary stone disease itself is a recognized risk factor for long-term renal functional decline due to recurrent obstruction, inflammation, infections, and underlying metabolic abnormalities. Therefore, the observed CKD incidence should be interpreted cautiously. These findings also suggest that currently used urinary biomarkers may have limited sensitivity to detect subtle or long-term renal functional changes following ESWL.

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Larger studies with longer follow-up and appropriate control groups are needed to better clarify the long-term renal effects of repeated ESWL exposure.

Fadallah et al. evaluated the optimal interval between repeated ESWL sessions by comparing 3-, 7-, and 14-day intervals and assessing renal injury using urinary KIM-1, NGAL, and IL-18 levels [15]. In that study, tubular injury biomarkers significantly increased after ESWL and remained elevated when the second session was performed after only 3 days. Moreover, a significant decline in ipsilateral renal split function at the 3-month follow-up was observed in the 3-day interval group, leading the authors to recommend an interval of at least 7 days between ESWL sessions to allow adequate renal recovery. In contrast, our findings did not demonstrate a significant difference in renal injury markers between the shorter and the longer protocol. Post-procedural NGAL and KIM-1 levels, as well as changes in GFR, were comparable between the groups, suggesting that the shorter treatment interval used in our protocol did not result in increased AKI. We believe that several methodological differences may explain this discrepancy. First, the shortest interval evaluated in the previous study was 3 days, whereas the shortest interval in our protocol was 4 days, which may allow additional time for renal recovery between sessions. Second, differences in patient population, ESWL parameters, and sample size may also have contributed to the variation in findings. With the light of these findings, while previous evidence suggested that very short intervals between ESWL sessions may impair renal recovery, our results demonstrate that a 4 day interval may still be safe in terms of short-term renal injury markers.

Although an evaluation based on biomarkers, as in our study, was not performed, Alzubir et al. investigated the optimal interval between ESWL sessions by assessing stone-free rates and complications [14]. In that study, patients were treated at intervals of 3 days, 1 week, and 2 weeks, and similar outcomes were observed among the subgroups in terms of stone-free rates and complication profiles. Our findings are consistent with these results; in our study, no significant differences were observed between the 0–4–8 day and 0–7–14 day protocols in terms of stone-free rates or complication rates. However, while the aforementioned study primarily focused on clinical outcomes and conventional laboratory parameters such as β2-microglobulinuria and microalbuminuria, our study additionally evaluated AKI using more specific urinary biomarkers. The absence of significant differences in these biomarkers between the groups further supports the notion that shorter treatment intervals do not increase the risk of AKI following ESWL.

The potential renoprotective effects of different ESWL application strategies, such as ramping and pause protocols, have also been investigated in the literature. In a large prospective randomized study including 320 patients, different energy escalation and pause protocols were compared in terms of renal injury, using imaging findings, clinical outcomes, and urinary biomarkers [22]. Ng et al. reported that neither ramping nor pause protocols significantly reduced the incidence of renal hematoma, nor did they lead to significant differences in urinary biomarker levels or overall complication rates between groups. Similarly, in our study, although different treatment protocols were evaluated, no significant differences were observed between the groups in terms of complication rates or overall renal injury markers. Taken together, these findings suggest that while technical modifications of ESWL protocols may not markedly reduce overt renal injury. We think that more sensitive

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biomarkers and functional assessments may be required to better understand their impact on renal physiology.

Aydin et al. investigated the role of KIM-1 in determining the optimal interval between ESWL sessions by evaluating urinary KIM-1 levels at several time points after the procedure [23]. The authors reported a significant increase in KIM-1 levels at 1 hour and 1 day following ESWL, suggesting acute tubular injury related to the procedure, while KIM-1 levels returned to baseline within one week. Based on these findings, they proposed that KIM-1 could be used as a biomarker to determine the appropriate interval between repeated ESWL sessions. In contrast to these findings, our study did not show an increase in KIM-1 levels after the ESWL; instead, a slight decrease was observed in both treatment groups. Several factors may explain this discrepancy. We believe that timing of post-procedural measurements differed between studies. In the previous study, KIM-1 was measured in the early hours following ESWL, when acute tubular injury markers are expected to peak, whereas in our study measurements were performed at later time points, which may have missed this transient elevation. Furthermore, it is also possible that the reduction in urinary KIM-1 levels observed in our cohort reflects the relief of stone-related tubular stress after fragmentation and improved urinary drainage. Therefore, variations in sampling time and clinical context should be considered when interpreting urinary biomarker changes following ESWL.

In addition to conventional urinary biomarkers such as NGAL and KIM-1, recent studies have focused on novel molecular biomarkers, including long non-coding RNAs (lncRNAs) and messenger RNAs (mRNAs), for the early detection of renal injury following ESWL. In a prospective study conducted by Tawfick [24] including 60 patients undergoing ESWL and 30 healthy controls, urinary levels of lncRNAs (SBF2-AS1, FENDRR-19) and mRNAs (GBP1, NLRP3) were measured before, 2 hours, and 24 hours after the procedure. The authors showed that these biomarkers were significantly elevated both at baseline and after ESWL, suggesting their potential role in detecting renal injury at an early stage. Unlike our study, which evaluated NGAL and KIM-1 levels, this study utilized molecular biomarkers that may reflect underlying inflammatory and cellular injury pathways more directly. We believe that while traditional biomarkers such as NGAL and KIM-1 provide valuable information regarding renal tubular injury, emerging biomarkers such as lncRNAs and mRNAs may offer additional insights into early and subclinical renal damage. Therefore, future studies integrating both conventional and molecular biomarkers may improve the early detection and risk stratification of renal injury following ESWL.

Although it may be suggested, as an expert opinion, that performing ESWL at shorter session intervals could potentially improve patient convenience and reduce the overall treatment duration, the short-interval protocol did not result in significantly different changes in GFR, NGAL, or KIM-1 levels compared with the 0–7–14 day protocol in terms of clinical outcomes. Moreover, neither protocol was associated with the development of AKI. Based on our findings, both ESWL session intervals appear to be safe and can be applied to patients with confidence. However, larger studies with longer follow-up are needed to confirm the long-term renal safety of shorter ESWL intervals.

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In addition, we consider it necessary to mention the kit costs at this stage: the kits were purchased in 2025. The unit cost for a 96-test urine NGAL kit is 569 euros, whereas the 96-test urine KIM-1 kit costs 391 euros. On a per-sample basis, these costs correspond to 5.92 euros for NGAL and 4.07 euros for KIM-1.

Limitations

This study has several limitations that should be acknowledged. First, urinary biomarkers were measured only before the first session and at the first hour after completion of the third ESWL session. The absence of early post-procedural measurements after each session may have limited our ability to capture transient peak elevations of NGAL and KIM-1. We believe that more frequent sampling could have provided a more detailed temporal profile of biomarker dynamics.

Second, urinary NGAL and KIM-1 levels were not normalized to urinary creatinine concentrations. Although samples were collected under standardized conditions to minimize variability, normalization could have improved the accuracy of biomarker interpretation.

Third, absence of systematic assessment of hydronephrosis before and after ESWL is a limitation of this study. Given that hydronephrosis may reflect ongoing obstruction and renal parenchymal stress, its presence or resolution could potentially influence urinary biomarker levels. Accordingly, the confounding effect of dynamic changes in hydronephrosis on NGAL and KIM-1 cannot be excluded. Moreover, long-term renal functional outcomes and the potential cumulative impact of repeated ESWL sessions were not evaluated.

Given the substantial biological variability of urinary NGAL and KIM-1, the present sample size was likely sufficient to detect only moderate-to-large intergroup differences. Therefore, smaller changes in renal injury biomarkers between protocols cannot be excluded. Furthermore, regional differences in ESWL practice patterns may limit the generalizability of our results. Finally, absence of a non-treated control group limits our ability to distinguish the effect of ESWL from the natural course of stone disease on changes in eGFR over time.

CONCLUSIONS

Our findings suggest that different ESWL session intervals do not significantly influence the development of short-term AKI when evaluated using urinary NGAL and KIM-1 biomarkers. Additionally, shorter interval protocol demonstrated comparable changes in complication rates, and stone-free outcomes when compared with the longer interval protocol. These findings indicate that, in terms of safety, there appears to be no significant difference between shorter and longer treatment intervals. Therefore, the selection of the appropriate interval should primarily be guided by the clinician’s preference, taking into account practical considerations, patient convenience, and overall feasibility of treatment.

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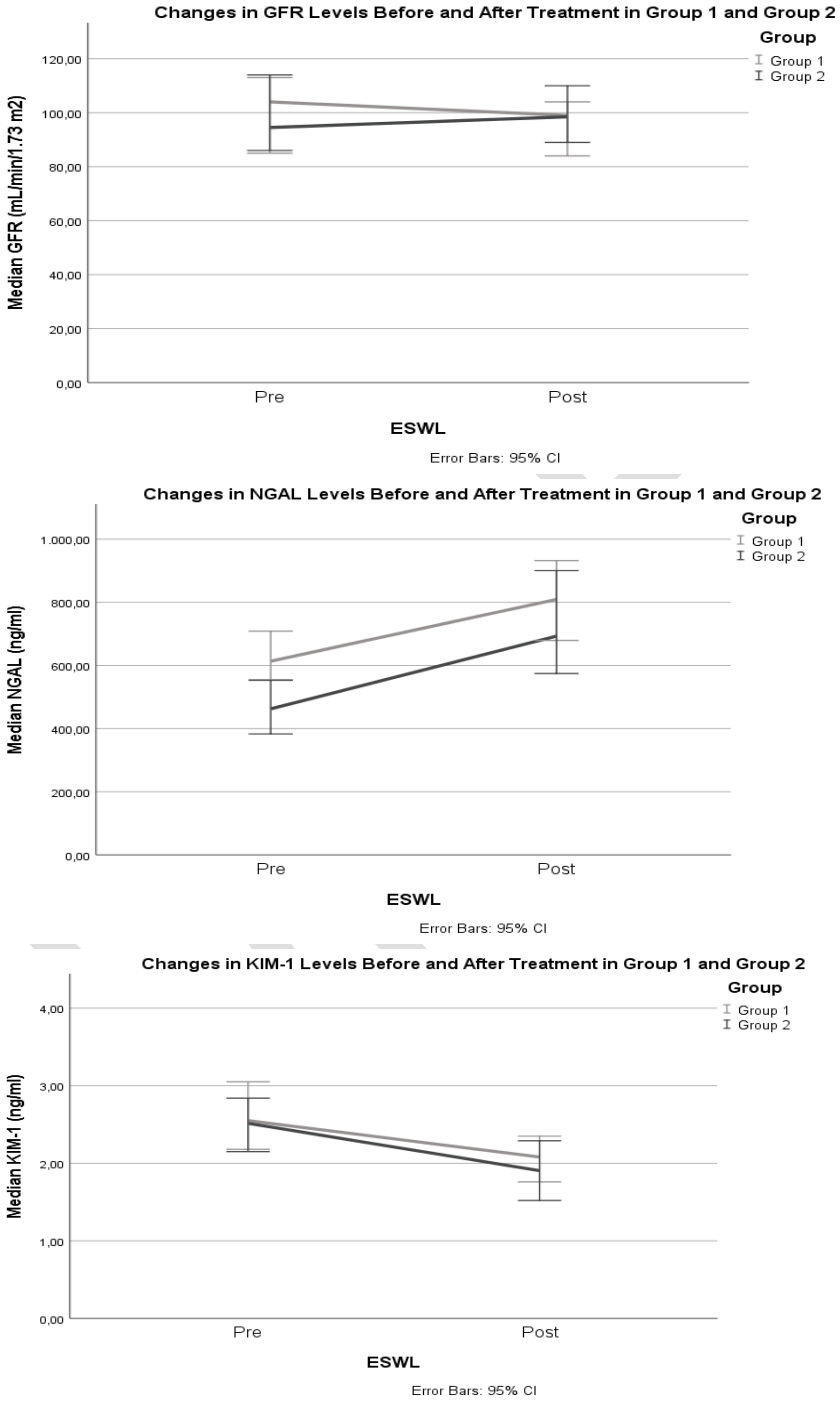
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FIGURES AND TABLES

Figure 1. Changes in renal function and urinary biomarker levels before and after ESWL in Group 1 and Group 2. Median GFR, urinary NGAL, and KIM-1 levels are shown at pre- and post-treatment time points.



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Figure 2. Comparison of changes in urinary NGAL and KIM-1 levels between groups after ESWL.

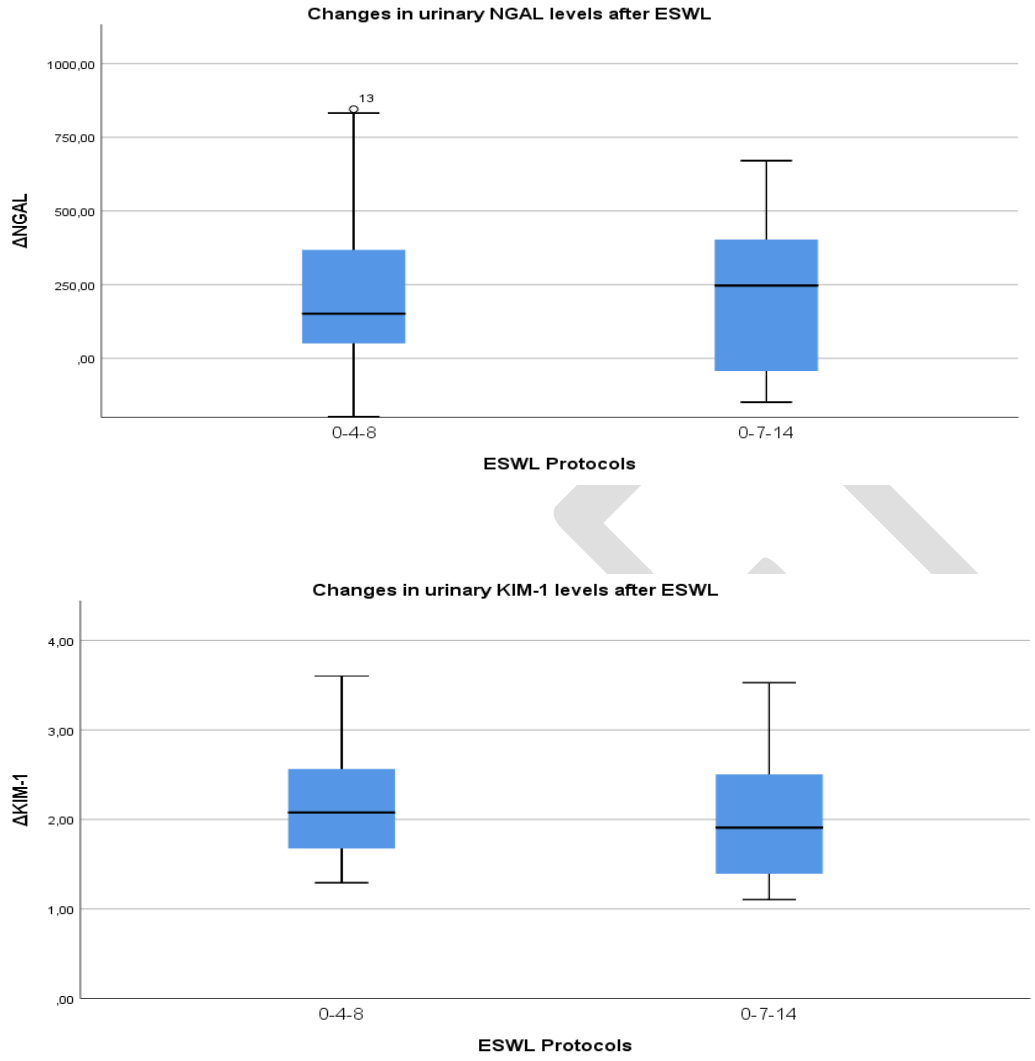


Table 1. Comparison of demographic characteristics, stone features, and renal function biomarkers between the study groups			
	Group 1 (n=25)	**Group 2 (n=26)**	**P**
Age (years)	48.5 (24.75–58.25)	41 (33–65.5)	0.564
Sex (male/female)	15/10 (60/40)	18/8 (69.2/30.8)	0.49
BMI (kg/m^2)	26.6 (23.88–27.72)	27.25 (25.97–28.88)	0.251
Diabetes mellitus	3 (12)	4 (15.4)	0.523
Hypertension	5 (20)	8 (30.8)	0.378
Coronary artery disease	1 (4)	3 (11.5)	0.32
Stone side			
Right	12 (48)	13 (50)	0.886
Left	13 (52)	13 (50)	
Stone location			

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Renal pelvis	17 (68)	15 (57.7)	0.689
Lower pole	2 (8)	4 (15.4)	
Middle pole	3 (12)	5 (19.2)	
Upper pole	3 (12)	2 (7.7)	
Stone diameter (mm)	12 (9.5−14.5)	12 (9.75−17.25)	0.698
Stone volume (mm^3)	505 (327.5−1247)	406.5 (188−947)	0.147
Stone density (Hounsfield unit)			
Maximum	940 (819−1100.5)	1040 (856−1132.5)	0.235
Average	722 (586.5−854)	750 (462.75−906.25)	0.814
Preprocedure			
GFR (mL/min/1.73 m^2)	104 (80.5−117.5)	94.5 (85−115.5)	0.88
NGAL (ng/mL)	613.58 (493.62−751.25)	462.53 (361.52−607.29)	0.009
KIM-1 (ng/mL)	2.54 (1.88−3.08)	2.51 (2.05−2.89)	0.578
Postprocedure			
GFR (mL/min/1.73 m^2)	99 (77.5−107)	98.5 (86.5−116)	0.456
NGAL (ng/mL)	809.35 (666.96−992.67)	666.97 (507.36−925.26)	0.095
KIM-1 (ng/mL)	2.07 (1.63−2.64)	1.9 (1.38−2.52)	0.429

All continuous variables are presented as median (interquartile range, IQR), and categorical variables are presented as numbers and percentages. BMI: body mass index; GFR: glomerular filtration rate; IQR: interquartile range; KIM-1: kidney injury molecule-1; NGAL: neutrophil gelatinase-associated lipocalin.

Table 2. Changes in biomarker levels between groups

	Group 1 (n=25)	**Group 2 (n=26)**	**p**
ΔGFR (mL/min/1.73 m^2)	-6 (-16−2)	0 (-11.75−12)	0.097
ΔNGAL (ng/mL)	151.39 (25.94−376.24)	247.03 (-45.42−404.91)	0.749
ΔKIM-1 (ng/mL)	-0.48 (-1.49−0.66)	-0.27 (-1.11 to -0.67)	0.638

All continuous variables are presented as median (interquartile range, IQR). GFR: glomerular filtration rate; IQR: interquartile range; KIM-1: kidney injury molecule-1; NGAL: neutrophil gelatinase-associated lipocalin.

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Table 3. Comparison of complications and stone-free status			
	Group 1 (n=25)	**Group 2 (n=26)**	**p**
Stone-free status			
Completely stone-free	10 (40)	11 (42.3)	0.918
Residual stone (<4 mm)	10 (40)	9 (34.6)	
Residual stone (≥4 mm)	5 (20)	6 (23.1)	
Complications			
Pain	6 (24)	7 (26.9)	0.811
Fever	0	2 (7.7)	0.255
Heamaturia	2 (8)	1 (3.8)	0.485
Urinary tract infection	1 (4)	1 (3.8)	0.745

All categorical variables are presented as numbers and percentages.

DRAFT

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