

# Late-Term Effects of Extracorporeal Shock Wave Lithotripsy on Renal Functions

## Ekstrakorporeal Şok Dalga Litotripsinin Böbrek Fonksiyonları Üzerinde Geç Dönem Etkileri

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### ABSTRACT

**Background:** It has been reported that ischemia-reperfusion injury due to extracorporeal shock wave lithotripsy (ESWL) may adversely affect renal function by causing renal tubular damage in the acute and chronic periods. The aim of this study was to determine the late effects of ESWL on renal function in the treatment of kidney stones.

**Materials and Methods:** Between June and December 2023, 96 patients with renal calculi who applied to the urology ESWL unit, met the study criteria, and did not have chronic renal disease were included in the study. Of the patients, 66 (69%) were male, 30 (31%) were female, and the mean age of the patients was 41±10 years. All patients underwent a total of 3 sessions of ESWL at 1 week intervals. Blood samples for preoperative baseline and 3 months postoperative serum blood urea nitrogen (BUN), creatinine, and C-reactive protein (CRP) levels and 24 hours urine samples for urine creatinine levels were obtained from all patients. Creatinine clearance in 24 hours urine (Ccr-24) was calculated using the standard creatinine clearance formula. The demographic characteristics of the patients as well as the total shock wave count (TSW) and total amount of energy (TAE) during the ESWL sessions were recorded.

**Results:** No statistically significant difference was found between serum BUN, creatinine, and CRP levels before and after ESWL application [28.2±9.0 vs. 28.6±7.4 mg/dL, 0.83 (0.40-2,70) vs. 0.84 (0.47-1.88) mg/dL and 3.0 (0.1-79.0) vs. 3.0 (0.1-70.5) mg/L]. The postop Ccr-24 value was statistically lower than the preop value (101.3±18.4 vs. 97.6±18.8 mL/min; p=0.0058). In addition, there were no significant differences in BUN, creatinine, CRP, and Ccr-24 values between the groups of patients with TSW <8000 and ≥8000 (p>0.05).

**Conclusion:** We found that ESWL may affect renal function by decreasing the glomerular filtration rate calculated by Ccr-24 in the late period, independent of the session number, TSW, and TAE.

**Keywords:** Kidney stone, ESWL, kidney function, Ccr-24, total shock wave count

### ÖZ

**Amaç:** Ekstrakorporeal şok dalga litotripsin (ESWL) uygulamasına bağlı iskemi-reperfüzyon hasarının akut ve kronik dönemde renal tübülere hasara neden olarak böbrek fonksiyonlarını olumsuz yönde etkileyebileceği bildirilmektedir. Bu çalışmada amaç, böbrek taşı tedavisinde uygulanan ESWL'nin böbrek fonksiyonu üzerindeki geç dönem etkilerini belirlemektir.

**Gereç ve Yöntemler:** Haziran-Aralık 2023 tarihleri arasında, üroloji ESWL ünitesine müracaat eden, çalışma kriterlerine uygun ve kronik renal hastalığı olmayan böbrek taşı olan toplam 96 hasta çalışmaya dahil edildi. Hastaların 66'sı (%69) erkek, 30'u (%31) kadın ve hastaların yaş ortalaması 41±10 idi. Tüm hastalara 1 haftalık aralıklarla toplam 3 seans ESWL uygulandı. Tüm hastaların operasyon öncesi bazal ve operasyon sonrası 3. aydaki serum BUN, kreatinin, C-reaktif protein (CRP) düzeyleri için kanları ve idrar kreatinin düzeyleri için 24 saatlik idrarları alındı. Standart kreatinin klirensi formülü ile 24 saatlik idrarda kreatinin klirensi (Ccr-24) hesaplandı. Hastaların demografik özellikleri yanı sıra ESWL seanslarında uygulanan toplam şok dalga sayısı (TŞD) ve toplam enerji miktarı (TEM) kayıt altına alındı.

**Bulgular:** ESWL uygulaması öncesi ve uygulama sonrası serum BUN, kreatinin ve CRP düzeyleri arasında istatistiksel anlamlı fark saptanmazken [sırasıyla 28,2±9,0'a karşı 28,6±7,4 mg/dL, 0,83'e (0,40-2,70) karşı 0,84 (0,47-1,88) mg/dL ve 3,0'a (0,1-79,0) karşı 3,0 (0,1-70,5) mg/L], postop Ccr-24 değeri preop değerinden istatistiksel olarak daha düşük saptandı (101,3±18,4'e karşı



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97,6±18,8 mL/dk; p=0,0058). Ayrıca TŞD<8000 olan ve ≥8000 olan hasta grupları arasında BUN, kreatinin, CRP ve Ccr-24 değerleri açısından fark yoktu (p>0,05).

**Sonuç:** ESWL uygulamasının seans sayısı, TŞD ve TEM'den bağımsız olarak geç dönemde Ccr-24 ile hesaplanan glomerüler filtrasyon hızını düşürerek böbrek fonksiyonlarını etkileyebileceği saptandı.

**Anahtar Kelimeler:** Böbrek taşı, ESWL, renal fonksiyon, Ccr-24, toplam şok dalga sayısı

## Introduction

Urinary tract stone diseases have become an important public health problem due to their increase in parallel with changes in lifestyle, nutritional content, and climatic conditions all over the world (1). Today, extracorporeal shock wave lithotripsy (ESWL), rigid and flexible ureterorenoscopy, percutaneous nephrolithotomy, robotic and laparoscopic methods, as well as open surgical methods, which are relatively rarely used, are used in the treatment of upper urinary tract stone diseases (2). Among these, ESWL is a highly effective and non-invasive treatment method and has been used since the 1980s (3). Although pregnancy, coagulopathy, and active urinary tract infection are absolute contraindications for ESWL, its use is becoming widespread worldwide due to its high success rates in renal and ureteral calculi. ESWL acts on urinary system stones by creating a series of mechanical forces, defined as pressure-induced fracture, fragmentation, cavitation, and dynamic fatigue, which causes the stones to disintegrate. Of these, cavitation is considered to play a major role in tissue damage. While mechanical forces create the desired effect on the stone, they also cause undesirable effects in the kidney and adjacent organs, such as the release of cellular inflammatory mediators and tissue infiltration of inflammatory response cells (4). These undesirable effects range from early complications, such as short-term hematuria and hematoma, to late complications affecting renal function and systemic hypertension. Studies showing histopathological changes in the kidneys after ESWL have demonstrated endothelial cell damage in the medium-sized arteries, veins, and glomerular capillaries of the kidneys (5,6). This damage is usually local and especially affects the arcuate veins located at the corticomedullary junction, resulting in hematuria and haematoma (5). Hematuria is the most common complication and resolves spontaneously within a few days. Hematoma is usually located intrarenal, subcapsular, or perirenal and is observed in less than 1% of patients (7).

Although there is no clear consensus regarding the effect of ESWL on renal function, the general consensus is that

renal function decreases in the acute period and returns to its previous values within a short period. On the other hand, there is still controversy about its late effects.

In this study, we aimed to retrospectively evaluate the late-term effects of ESWL on renal function using BUN, creatinine, C-reactive protein (CRP), and creatinine clearance in 24 hours urine (Ccr-24) levels. In addition, the relationship between this late-term effect and the number of sessions, the total shock wave count (TSW) and total amount of energy (TAE) was analyzed.

## Materials and Methods

Between June 2023 and December 2023, a total of 96 patients who met the study criteria among 108 patients who applied to the ESWL unit of the Urology Clinic of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital for kidney stones were included in the study. Patients with bleeding disorder, solitary kidney, urogenital system abnormality, acute or chronic renal failure, rheumatic disease (systemic lupus erythematosus, rheumatoid arthritis, Behçet's disease, ankylosing spondylitis, etc.), and previous treatment with urolithiasis were excluded. Before starting the ESWL procedure, all patients' medical histories were obtained, and physical examinations were performed. Age, gender, imaging method, and stone location and size were recorded. Serum BUN, creatinine, CRP, and 24 hours urine creatinine levels were measured before ESWL. To estimate the glomerular filtration rate (GFR), Ccr-24 was calculated using the following formula (8):

$$Ccr24 = [(Ucr \times V) / Scr] \times 1.73 / A,$$

Ccr=(mL/min/1.73 m<sup>2</sup>), Ucr=Urinary creatinine (µmol/L)  
Scr=Serum creatinine (µmol/L), V=Urine volume (mL/min)  
A=Body surface area=(4×weight+7)/(weight+90)

Urine analysis and/or urine culture were performed in all patients. Appropriate antibiotic treatment was started in patients with urine culture growth, and ESWL sessions were postponed until urine culture was negative.

The ESWL procedure was performed with a Storz Medical X-FP-S device while the patient was in the supine position. A maximum of 4000 shock waves with 60-80 kV power were applied in each session. Fluoroscopy

was used for localization of radiopaque stones and ultrasonography for radiolucent stones. At the end of the ESWL session, if the stone did not break (or did not shrink sufficiently) and no complications developed, a repeat session was planned 7 days later, and a total of 3 sessions were performed. Success was defined as a stone-free status or the presence of clinically insignificant residual fragments ( $\leq 4$  mm). Patients who were not successful at the end of the third session were referred to alternative treatment approaches. Patients considered successful were called for follow-up at 3 months after ESWL. Serum BUN, creatinine, and CRP levels and 24 hours urine creatinine levels were measured in these patients. Ccr-24 values were recalculated.

### Statistical Analysis

SPSS Statistic (IBM Corp, 25 Version, Chicago, USA) software was used for data analysis. The Kolmogorov-Smirnov normality test was applied to test the data distribution. The chi-square test was used to analyze categorical variables. The paired t-test was used to compare parametric data of dependent groups consisting of two groups, and the Wilcoxon matched-pairs test was used to compare non-parametric data. The unpaired t-test and Mann-Whitney U test were used to compare parametric data of independent groups consisting of two groups and non-parametric data, respectively. Pearson's correlation analysis was used for parametric data and Spearman's correlation analysis for non-parametric data to evaluate the relationship between independent variables.

### Ethical Approval

Ethical approval for this study was granted by the Scientific Research Ethics Committee of Sancaktepe Őehir Prof. Dr. İlhan Varank Training and Research Hospital (approval number: E-46059653- 050.99-243909969, dated: 16.05.2024). All patients were informed about the study and provided informed consent.

### Power Analysis of the Study

The minimum number of subjects required for this study was based on data from a study investigating renal function markers after percutaneous nephrolithotomy in patients with one kidney (9). Based on these data, an a priori power analysis (G\*Power, Version 3.1, Düsseldorf, Germany) estimated that a study using the eGFR test to estimate GFR required at least 70 dependent experimental subjects (effect size  $d=0.3021$ ,  $\alpha=0.05$ , power=0.80). However, for a stronger prediction, the dependent group of this independent study comprised 96 subjects.

## Results

The mean age of the 96 patients (Male/Female: 66/30) included in the study was  $41\pm 10$  years and the mean body mass index (BMI) was  $27.1\pm 4.7$  (Table 1). The right/left location of the stones was 61/38 (63%/39%). There were 52 (55%) stones localized in the renal pelvis, 19 (20%) in the upper calyx, 12 (12.5%) in the middle calyx and 13 (13.5%) in the lower calyx. Complications developed in a total of 6 patients after ESWL procedure. One patient with intrarenal hematoma was hospitalized and treated conservatively. Two patients who developed the stone-tract were treated with ureteroscopy. Two patients with severe pain and 1 patient with high fever were treated conservatively.

When serum BUN, creatinine, and CRP levels before (preop) and after (postop) ESWL application were analyzed, there was no statistically significant difference between pre-op and post-op BUN, creatinine, and CRP levels ( $p>0.05$ ) (Figures 1A, 1B, 1D, Table 2). However, there was a statistically significant difference between preop and postop Ccr-24 values (Figure 1C). The postop Ccr-24 values were statistically lower compared to preop ( $p=0.0058$ ). In the correlation analysis performed to explain this decrease in postop Ccr-24 levels after ESWL, there was no statistically significant correlation between postop Ccr-24 levels and TAE, session number, and TSW values [Spearman's  $r$  ( $r_s$ )  $<0.20$  and  $p>0.05$ ] (Figure 2). There was a high positive correlation between TAE values, session number, and TSW ( $r_s=0.8913$ , 95% CI: 0.8393-0.9271,  $p<0.0001$  and  $r_s=0.8668$ , 95% CI: 0.8043-0.9103,  $p<0.0001$ , respectively). There was also a statistically strong positive correlation between session number and TSW ( $r_s=0.8978$ , 95% CI: 0.8488-0.9316,  $p<0.0001$ ).

**Table 1. Demographic and clinical characteristics of patients included in the study**

Demographic and clinical characteristics		n (%)
Gender, M/F		66/30 (69%/31%)
Kidney with stone, right or left		61/38 (63%/39%)
Stone location	Pelvis	52 (55%)
	Upper calyx	19 (20%)
	Middle calyx	12 (12.5%)
	Lower calyx	13 (13.5%)
Complications	Hematoma	1 (1%)
	Stone pathway	2 (2.1%)
	Severe pain	2 (2.1%)
	High fever	1 (1%)
	Total	6 (6.25%)

M/F: Male/Female

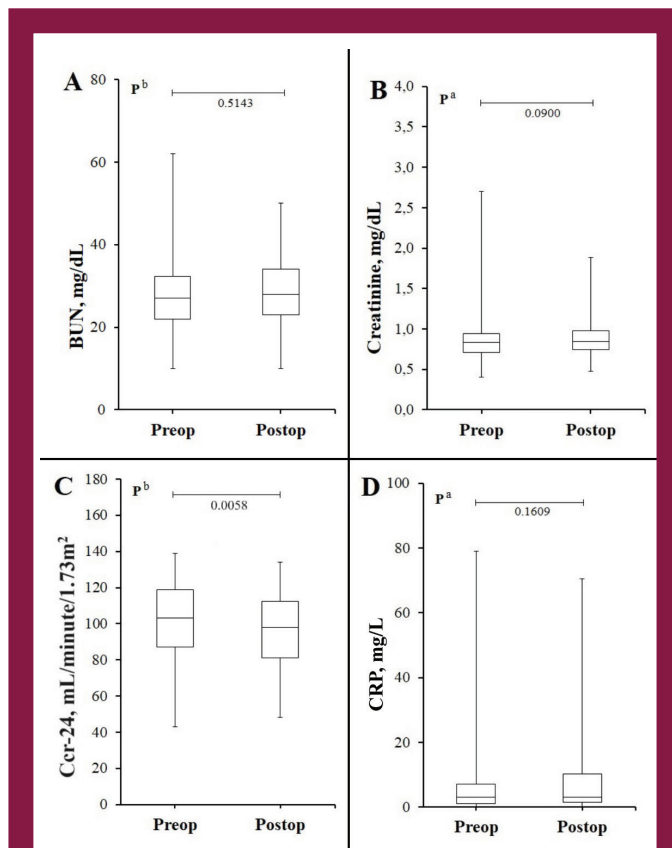
These significant correlations were expected. Because the number of sessions increased, the amount of TAE and TSW naturally applied increased.

When the ESWL-treated patients were compared according to the TSW (Table 3), no significant difference was observed between the groups with TSW <8000 and TSW ≥8000 in terms of gender, age, BMI, stone size and stone hardness ( $p>0.05$ ). Similarly, there was no statistically significant difference between preop and postop BUN, creatinine, CRP, and Ccr-24 levels in these groups ( $p>0.05$ ). The TAE and session number values of the group with TSW≥8000 were found to be statistically significantly higher than those of the group with TSW <8000 [180 (120-210) vs. 65 (40-140) and 3.0 (2.0-3.0) vs. 1.0 (1.0-2.0);  $p<0.0001$ ]. These results are expected. Because the number of exposed joules and the number of

sessions will also be high in those with high TSW values. As a result, there would be no difference in terms of renal function between those who were exposed to high-energy (or sessions number) and those who were not.

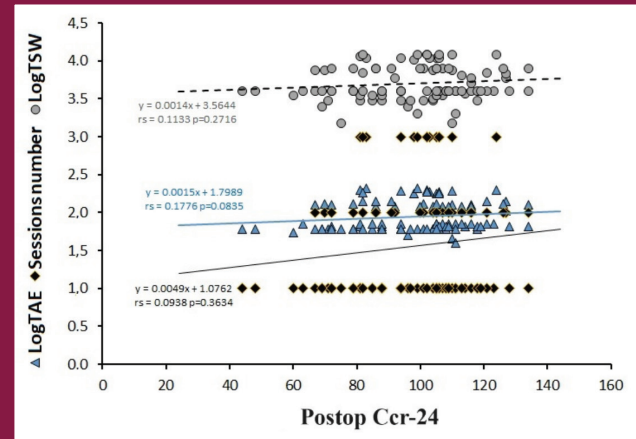
## Discussion

ESWL has been frequently accepted and applied as the first choice in the treatment of upper urinary tract stone diseases. The fact that it does not require hospitalization and is non-invasive are among the reasons for its preference. It is also one of the most useful methods available for the treatment of urolithiasis because



**Figure 1.** Bar graph representing (A) serum BUN, (B) creatinine, (C) Ccr-24, and (D) CRP levels before (preop) and after (postop) ESWL application. There was no difference between A) serum BUN, B) creatinine, and D) CRP levels before (preop) and after (postop) ESWL application. C) On the other hand, postop Ccr-24 values were observed to be statistically lower than preop values. <sup>a</sup>Wilcoxon matched-pairs test, <sup>b</sup>Paired t-test

BUN: Blood urea nitrogen, Ccr-24: Creatinine clearance in 24 hours urine, CRP: C-reactive protein, ESWL: Extracorporeal shock wave lithotripsy



**Figure 2.** Corelation between Ccr-24 and TAE, session number, and TSW. TAE, sessions number and TSW values were not statistically significant correlations between the postop Ccr-24 values in the correlation analysis

rs: Spearman correlation coefficient, Ccr-24: Creatinine clearance in 24 hours urine, TSW: Total shock wave count, TAE: Total amount of energy

**Table 2. Comparison of kidney function tests and Ccr-24 values preop and postop ESWL application**

	ESWL		p-value
	Preop	Postop	
n	96	96	
BUN, mg/dL	28.2±9.0	28.6±7.4	<sup>b</sup> 0.5143
Kreatinin, mg/dL	0.83 (0.40-2.70)	0.84 (0.47-1.88)	<sup>a</sup> 0.0900
Ccr-24, mL/min/1.73 m <sup>2</sup>	101.3±18,4	97.6±18.8	<sup>b</sup> 0.0058
CRP, mg/L	3.0 (0.1-79.0)	3.0 (0.1-70.5)	<sup>a</sup> 0.1609

<sup>a</sup>Wilcoxon matched pairs test; <sup>b</sup>Paired t-test. The statistical significance level is  $p<0.05$ . Parametric data were presented as mean ± standard deviation, and non-parametric data were presented as median (minimum-maximum), ESWL: Extracorporeal shock wave lithotripsy, BUN: Blood urea nitrogen, Ccr-24: Creatinine clearance in 24 hours urine, CRP: C-reactive protein





there is no alternative to this method, and this method is currently being developed. After its widespread use, various studies have been conducted to investigate the early and late adverse effects of ESWL on renal function, and reversible histological changes have been observed in the renal parenchyma in the acute period (10,11). Ischemia-reperfusion-mediated oxidative stress during the procedure was attributed to the physiopathology of the event. This condition has been suggested to cause parenchymal or tubular damage in the kidney. Renal parenchymal damage may affect renal function and GFR, leading to decreased urea/creatinine excretion (or serum retention). These changes led to the observation of ESWL-induced renal injury (11). Among these, serum creatinine is still the gold standard for renal injury despite its many interferences and renal excretion problems. In recent years, biomarkers such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C have been proposed for the detection of renal injury (12). However, for most such devices, the problem of standardization or harmonization for routine use has still not been solved. Studies showing the effects of ESWL on renal function have shown that GFR decreases after ESWL, but this change returns to normal within the first 24 hours (13,14). Until recently, several markers that may reveal renal damage before and after ESWL treatment

have been evaluated. However, because their results are not conclusive, more detailed studies with larger samples should be performed (11). In this study, urea, creatinine, Ccr-24, and CRP (an important indicator of tissue damage/inflammation), which are routine laboratory tests, were used to monitor the presence of ESWL-induced damage in our patients.

Although various mechanisms have been proposed to explain the mechanism of tissue damage, cavitation is more prominent. In addition to the direct mechanical effects caused by cavitation, free radicals play an important role in cell destruction (15). There are also various studies showing that it causes morphological changes in renal tissues, such as focal parenchymal damage and subcapsular haematoma (16). In our study, renal hematoma developed in 1 patient. In animal experiments, ESWL has been shown to cause damage to blood vessels, renal tubules, Bowman's capsule, renal corpuscles, and mesangial cells (17). Studies on urinary enzymes indicating renal damage have also shown that urinary enzyme levels are transiently elevated and return to normal within a few days (18).

To date, there are no studies showing the long-term effects of ESWL on the kidneys. Animal studies in rabbits and dogs have shown that renal fibrosis develops in a dose-dependent manner (17,19). Willis et al. (20) showed that renal damage after ESWL is directly proportional to the number

**Table 3. Comparison of renal function and CRP levels according to the total number of shock waves received by patients with ESWL**

	Total shock number		p-value
	<8000	≥8000	
n	69	27	-
Sex, M (%)	48 (70%)	18 (67%)	°0.810
Age	41 (21-63)	44 (15-65)	°0.2556
BMI, kg/m <sup>2</sup>	27 (18-38)	26 (17-38)	°0.6956
Stone size (mm)	10 (5-16)	9 (5-12)	°0.1389
Stone hardness, HU,	890 (312-1615)	1040 (508-1456)	°0.1749
Number of sessions, n	1.0 (1.0-2.0)	3.0 (2.0-3.0)	°<0.0001
TAE, joule	65 (40-140)	180 (120-210)	°<0.0001
Preop BUN level, (mg/dL)	29 (10-62)	25 (18-44)	°0.3944
Postop BUN, (mg/dL)	30 (10-50)	25 (17-38)	°0.0841
Preop kreatinin level, (mg/dL)	0.82 (0.40-2.70)	0.84 (0.49-1.14)	°0.9902
Postop kreatinin (mg/dL)	0.88 (0.47-1.88)	0.83 (0.50-1.22)	°0.3202
Preop Ccr-24, mL/min/1.73m <sup>2</sup>	105 (43-139)	103 (62-140)	°0.6249
Postop Ccr-24, mL/min/1.73m <sup>2</sup>	102 (44-134)	102 (72-134)	°0.8930
Preop CRP level, (mg/L)	3.0 (0.1-79.0)	4.6 (0.6-69.0)	°0.3472
Postop CRP level, (mg/L)	3.0 (0.1-70.5)	3.0 (0.1-30.0)	°0.9297

°Chi-square test, °Mann-Whitney U test, ° Unpaired t-test, the statistical significance level is p<0.05. Parametric data were presented as mean ± standard deviation, and non-parametric data were presented as median (minimum-maximum), CRP: C-reactive protein, ESWL: Extracorporeal shock wave lithotripsy, M: Male, BMI: Body mass index, HU: Hounsfield unit, TAE: Total amount of energy, BUN: Blood urea nitrogen, Ccr-24: Creatinine clearance in 24 hours urine

of shock waves and the amount of energy (20). In studies conducted to investigate the effects of ESWL on GFR, Sheir and Gad (21) reported a significant increase in GFR after ESWL, Saxby (22) reported a significant decrease in GFR, and Cass (23) reported a decrease in GFR in some patients and an increase in others. When these reports are compared with the results obtained in our study, it can be understood that some of the results do not completely overlap with other results. The finding of a significant decrease in Ccr-24, which is still the most important indicator of GFR, overlapped with our study. In addition, the lack of significant changes in BUN, creatinine, and CRP among the parameters evaluated in our study was similar to previous studies (24,25).

It was an interesting finding that there was no difference in blood creatinine levels before and 3 months after ESWL, but there was a difference in Ccr-24 levels calculated from the creatinine levels. The possible reason for this was the fact that blood creatinine levels were not a sensitive indicator of kidney damage. However, Ccr-24, which was performed using both urine and blood creatinine levels and was found to have a high correlation with GFR, is a more sensitive measure of kidney function than serum creatinine (26,27). Creatinine is the breakdown product of creatine phosphate found in dietary meat and skeletal muscle. Its production in the body depends on muscle mass. Because the glomerulus freely filters creatinine, the Ccr-24 ratio is close to the GFR calculation. When blood creatinine levels are very high, Ccr-24 may overestimate GFR by approximately 10% because creatinine excretion by peritubular capillary increases. However, this error is relatively minor in people without renal problems and those with creatinine conversion within the physiological limits. In addition, despite problems such as incomplete urine collection in non-cooperative patients, Ccr-24 measurement is a standardized method widely used in GFR measurement due to its high accuracy (26,28). In this study, we investigated whether ESWL application has a constructive effect on renal damage in the postoperative chronic period. We actually found a significant decrease in Ccr-24 levels, while we did not detect a significant change in blood creatinine and BUN levels to coincide with the above information. The possible physiopathological explanation for this finding is that loss of renal function or damage in the chronic period should be detected using more sensitive biomarkers. In conclusion, a well-organized Ccr-24 test is a good indicator of renal function loss during the chronic period of ESWL. In this context, ESWL is not a completely noninvasive approach. It should be kept in mind that it may have chronic effects as well as acute effects.

## Study Limitations

Because this study is a retrospective analytical study, the cause-effect relationship is weaker than that in prospective studies. Whether the change in Ccr-24 values in the late period is related to the number of sessions, TSW, and TAE needs to be tested with a larger sample. In addition, the study should be confirmed with a study including other markers of renal damage, such as NGAL and KIM-1, since incomplete collection of 24 hours urine in some patients may affect the results.

## Conclusion

It was found that ESWL may affect renal function by decreasing the GFR calculated using Ccr-24 in the late period. However, no significant relationship was found between this late effect and the number of sessions, TSW, and TAE.

## Ethics

**Ethics Committee Approval:** Ethical approval for this study was granted by the Scientific Research Ethics Committee of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval number: E-46059653-050.99-243909969, dated: 16.05.2024).

**Informed Consent:** All patients were informed about the study and provided informed consent.

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## Footnotes

## Authorship Contributions

Surgical and Medical Practices: E.E, Concept: E.E, Design: E.E, Data Collection or Processing: E.E, Analysis or Interpretation: E.E, M.Ş., Literature Search: E.E, M.Ş., Writing: E.E, M.Ş.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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