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Original Article

ORIGINAL ARTICLE

The effect of standard percutaneous nephrolithotomy, miniaturized percutaneous nephrolithotomy and retrograde intrarenal surgery on biomarkers of renal injury: a randomized clinical trial

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ABSTRACT

Background. Observational studies on the association of endourological procedures with renal parenchymal damage are lacking. This randomized trial examined the effect of standard percutaneous nephrolithotomy (sPCNL) in comparison with miniaturized-PCNL (mini-PCNL) and retrograde intrarenal surgery (RIRS) for nephrolithiasis treatment on novel biomarkers of renal injury.

Methods. Seventy-five patients were randomized in a 1:1:1 ratio to receive sPCNL, mini-PCNL and RIRS for nephrolithiasis. The ratios of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18) normalized for urinary creatinine (Cr) were calculated from urine samples collected at baseline (2-h preoperatively) and at 2-, 6-, 24- and 48-h postoperatively. Two-way mixed analysis of variance (ANOVA) for repeated measurements was used to evaluate the effects of type of procedure and time on studied biomarkers.

Results. Between baseline and 2-h postoperatively, no significant differences were observed in NGAL/Cr changes between sPCNL [median (interquartile range) 9.46 (4.82–14.9)], mini-PCNL [12.78 (1.69–25.24)] and RIRS [6.42 (2.61–23.90)] ($P = .902$). Similarly, no between-group differences were observed for KIM-1/Cr ($P = .853$) and IL-18 ($P = .980$) at 2 h, and all biomarkers at any time-point postoperatively. Within-groups, significant increases from baseline were noted for NGAL/Cr (sPCNL, $P < .001$; mini-PCNL, $P < .001$; RIRS, $P = .001$), KIM-1/Cr and IL-18/Cr at 2 h; progressively lower increases from baseline were noted in all groups for KIM-1/Cr and IL-18/Cr at 6-, 24- and 48-h postoperatively. As such, a significant effect of time but not of type of procedure was evidenced with two-way mixed ANOVA. No significant between-group differences were observed in acute kidney injury incidence and complications.

Conclusions. The endourological procedures under study are associated with similar patterns of early tubular injury, detected by novel biomarkers, which is largely reduced within 48 h and no changes in glomerular function.

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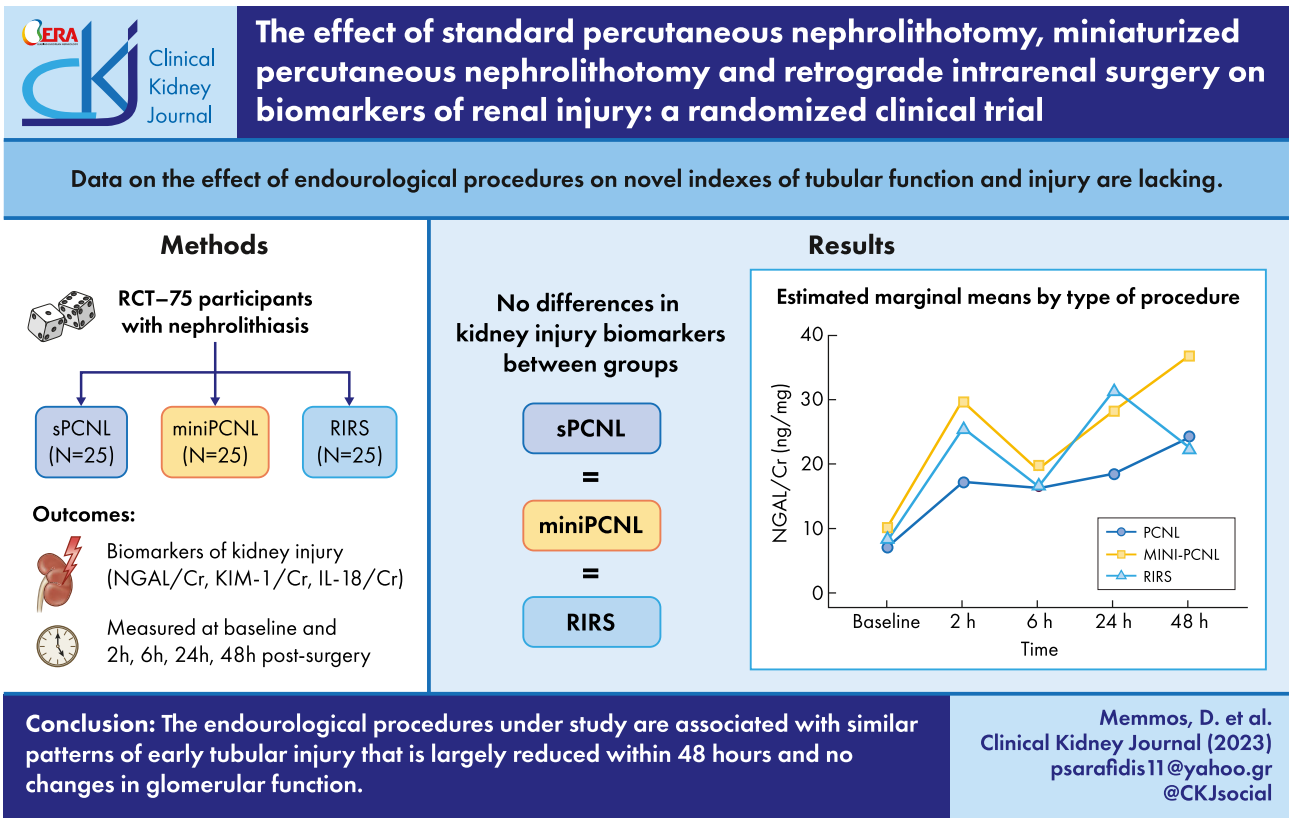
LAY SUMMARY

This randomized controlled trial compares the effects on renal function of each one of the three more common surgical treatments of nephrolithiasis. The biomarkers studied are very sensitive indices of early kidney dysfunction. The study shows that despite the previously proposed mechanisms of injury, renal function deteriorates in an almost parallel fashion in each of the procedures. Eventually, the renal dysfunction is reduced at 48-h postoperatively, demonstrating the safety of the procedures regarding renal function.

GRAPHICAL ABSTRACT



Keywords: AKI, endourology, nephrolithiasis, PCNL, renal function

INTRODUCTION

Nephrolithiasis is a common urological condition with high recurrence rates and huge socioeconomic impact [1]. Selection of the appropriate treatment is critical, with endourological procedures becoming the standard of care nowadays [1, 2]. Together with retrograde intrarenal surgery (RIRS) and percutaneous nephrolithotomy (PCNL), the continuous evolution of technological continuous evolution of advances (newer and better lithotripters/lasers) has led to the implementation of "miniaturization" techniques, with the most popular one being the mini-PCNL [2, 3]. In order to comparatively assess the efficacy and safety of these techniques, previous research has mainly focused on stone-free rates (SFR), need for auxiliary procedures and complications such as infection and bleeding [4–6]. Moreover, their impact on renal function has been evaluated solely on the basis of serum creatinine (Cr) levels, an index of glomerular function that may not fully reflect the underlying injury, whereas assessment of acute kidney injury (AKI) incidence with modern markers is scarce [7, 8].

In recent years, numerous studies have evaluated the prognostic importance of AKI and reported on the role of novel biomarkers in its diagnosis in different settings and populations, including intensive care unit patients and patients in the postoperative period [9]. Commonly used serum and urinary biomarkers of AKI include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18) and *N*-acetyl-β-D-glucosaminidase (NAG). In patients who underwent PCNL for renal stones >2 cm, a significant increase in levels of KIM-1 normalized for urinary Cr (KIM-1/Cr), and accordingly NAG/Cr and NGAL/Cr ratios, has been reported 24-h postoperatively [10]. Although no single perfect biomarker currently exists, it has been reported that the combination of multiple biomarkers at different time-points postoperatively improves diagnostic accuracy [11].

Data on the effect of endourological procedures on novel indexes of tubular function and injury, especially from head-to-head randomized clinical trials, are lacking. Therefore, the aim of this study was to assess the effect of standard PCNL (sPCNL), mini-PCNL and RIRS on renal parenchymal injury at several time-points postoperatively using three novel AKI urine biomarkers (NGAL, KIM-1 and IL-18).

MATERIALS AND METHODS

Study population

This open-label, three parallel-arm, randomized clinical trial (RCT) recruited patients from the Lithiasis Outpatient Clinic of our hospital from November 2018 to February 2021. We included adult patients (>18 years) with kidney stones of 10–30 mm in maximal diameter on computed tomography (CT) scan who had accepted receipt of surgical treatment and provided written informed consent. Patients were excluded from the study in case of: (i) solitary kidney (functional or anatomic), (ii) malignant tumor in the affected kidney, (iii) stone in the ipsilateral system causing ureteral obstruction, (iv) stone in calyceal diverticulum, (v) diabetes, renal or coronary heart disease, (vi) history of surgery in the kidney, (vii) recent intake of drugs affecting renal function or intravenous contrast agent, (viii) concomitant urinary infection and (ix) congenital anomalies of the urinary tract.

The study protocol was approved by the Ethics Committee of Aristotle University of Thessaloniki and was registered at the ClinicalTrials.gov Registry (NCT03112499).

Study protocol and interventional arms

Baseline evaluation included the recording of demographic characteristics, medical history, assessment of stone composition and size based on CT findings, a detailed physical examination, and collection of blood and urine samples for the evaluation of routine hematological and biochemical laboratory tests and the biomarkers under study. After baseline evaluation, patients were randomized in a 1:1:1 ratio into three intervention groups (sPCNL, mini-PCNL and RIRS) via a computer-generated randomization schedule. The urologists performing these procedures were experienced endourologists who were blinded to the results of obtained blood and urine samples. All procedures were performed using the same protocol of anesthesia. The three intervention groups were as follows.

sPCNL group: the procedure was performed with the patient placed in prone position. A ureteral catheter was placed in the ipsilateral pelvis using a flexible cystoscope. Access to the pyelocaliceal system was achieved by percutaneous puncture, performed under fluoroscopic guidance using the bull's-eye technique. An extra-stiff guidewire was placed through the puncture needle down the ipsilateral ureter and dilatation of the track was performed using serial dilators up to 30Fr in order to place a percutaneous sheath. A 24Fr nephroscope (Hopkins, Karl Storz GmbH, Germany) with an ultrasonic lithotripter (Karl Storz GmbH, Germany) was inserted and used to perform the lithotripsy. After stone fragment removal through the sheath, a double-J (DJ) ureteral stent and a nephrostomy tube (18Fr council catheter) were placed.

Mini-PCNL group: the procedure followed the same principles as in the sPCNL group, with differentiations in the outer diameter of the dilator and the sheath. The dilatation was performed with a single-shot metal dilator of 16Fr. A 12Fr mini nephroscope (MIP M, Karl Storz GmbH, Germany) and a Ho: YAG (Dornier MedTech, Germany) laser were used for lithotripsy. Similarly, the procedure was completed with placement of a DJ stent and a nephrostomy tube.

RIRS group: the procedure was performed with the patient placed in the lithotomy position. A safety and a working guidewire were placed at the ipsilateral kidney using an 8–10Fr dilator. An access sheath of 11/13Fr or 12/14Fr (depending on the case) was placed. A flexible ureteroscope (Flex Xc, Karl Storz GmbH, Germany) was advanced to the kidney through the access sheath and lithotripsy was performed using a Ho: YAG laser (Dornier MedTech). After the procedure was completed, a DJ stent was placed.

During postoperative care all patients followed the same postoperative care protocol (3 L of hydration with Ringer's Lactate per day). From the first postoperative day, they were also allowed to hydrate freely per os. A single dose of intravenous antibiotic prophylaxis was administered 2 h before the procedure.

In all treatment arms, urine and blood samples were collected at five time-points: 2-h preoperatively as baseline evaluation, and at 2-, 6-, 24- and 48 -h postoperatively.

Patients without complications were discharged on the second postoperative day. For patients allocated to the sPCNL and mini-PCNL groups, the nephrostomy tubes were removed before hospital discharge. In all treatment arms, the DJ stents were removed at the 10th postoperative day (±2 days). Follow-up visits were scheduled 1-month postoperatively when, among others, blood sampling and CT scan was performed, and at 3-months postoperatively, when blood sampling for measurement of serum Cr levels was drawn.

Study outcomes

The primary outcome of the study was the difference between the three groups in the change (Δ) of NGAL/Cr between preoperative (baseline) and 2-h postoperative measurement. Secondary outcomes included within-group changes and between-group differences in changes (Δ) in NGAL/Cr, KIM-1/Cr and Il-18/Cr between baseline and all time-points, as well as between-group differences in operative time, complications, postoperative pain, SFR, need for auxiliary procedures, estimated glomerular filtration rate (eGFR), incidence of AKI according to the 2012 Kidney Disease: Improving Global Outcomes classification system [12] and hospitalization length.

Laboratory analyses

Urine samples collected for the main parameters under study were immediately centrifuged and the supernatants were stored at –80°C until quantitative determination. Levels of NGAL, KIM-1 and IL-18 were evaluated using the quantitative sandwich enzyme-linked immunosorbent assay method with commercially available kits (QuantiKine ELISA, USA). Routine hematological and biochemical parameters were measured by standard laboratory methods. NGAL, KIM-1 and IL-18 levels were normalized for urine Cr and reported in ng/mg and pg/mg Cr at each time-point. The eGFR was calculated using the CKD Epidemiology Collaboration equation [13]. The technician performing the analyses was blinded to patient data.

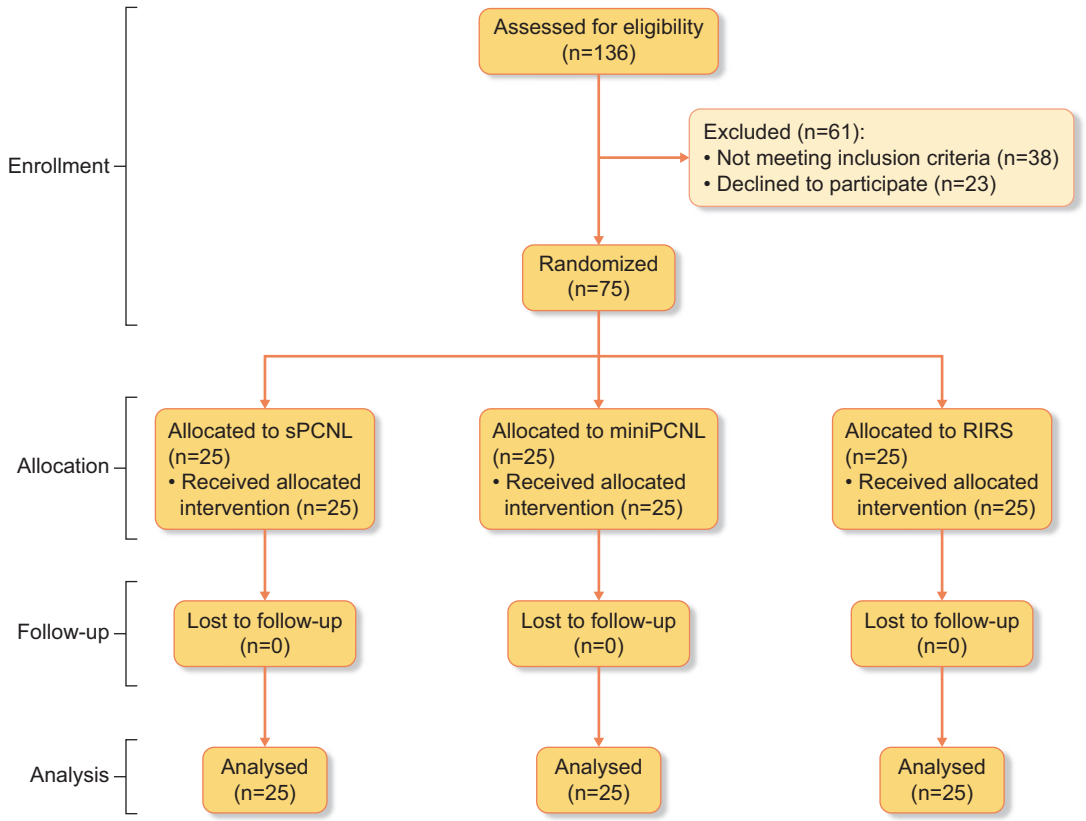


Figure 1: Study flowchart.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 22.0 (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range) according to the normality of the distribution. Categorical variables are presented as absolute frequencies and percentages (*n*, %). One-way analysis of variance (ANOVA) or relevant non-parametric tests, where applicable, were used for between-group comparisons of continuous variables; Bonferroni post-hoc test was used for pairwise comparisons. Within-group comparisons were performed with the paired *t*-test or the respective non-parametric test where applicable. To evaluate the effect of type of intervention and time on the trends of NGAL/Cr, KIM/Cr, IL-18/Cr and eGFR, and to determine whether an interaction between the two exists, the estimated marginal means were calculated for baseline, 2-, 6-, 24- and 48-h post-procedure using two-way mixed ANOVA analysis for repeated measurements. Greenhouse–Geiser correction was applied to overcome the violation of the sphericity assumption. Bivariate correlation coefficients (r) were calculated using the Pearson's product formula to assess the association between between parameters of stone size and markers of AKI in urine. Categorical variables were compared with the Chi-square test. A study sample of 75 patients (22 per treatment arm plus 10% for possible loss to follow-up) was calculated to have 80% statistical power, at $\alpha = 0.05$ levels, to detect a difference between groups of 9 ng/mg in the change (Δ) of NGAL/Cr between baseline and 2-h postoperatively, assuming an SD value of 11 ng/g. Probability values of $P < .05$ (two-tailed) were considered statistically significant.

RESULTS

Study flowchart and baseline characteristics of study participants

The Consolidated Standards of Reporting Trails flow chart of the study is presented in Fig. 1. A total of 136 patients were screened for eligibility, and 75 patients were randomized. Table 1 shows demographic, clinical and laboratory characteristics of the three study groups. At baseline, there were no differences between the three groups with regards to age, gender, anthropometric characteristics, stone localization, routine laboratory parameters and urinary biomarkers. Differences between groups were noted in stone size measurements (stone surface and total stone size).

Comparisons of changes in urinary biomarkers of renal injury and eGFR between study groups

Table 2 presents comparisons of net changes (Δ) in NGAL/Cr, KIM-1/Cr, Il-18/Cr ratios and eGFR between baseline and different time-points postoperatively between the three study groups. No significant differences were observed between patients assigned to sPCNL, mini-PCNL and RIRS group regarding the changes in NGAL/Cr [9.46 (4.82–14.9) vs 12.78 (1.69–25.24) vs 6.42 (2.61–23.90) ng/mg, respectively, $P = .902$], KIM-1/Cr ($P = .853$) and IL-18 ($P = .980$) between baseline and 2-h postoperatively. Similarly, no significant differences were detected between the three study groups in changes between baseline and postoperative measurements at 6, 24 and 48 h in all biomarkers under study [change in NGAL/Cr 48-h postoperatively: 14.07 (7.81–

Table 1: Baseline characteristics of study participants.

	sPCNL (N = 25)	Mini-PCNL (N = 25)	RIRS (N = 25)	P-value
Age (years)	60.76 ± 8.71	55.36 ± 10.46	56.68 ± 9.83	.129
Male (*n*, %)	17 (68.0)	15 (60.0)	9 (36.0)	.063
BMI (kg/m^2)	28.47 ± 4.16	28.55 ± 4.33	30.46 ± 5.67	.255
Stone lateralization (*n*, %)				1.000
Left	16 (64.0)	16 (64.0)	16 (64.0)	
Right (≥2)	9 (36.0)	9 (36.0)	9 (36.0)	
Stone surface (mm^2)	254.34 (170.35–357.96)	141.30 (89.88–292.41)	142.87 (94.99–167.21)	.002
Total stone size (mm^3)	3193.47 (1698.99–4299.92)	1604.60 (976.40–3633.95)	1372.83 (799.94–2137.37)	<.001
CT value of stone (HU)	936.32 ± 316.58	864.44 ± 209.75	972.92 ± 338.79	.418
No. of implicated calyces	0.80 ± 0.82	0.56 ± 0.71	0.88 ± 0.88	.350
Stone localization (*n*, %)				.187
Upper calyx	0 (0.0)	0 (0.0)	1 (4.0)	
Middle calyx	0 (0.0)	0 (0.0)	1 (4.0)	
Lower calyx	5 (20.0)	8 (32.0)	11 (44.0)	
Renal pelvis	19 (76.0)	15 (60.0)	12 (48.0)	
Multiple	1 (4.0)	2 (0.0)	0 (0.0)	
WBC (μmol/L)	7408.00 ± 2321.08	7708.00 ± 2381.51	7624.00 ± 1693.68	.879
Hb (g/L)	14.42 ± 1.21	13.65 ± 1.41	13.79 ± 1.42	.109
Serum Cr (mg/dL)	0.93 ± 0.26	0.96 ± 0.28	0.86 ± 0.24	.337
Urine Cr (mg/dL)	88.27 ± 59.95	97.63 ± 66.70	104.03 ± 57.38	.661
Serum sodium (mEq/L)	140.92 ± 3.66	141.52 ± 2.22	141.80 ± 3.18	.589
Serum potassium (mEq/L)	4.60 ± 0.47	4.60 ± 0.41	4.62 ± 0.41	.986
Serum urea (mg/dL)	32.00 ± 8.27	40.00 ± 11.66	35.24 ± 10.50	.026
Serum calcium (mg/dL)	9.68 ± 0.41	9.71 ± 0.32	9.67 ± 0.45	.931
Serum uric acid (mg/dL)	4.88 ± 1.22	4.82 ± 0.86	4.72 ± 1.38	.883
PTH (pg/mL)	45.19 ± 16.39	47.11 ± 20.87	46.36 ± 9.73	.969
eGFR (mL/min/1.73 m^2)	83.51 ± 14.61	82.21 ± 21.29	85.51 ± 18.22	.813
NGAL/Cr (ng/mg)	3.76 (2.13–8.64)	8.64 (4.99–15.56)	5.62 (1.36–11.40)	.454
KIM-1/Cr (ng/mg)	1.66 (1.06–3.76)	2.59 (1.18–3.64)	1.26 (0.93–2.17)	.876
IL-18/Cr (pg/mg)	125.24 (63.98–237.02)	81.2 (39.54–168.29)	54.60 (27.47–138.09)	.628

Continuous variables with normal distribution are presented as mean ± SD, variables with skewed distribution are presented as median (interquartile range).
eGFR calculated using CKD Epidemiology Collaboration equation.
BMI: body mass index; WBC: white blood cell count; Hb: hemoglobin; PTH: parathormone.

27.75) vs 18.40 (6.59–23.32) vs 12.58 (7.83–20.02) ng/mg, respectively, $P = .610$; Table 2].

Regarding the changes in eGFR from baseline, again, no significant differences were noted between the three study groups at any time-point postoperatively, as shown in Table 2.

Within-group comparisons and trajectories of urinary biomarkers of renal injury and eGFR in the three study groups

Within-group differences in the urinary biomarkers of renal injury between baseline and different time-points postoperatively are presented in Table 3. At 2-h postoperatively, significant increases from baseline were noted in all study groups for NGAL/Cr [sPCNL 3.76 (2.13–8.64) vs 15.97 (8.14–29.86), $P < .001$; mini-PCNL 8.64 (4.99–15.56) vs 20.06 (9.39–39.14), $P < .001$; RIRS 5.62 (1.36–11.40) vs 11.00 (6.58–34.88), $P = .001$]. This was the case for KIM-1/Cr [sPCNL 1.66 (1.06–3.76) vs 6.21 (5.02–11.84), $P < .001$; mini-PCNL 2.59 (1.18–3.64) vs 6.43 (3.52–12.54), $P < .001$; RIRS 1.26 (0.93–2.17) vs 8.33 (5.02–13.43), $P < .001$] and IL-18/Cr. At 6 h, significant increases from baseline were observed in all study groups in NGAL/Cr and KIM-1/Cr ratios, but no differences were noted in IL-18/Cr (Table 3). At 24 h, significant increases were evidenced for NGAL/Cr (sPCNL $P = .001$; mini-PCNL $P < .001$; RIRS $P < .001$), KIM-1/Cr and IL-18 in all study groups (Table 3). At 48 h, similar observations were made for NGAL/Cr ($P < .001$ for all study groups) and KIM-1/Cr, but not for IL-18 (Table 3). With regards to eGFR, no significant differences were detected in any of the study groups between baseline and 2-h (sPCNL $P = .129$; mini-PCNL $P = .199$; RIRS $P = .098$), 6-h, 24-h and 48-h postoperatively.

Figure 2A–C depicts the trajectories of urinary biomarkers, estimated using two-way mixed ANOVA for repeated measurements, from preoperatively (baseline) to 2-, 6-, 24- and 48-h postoperatively in patients allocated to sPCNL, mini-PCNL and RIRS groups. As shown in the Fig. 2A, similar patterns of renal injury were observed for the three intervention groups across the study period, with a trend for a biphasic increase initially at 2 h and then further at 24 h, according to the depicted estimated marginal means of NGAL/Cr. For KIM-1/Cr (Fig. 2B) and IL-18/Cr (Fig. 2C), an increase at 2 h followed by a reduction at 6 h and stable levels until 48 h postoperatively was observed. More specifically, a significant effect of time for all studied biomarkers [NGAL/Cr $F(4, 288) = 12.111$, $P < .001$, partial $\eta^2 = 0.144$; KIM-1/Cr $F(4, 288) = 26.363$, $P < .001$, partial $\eta^2 = 0.268$; IL-18/Cr $F(4, 288) = 10.702$, $P < .001$, partial $\eta^2 = 0.129$] but not of type of intervention [NGAL/Cr $F(2, 72) = 2.240$, $P = .114$, partial $\eta^2 = 0.059$; KIM-1/Cr $F(2, 72) = 0.849$, $P = .432$, partial $\eta^2 = 0.023$; IL-18/Cr $F(2, 72) = 2.250$, $P = .113$, partial $\eta^2 = 0.059$] was observed. In addition, there was no significant interaction between time and type of intervention in any time-point of the study period [NGAL/Cr $F(8, 288) = 1.072$, $P = .381$, partial $\eta^2 = 0.029$; KIM-1/Cr F(8, 288)

Table 2: Comparisons of between study-groups differences in changes (Δ) of urinary markers of AKI from baseline to 2-, 6-, 24- and 48-h postoperatively.

	sPCNL (N = 25)	Mini-PCNL (N = 25)	RIRS (N = 25)	P-value
Change in NGAL/Cr (ng/mg)				
2-h postoperatively	9.46 (4.82 to 14.9)	12.78 (1.69 to 5.24)	6.42 (2.61 to 23.90)	.902
6-h postoperatively	8.90 (3.21 to 17.29)	5.87 (2.24 to 10.63)	8.40 (4.13 to 14.04)	.433
24-h postoperatively	9.81 (3.75 to 18.17)	14.99 (5.39 to 25.72)	11.07 (5.24 to 23.86)	.423
48-h postoperatively	14.07 (7.81 to 27.75)	18.40 (6.59 to 23.32)	12.58 (7.83 to 20.02)	.610
Change in KIM-1/Cr (ng/mg)				
2-h postoperatively	5.18 (1.10 to 9.76)	4.64 (2.27 to 10.55)	7.25 (2.79 to 11.63)	.853
6-h postoperatively	0.99 (–0.28 to 1.96)	0.72 (–0.41 to 2.74)	1.30 (0.41 to 2.82)	.669
24-h postoperatively	1.10 (–0.74 to 3.72)	2.80 (–0.04 to 4.50)	2.15 (0.72 to 3.81)	.490
48-h postoperatively	1.83 (–0.17 to 2.63)	1.56 (–0.31 to 6.15)	0.88 (–0.03 to 2.47)	.402
Change in IL-18/Cr (pg/mg)				
2-h postoperatively	343.59 (–10.29 to 788.54)	283.24 (37.21 to 490.67)	332.59 (74.58 to 536.56)	.980
6-h postoperatively	60.80 (–34.80 to 176.88)	51.75 (–40.8 to 169.93)	45.95 (–19.53 to 125.26)	.987
24-h postoperatively	116.97 (–31.41 to 289.41)	215.27 (3.56 to 389.04)	57.06 (8.33 to 196.89)	.225
48-h postoperatively	92.64 (–3.67 to 309.72)	92.86 (–3.94 to 256.53)	70.89 (–23.89 to 132.47)	.426
Change in eGFR (mL/min/1.73 m^2)				
2-h postoperatively	–3.12 ± 9.90	–2.46 ± 9.33	–2.62 ± 7.60	.965
6-h postoperatively	–3.66 ± 11.02	–1.31 ± 9.15	–2.48 ± 9.74	.711
24-h postoperatively	–3.61 ± 12.12	–0.03 ± 10.54	–0.00 ± 8.17	.376
48-h postoperatively	2.20 ± 10.64	5.04 ± 12.65	1.73 ± 10.61	.540

Continuous variables with normal distribution are presented as mean ± SD, variables with skewed distribution are presented as median (interquartile range).

= 0.980, $P = .435$, partial $\eta^2 = 0.027$; IL-18/Cr $F(8, 288) = 0.486$, $P = .817$, partial $\eta^2 = 0.013$]. Figure 2D depicts the trajectories of eGFR, in patients assigned to the sPCNL, mini-PCNL and RIRS groups over time. Similarly, a significant effect of time [$F(4, 288) = 7.807$, $P < .001$, partial $\eta^2 = 0.098$] but not of type of intervention [$F(2, 72) = 0.180$, $P = .836$, partial $\eta^2 = 0.005$] was evidenced on eGFR; no significant interaction between time and type of intervention was noted [$F(8, 288) = 0.547$, $P = .801$, partial $\eta^2 = 0.015$].

Correlations between stone size and urinary biomarkers of renal injury

In order to explore possible associations between parameters of stone size and markers of AKI in urine at 2-, 6-, 24- and 48-h postoperatively, we have examined correlations between total stone size and stone surface and the levels of urine biomarkers studied. At all time-points studied no correlations between stone size and NGAL/Cr (2 h: total stone size r = –0.016, $P = .894$ and stone surface r = –0.038, $P = .747$), KIM/Cr (2 h: total stone size r = 0.036, $P = .757$ and stone surface r = 0.031, $P = .789$) and Il-18/Cr (2 h: total stone size r = 0.012, $P = .921$ and stone surface r = 0.004, $P = .971$) were observed.

Operative characteristics and postoperative outcomes

No significant between-groups differences were noted in total operative time, hospitalization length, visual-analog pain scale, residual stone, need for auxiliary procedures or in rates of AKI episodes ($P = .769$) postoperatively. In the sPCNL group, one patient underwent arterial embolization due to postoperative hemorrhage, and another presented with urine leak from the percutaneous track which was treated with bladder catheterization for 2 days (Table 4). No significant differences were noted between study groups in eGFR levels at 3-months postoperatively (sPCNL 87.00 ± 20.16; mini-PCNL 84.58 ± 24.23; RIRS 89.58 ± 22.14 mL/min/1.73 m^2, $P = .730$).

DISCUSSION

This is the first randomized clinical trial comparing the effect of three endourological procedures (sPCNL, mini-PCNL and RIRS) on urinary biomarkers of renal injury. No significant between-group differences were evident in changes in NGAL/Cr, KIM-1/Cr and IL-18/Cr between baseline and 2-, 6-, 24- and 48-h postoperatively. However, a significant increase from baseline was observed in NGAL/Cr, KIM-1/Cr and IL-18/Cr in all study groups over most time-points during the 48 h study period postoperatively. The trajectories of all biomarkers over time revealed a similar pattern between the three methods; for NGAL/Cr suggested a drop at 2 h with a marginal biphasic pattern, while for KIM-1/Cr and IL-18/Cr indicated an increase at 2 h that was further reduced close to preoperative levels without major shifts up to 48-h postoperatively. Notably, no significant between-group and within-group differences were noted in eGFR in any of the time-points under study. Moreover, no significant differences were observed between study groups in operative characteristics, postoperative complications, AKI incidence, using a standard definition and renal function at 3-months follow-up. Overall, our findings suggest that the three endourological procedures are associated with similar patterns of renal injury, suggesting a rather mild tubular damage directly after surgery, with no acute effects on glomerular function, no increase in AKI incidence, and a trend towards amelioration of tubular injury within 48 h.

Endourological procedures for the management of renal calculi were suggested to be associated with decreases in renal function in the early postoperative period, with recovery in the long term [1]. However, identification of renal injury may prove problematic when assessment is based on serum Cr levels, and therefore eGFR; this is mainly due to the fact that for an increase in Cr levels to be observed, there must have previously occurred an important decline in glomerular filtration function [14]. Apart from its limited sensitivity in detecting rapid changes in glomerular filtration, serum Cr may not be an appropriate

Table 3: Changes of markers of AKI in urine between baseline and 2-, 6-, 24- and 48-h postoperatively among patients having undergone sPCNL, mini-PCNL and RIRS.

	sPCNL ($N = 25$)			Mini-PCNL ($N = 25$)			RIRS ($N = 25$)		
	Preoperatively	Postoperatively	*P*-value	Preoperatively	Postoperatively	*P*-value	Preoperatively	Postoperatively	*P*-value
2 h									
NGAL/Cr (ng/mg)	3.76 (2.13–8.64)	15.97 (8.14–29.86)	<.001	8.64 (4.99–15.56)	20.06 (9.39–39.14)	<.001	5.62 (1.36–11.40)	11.00 (6.58–34.88)	.001
KIM/Cr (ng/mg)	1.66 (1.06–3.76)	6.21 (5.02–11.84)	<.001	2.59 (1.18–3.64)	6.43 (3.52–12.54)	<.001	1.26 (0.93–2.17)	8.33 (5.02–13.43)	<.001
IL-18/Cr (pg/mg)	125.24 (63.98–237.02)	381.83 (147.65–1051.511)	.003	81.2 (39.54–168.29)	317.14 (166.11–721.85)	<.001	54.60 (27.47–138.09)	125.65 (379.09–661.00)	<.001
eGFR (mL/min/1.73 m^2)	83.51 ± 14.61	80.39 ± 15.70	.129	82.21 ± 21.29	79.75 ± 21.53	.199	85.51 ± 18.22	82.90 ± 16.87	.098
6 h									
NGAL/Cr (ng/mg)	3.76 (2.13–8.64)	14.0 (10.43–21.55)	<.001	8.64 (4.99–15.56)	13.10 (7.33–23.54)	<.001	5.62 (1.36–11.40)	12.14 (8.92–21.81)	<.001
KIM/Cr (ng/mg)	1.66 (1.06–3.76)	2.55 (1.56–4.78)	.045	2.59 (1.18–3.64)	3.33 (1.75–5.24)	.042	1.26 (0.93–2.17)	2.78 (1.73–4.88)	.006
IL-18/Cr (pg/mg)	125.24 (63.98–237.02)	(158.57 (98.00–337.46)	.074	81.2 (39.54–168.29)	121.17 (84.54–244.14)	.135	54.60 (27.47–138.09)	141.28 (67.57–249.34)	.058
eGFR (mL/min/1.73 m^2)	83.51 ± 14.61	79.85 ± 16.96	.110	82.21 ± 21.29	80.90 ± 23.47	.479	85.51 ± 18.22	83.04 ± 18.75	.216
24 h									
NGAL/Cr (ng/mg)	3.76 (2.13–8.64)	15.27 (11.62–20.55)	.001	8.64 (4.99–15.56)	23.53 (16.11–40.58)	<.001	5.62 (1.36–11.40)	17.38 (10.78–40.74)	<.001
KIM/Cr (ng/mg)	1.66 (1.06–3.76)	2.96 (2.09–4.52)	.026	2.59 (1.18–3.64)	4.81 (3.22–6.78)	.002	1.26 (0.93–2.17)	3.33 (1.73–6.95)	<.001
IL-18/Cr (pg/mg)	125.24 (63.98–237.02)	213.48 (170.69–410.96)	.006	81.2 (39.54–168.29)	301.00 (134.97–512.34)	.001	54.60 (27.47–138.09)	173.18 (66.57–297.16)	.006
eGFR (mL/min/1.73 m^2)	83.51 ± 14.61	79.90 ± 17.30	.150	82.21 ± 21.29	82.18 ± 23.33	.987	85.51 ± 18.22	85.51 ± 18.48	.999
48 h									
NGAL/Cr (ng/mg)	3.76 (2.13–8.64)	19.65 (12.17–32.08)	<.001	8.64 (4.99–15.56)	22.80 (17.30–33.68)	<.001	5.62 (1.36–11.40)	19.01 (13.21–31.50)	<.001
KIM/Cr (ng/mg)	1.66 (1.06–3.76)	3.50 (1.60–5.38)	.014	2.59 (1.18–3.64)	5.00 (2.83–8.24)	.003	1.26 (0.93–2.17)	2.50 (1.42–4.91)	.032
IL-18/Cr (pg/mg)	125.24 (63.98–237.02)	300.00 (67.73–454.04)	.013	81.2 (39.54–168.29)	188.37 (88.40–332.71)	.005	54.60 (27.47–138.09)	116.14 (78.19–223.84)	.061
eGFR (mL/min/1.73 m^2)	83.51 ± 14.61	85.71 ± 18.17	.311	82.21 ± 21.29	87.25 ± 25.64	.058	85.51 ± 18.22	87.25 ± 20.73	.422

Continuous variables with normal distribution are presented as mean ± SD, variables with skewed distribution are presented as median (interquartile range).

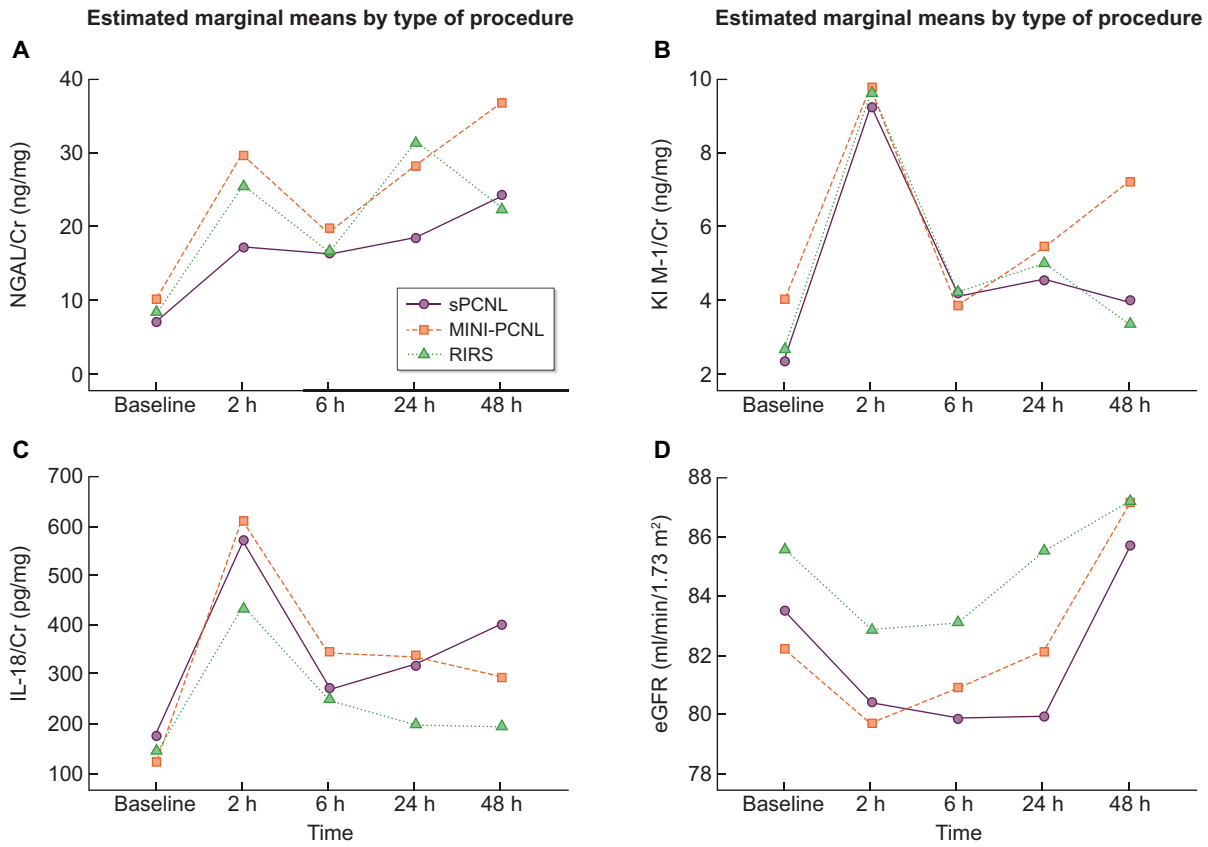


Figure 2: Trajectories of (**A**) NGAL/Cr, (**B**) KIM-1, (**C**) IL-18 and (**D**) eGFR in patients having undergone sPCNL, mini-PCNL and RIRS from baseline evaluation at different assessment time-points.

indicator of tubular injury [15]. Urinary and plasma NGAL levels may detect tubular injury before impaired filtration function occurs [15]. In our study an increase in NGAL/Cr and other urinary biomarkers studied was observed in all study groups, as early as 2-h postoperatively, in the absence of changes observed in filtration function assessed by eGFR. NGAL/Cr showed a slight biphasic pattern with an increase initially at 2 h and then further at 24 h/48 h (pairwise comparison between 2 and 24 h $P = .024/.042$, for mini-PCNL/RIRS, and between 2 and 48 h $P = .031/.027$, for sPCNL/mini-PCNL), suggesting the possibility of two different hits. This could include a slight initial damage of local renal parenchyma followed by another hit. A phenomenon such as a slight ischemia–reperfusion injury following a minor initial parenchymal trauma [1] could be hypothesized, but cannot be ascertained by the present study and, thus, further research in this area is needed. Of importance, both KIM-1/Cr and IL-18/Cr presented an increase at 2-h that was reduced progressively reduced at 6-h and remained stable and near to preoperative levels within 48-h postoperatively. Therefore, the totality of our findings are rather in line with previous evidence favoring the use of modern biomarkers for the early diagnosis of AKI after urological procedures, as well as in other settings [15–17] (intensive care unit, emergency department, pediatric patients), as well as the procedures under study are generally well-tolerated, despite the increase in all biomarkers immediately postoperatively.

An increase in KIM-1, NGAL, NAG and in KIM-1/Cr, NGAL/Cr and NAG/Cr ratios has been previously reported in observational studies after RIRS [18] and PCNL [7, 10]. In a prospective study evaluating the effects of both kidney stone size and different endourological procedures on KIM-1/Cr, before and at 4 h and 14 days after RIRS, sPCNL and micro-PCNL, a positive correlation between stone size and KIM-1/Cr was evidenced; at 4-h postoperatively significant increases from baseline were noted for patients who underwent RIRS and micro-PCNL, and significant decrease for sPCNL, while at 14 days significant decreases in KIM-1/Cr were observed for the RIRS and sPCNL group, but not for the mini-PCNL group [19]. Our findings significantly expand the above knowledge, since the patients were randomly allocated to sPCNL, mini-PCNL and RIRS groups, and assessments included evaluation of multiple biomarkers at more frequent time-points postoperatively, suggesting a specific pattern of rather mild and reversible tubular injury that was similar between the three methods and no changes in filtration function.

With regards to potential mechanisms of injury, it has been speculated that high intrarenal pressures, due to high irrigation in combination with low outflow, cause renal trauma in the case of endoluminal procedures (ureteroscopy and RIRS) [20, 21]. In view of the above, implementation of protocols that involve an access sheath and provide adequate outflow, and reduction of intrarenal operation time were advocated as methods to minimize renal injury [20–22]. For procedures with percutaneous access, it has been hypothesized that the puncture itself has a major role in renal injury by inducing vasoconstriction near the puncture site [23–25]. Miniaturized PCNL techniques were considered to be associated with limited renal injury as a result of

Table 4: Comparisons of operative characteristics and postoperative outcomes among patients having undergone sPCNL, mini-PCNL and RIRS.

	sPCNL (N = 25)	Mini-PCNL (N = 25)	RIRS (N = 25)	P-value
Total operative time (min)	75.00 ± 30.92	78.80 ± 31.00	67.28 ± 24.44	.363
Hospitalization length (days)	2.36 ± 1.15	2.12 ± 0.44	2.40 ± 1.63	.664
Number of punctures (*n*)	1.52 ± 0.82	1.32 ± 0.75	NA	.373
48-h postoperative pain VAS score	1.20 ± 0.82	1.00 ± 0.00	1.16 ± 0.8	.529
Postoperative residual stone (*n*, %)				.443
No residual stone	15 (60.0)	20 (80.0)	18 (72.0)	
<4 mm	6 (24.0)	3 (12.0)	3 (12.0)	
4–8 mm	2 (8.0)	1 (4.0)	0 (0.0)	
>8 mm	2 (8.0)	1 (4.0)	4 (16.0)	
Need for auxiliary procedures (*n*, %)				.315
No procedures	24 (96.0)	24 (96.0)	22 (880)	
ESWL	1 (4.0)	0 (0.0)	0 (0.0)	
RIRS	0 (0.0)	1 (0.0)	3 (12.0)	
sPCNL	0 (0.0)	0 (0.0)	0 (0.0)	
Clavien-Dindo classification (*n*, %)				1.000
Grade 0	22 (88.0)	23 (92.0)	23 (92.0)	
Grade 1	2 (8.0)	2 (8.0)	2 (8.0)	
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 3				
Grade 3a	1 (4.0)	0 (0.0)	0 (0.0)	
Grade 3b	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 4				
Grade 4a	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 4b	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative obstruction (*n*, %)	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative fever (T > 38.5°C) (*n*, %)	2 (8.0)	2 (8.0)	2 (8.0)	1.000
Postoperative hemorrhage necessitating transfusion (*n*, %)	1 (4.0)	0 (0.0)	0 (0.0)	1.000
Postoperative hemorrhage necessitating embolization (*n*, %)	1 (4.0)	0 (0.0)	0 (0.0)	1.000
Postoperative renal leak (*n*, %)	1 (4.0)	0 (0.0)	0 (0.0)	1.000
eGFR (mL/min/1.73 m^2) at 3-months post-procedure	87.00 ± 20.16	84.58 ± 24.23	89.58 ± 22.14	.730
Incidence of AKI (Stage 1/Stage 2/Stage 3) according to KDIGO classification (*n*, %)	1 (4.0)/0 (0.0)/0 (0.0)	2 (8.0)/0 (0.0)/0 (0.0)	0 (0.0)/0 (0.0)/0 (0.0)	.769

VAS: visual-analog pain scale; NA: non-applicable; T: temperature; ESWL: extracorporeal shockwave lithotripsy.

the smaller dilatation performed; however, the data provided from our study do not confirm this hypothesis, since the pattern of injury was similar between the three methods.

To our knowledge, this is the first randomized clinical trial to actively compare the effect of three commonly performed endourological procedures (sPCNL, mini-PCNL and RIRS) for treatment of nephrolithiasis on novel diagnostic indexes of renal injury. We used three different validated biomarkers of tubular injury, as well as parallel measurements of serum Cr to capture both tubular and glomerular function; furthermore, the present study examined the effects of these three procedures in a number of pre-defined renal endpoints, including AKI incidence and safety parameters. A meticulous protocol was followed with consecutive measurements at multiple time-points (2-, 6-, 24- and 48-h postoperatively), and a rigorous analysis was performed in order to assess the trajectories of these biomarkers postoperatively. Finally, scheduled follow-up visits at 1 month and 3 months, including laboratory tests/CT scan, confirmed the absence of between treatment-group differences in postoperative complications and renal function in the long-term. A limitation of this study could be the imbalances in baseline stone size between the three groups; imbalances at a few baseline characteristics (in this case 2 out of more than 20 studied) are not rare in randomized trials with sample size similar to ours. As no correlations between stone size and urinary markers of renal injury were observed, this imbalance in stone size most likely did not affect our findings. The relatively small sample size could be considered as another limitation; if a much larger sample had been included, minor differences between the three arms in the biomarkers studied could have been observed. However, given the patterns noticed, it is highly unlikely that such differences would be of clinical importance.

In conclusion, the three endourological procedures under study (sPCNL, mini-PCNL and RIRS) are accompanied by similar patterns of rather mild acute tubular injury, as detected by novel urinary biomarkers, which is largely reduced within 48 h, without changes in glomerular function. With regards to postoperative complications and the long-term impact on renal function, they were shown to be equally safe procedures. Thus, the present RCT provides reassurance with regards to the safety of the three endourological procedures studied and their possible adverse effects on renal parenchyma. Future studies in larger samples of patients are needed, examining the effects of these procedures in patients' groups with already compromised renal function or those undergoing repeated procedures.

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AUTHORS' CONTRIBUTIONS

Research idea and study design: P.S. and D.H.; data acquisition: D.M., A.A., I.M. and G.D.; data analysis/interpretation: D.M., P.S., I.M. and D.H.; statistical analysis: M.A.and M.T.; manuscript drafting: D.M., P.S. and M.A.; supervision or mentorship: P.S., G.D. and D.H.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

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