REVIEW

The Prevalence of Renal Stones and Outcomes of Conservative Treatment in Kidney Transplantation: A Systematic Review and Meta-Analysis

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Background: Nephrolithiasis is a rare complication in the transplanted kidneys, and limited information is available regarding its therapeutic options. This study aimed to review the conservative management of nephrolithiasis and its outcomes in kidney transplanted recipients.

Methods: A systematic review and meta-analysis of the scientific literature were performed in Medline, Scopus, and Embase databases between January 1st, 1980, and May 19th, 2020. Inclusion criteria were deemed as studies encompassing patients with renal stones in the transplanted kidney, either de-novo or donated stones, and used conservative treatment for all or part of their patients. Exclusion criteria were considered as studies reporting bladder or ureteral stones, conference abstracts, and full-text unavailability. Results of the included studies were combined using a random-effect model, and the prevalence of renal stones and conservative treatment with their corresponding 95% confidence intervals (CIs) were reported.

Results: A total of eight studies (consisting of 14,988 transplanted patients) were included. Among these, 195 patients suffered from renal stones, and the prevalence of renal stones was 1.3% (95%CI 0.89%-1.7%). Conservative management was utilized in 35% (95%CI 19%-51%) of these patients. The mean stone size ranged from 0.29 cm to 1 cm. Three studies reported a stone-free rate (SFR) of %100. Except for two studies that did not report complications, other studies reported zero percent.

Conclusion: More than one-third of nephrolithiasis cases were conservatively managed in transplanted patients. Despite limited data, conservative treatment can be adopted in less than 4 mm stones with high SFR and few complications.

Keywords: conservative treatment; kidney calculi; kidney transplantation; nephrolithiasis

INTRODUCTION

As the most effective treatment of advanced renal failure, renal transplantation has attracted increasing attention. By applying effective immunosuppressive regimens, recent advances in the diagnosis and treatment of short-term complications have prolonged graft survival[1] and have increased the risk of rare and long-term complications [2, 3]. Urinary stone in transplanted kidneys is an uncommon complication occurring over an average time of 1.6 to 3.5 years after transplantation, with the prevalence ranging from 0.2% to 6.3% [1,4]. Despite its rare incidence, allograft stone formation can lead to significant morbidity, increased risk of infection, and deterioration of renal function through obstruction development[1,3,5]. Some factors such as the immunosuppressive status of the patient, the extra-anatomic site, and denervation of the transplanted kidney can cause challenges for the accurate diagnosis and treatment of renal stones in kidney transplant patients[1,3,6].

Overall, allograft stones' formation could be due to the following conditions. First, allograft stones could exist in the transplanted kidney, which is called "donor-gifted renal stones". Second, de-novo stones could develop after transplantation, which might be originated from metabolic, anatomic, or physiological factors. Some of these factors are urinary stasis or reflux, nonabsorbable suture material, recurrent urinary tract infections (UTI), hyperparathyroidism, hypercalcemia, hypercalciuria, hypocitraturia, and immunosuppressive drugs[3,5].

Nephrolithiasis in the transplanted kidney is often asymptomatic, although, in those with clinical symptoms, the most common ones include unexplained fever, increased creatinine, decreased urinary output, hematuria, and pain[6,7]. Therapeutic strategies for transplanted renal stones include Extracorporeal Shock Wave

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Received September 2019 & Accepted May 2020

Table 1. Summary of results recruited from the included studies.

First Author	Year	Study design	Country	Total patients (n)	Nephro-lithiasis (n)	Prevalence of enal stones (%)	Donated (n)	De-novo (n)	Mean age (years)	Conservative management (n)	Mean stone size (cm)	SFR (%)	Complications	NOS score
Lancia martin (11)	1997	Retro-spective	Spain	794	16	2.01	3	13	NA	12	NA	NA	NA	5
Devasia (9)	2004	Case series	India	5	5	-	5	0	NA	3	0.33	100	0	-
Strav-odimos (3)	2012	Case series	Greece	1525	7	0.46	0	7	NA	1	NA	100	0	-
Verrier (12)	2012	Retro-spective	France	3000	31	1.03	0	31	40.5	12	NA	16	0	5
Xing (13)	2012	Retro-spective	China	974	19	1.95	0	19	47	11	NA	NA	NA	5
Yuan (1)	2015	Retro-spective	China	1615	19	1.17	0	19	38.7	2	0.42	100	0	5
Haraz (10)	2017	Cross sectional	Egypt	1208	16	2.02	0	16	41	2	1	66	0	-
Emiliani (4)	2018	Retro-spective	Spain	2115	51	2.41	0	51	48.9	14	NA	35	0	7

Abbreviations: NA, not available; NOS, The Newcastle-Ottawa Scale; SFR, stone-free rate

Lithotripsy (ESWL), Flexible Ureteroscopy (F-URS), Percutaneous Nephrolithotomy (PCNL), open surgery, and conservative medical treatment. Endourological management is generally challenging, needs high-volume experience, and sometimes is associated with important complications. However, conservative treatment is recommended when stones are asymptomatic and small, which are often passed spontaneously[1,4]. Excessive fluid intake, urinary alkalization, and dietary changes are considered conservative therapies in these patients[8].

Ascertaining the overall view of conservative management and its outcomes in kidney transplant recipients is of utmost importance given that limited information exists on the treatment of nephrolithiasis in these patients due to its low prevalence. In addition, no prior study has systematically reviewed the topic. Hence, in this study, we aimed to investigate the prevalence of renal stones and outcomes of conservative treatment in kidney transplanted patients.

MATERIALS AND METHODS

Study population and outcomes

The target population was deemed as kidney transplant recipients with renal stones. The intervention was considered conservative treatment, defined as expectant management, dietary manipulation, or urinary alkalization without invasive endourological interventions. The outcomes were regarded as the prevalence of renal stones in the transplanted patients, the proportion of patients managed conservatively, stone-free rate (SFR), defined as the absence of stone fragments and passage of stones during the follow-up period, and any complications following conservative management.

Inclusion and exclusion criteria

This systematic review was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Inclusion criteria were considered as studies encompassing patients with renal stones in the transplanted kidney, either de-novo or donated stones, and used conservative treatment for all or part of their patients. Exclusion criteria were considered as studies reporting bladder or ureteral stones, conference abstracts, and studies without available full-texts. According to the predefined inclusion and exclusion criteria, articles were assessed, and relevant observational studies (case-series, cross-sectional, and cohort studies) were carefully chosen.

Search strategy and study selection

A systematic search of three main target databases, Medline (PubMed), Scopus, and Embase, were performed from January 1st, 1980, to the May 19th, 2020, with MeSH search syntax grouping of "Renal Transplantation", "Kidney Grafting", "Kidney Stones", "Ureterolithiasis", "Litholapaxy", "Percutaneous Nephrolithotomy", "Percutaneous Ultrasonic Lithotripsies", "Extracorporeal Shockwave Lithotripsy", "ESWL", "Noninvasive Litholapaxy", "Laparoscopic Surgical Procedure", "Minimally Invasive Surgery", and "Ureteroscopies" (provided in supplementary file 1). An expert urologist (SMKA) designed the search strategy and found all relevant documents from three targeted databases. To minimize the selection bias, two investigators (AMFY and HD) selected articles independently by scanning titles and abstracts. Disagreements were solved by a discussion with a third investigator (FKH). In order to find additional documents, the list of references of each candidate article was reviewed as well. The full texts of relevant articles were evaluated carefully against the inclusion and exclusion criteria.

Data Extraction and quality assessment

The following data were extracted from the included studies: the name of the first author, publication year, study design, country where the study was performed, total transplant patients and their demographics, the total number of patients with nephrolithiasis, donated or de-novo stones, the number of patients managed conservatively, SFR, and complications after conservative management. The quality of the included studies was assessed based on the Newcastle–Ottawa Scale (NOS)

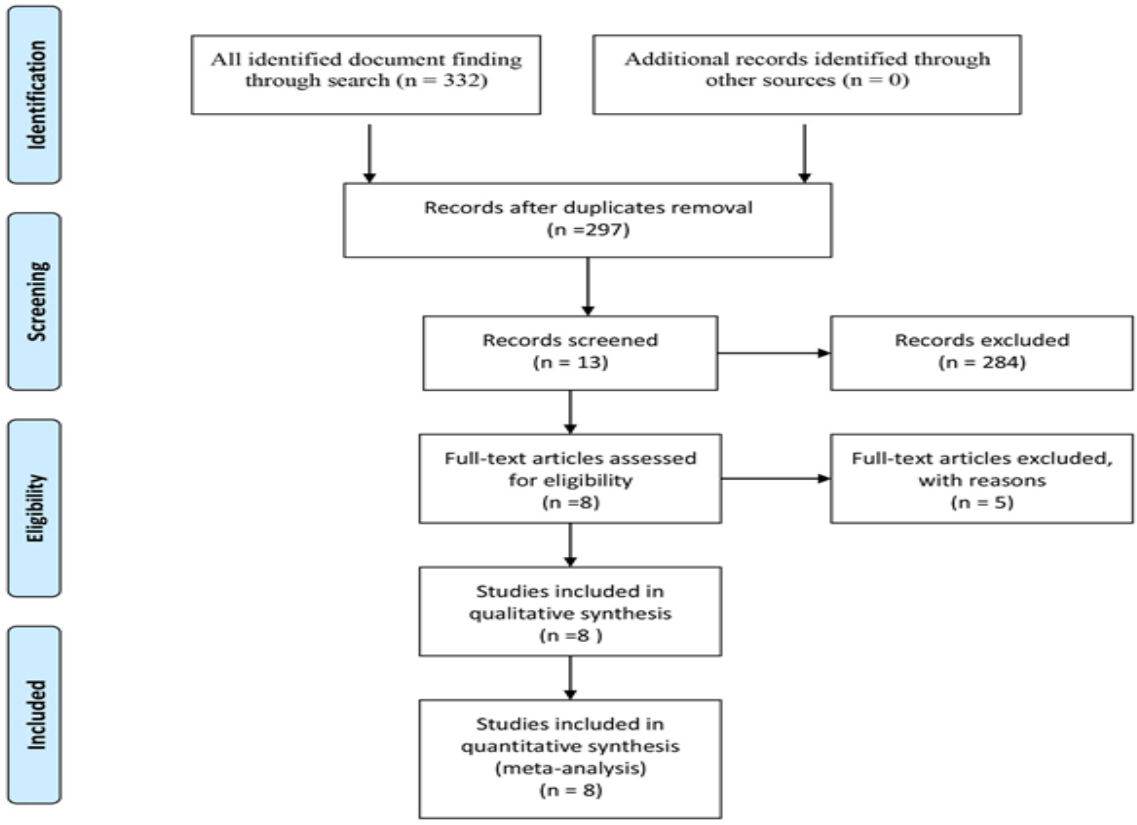

Figure 1. Flowchart of study selection according to PRISMA guidelines.

assessment tool. Each study that reached six points or above (from a maximum of nine scores) was considered "high-quality".

Statistical Analysis

The results of included studies, in the final analysis, were combined using a random-effect model with "metaprop" command, a routine for pooling proportions, and the prevalence of renal stones and conservative treatment with their corresponding 95% confidence intervals (CIs) were reported. The Cochrane's Q-test of heterogeneity at a rank of 5% was considered to assess statistical heterogeneity of the studies, and I2 was applied for quantitative estimation of heterogeneity among outcomes according to the Higgins classification, in which I2 value ≥75% can be indicative of high heterogeneity. Egger's test was employed to assess publication bias. All relevant extracted data were recorded in an Excel spreadsheet, and analyses were conducted using STATA v.14.0 SE (College Station, TX, USA) and RevMan 5.

RESULTS

A total of eight studies[1,3,4, 6,9-13] (consisting of 14,988 transplant patients) met the inclusion criteria for the final review (**Figure 1**). Of the included studies, two were from Spain[4,11], two from China[1,13], and one from France[12], Turkey[6], Greece[3], Egypt[10], and India [9]. Regarding the study design, five articles were retrospective cohorts[1,3,4,6,11-13], one cross-sectional[10], and two case series[9](**Table 1**). According to Egger's test, there was no publication bias in the included study (P = 0.224). The mean age of the patients was 43 years, and the range of male to female ratio was from 0.19 in the Sarier and et al.[6] study to 19.5 in the Emiliani and et al. [4] study.[4,14]

Prevalence of renal stone

In order to estimate the prevalence of renal stones, the study by Devasia et al.[9] was excluded due to the impossibility of calculating the prevalence. A total of 195 patients suffered from renal stones, and the prevalence of renal stones was 1.3% (95% CI 0.89 % - 1.7%) (Figure 2). The lowest and highest prevalence of renal stones was 0.4% [3] and 2.4% [4], respectively. Prevalence of conservative treatment

The prevalence of conservative treatment in 195 patients with nephrolithiasis was 35% (95% CI 19% - 51%). This measure ranged from 11% in the study of Yuan et al. to 58% in the study of Xing and et al. (**Figure 3**)[1,13].

Stone-free rate (SFR) and complications

Two studies did not report the SFR [11,13]. Three studies reported %100 [1,3,9], and the lowest rates were reported by Verrier et al.[12], only 16%. Except for two studies that did not report complications[9,13], other studies reported zero percent. Risk factors for renal stone in transplant patients were not reported in most studies. Hyperparathyroidism and gout (hyperuricosuria) were the only risk factors reported in the three studies[3,4, 13].

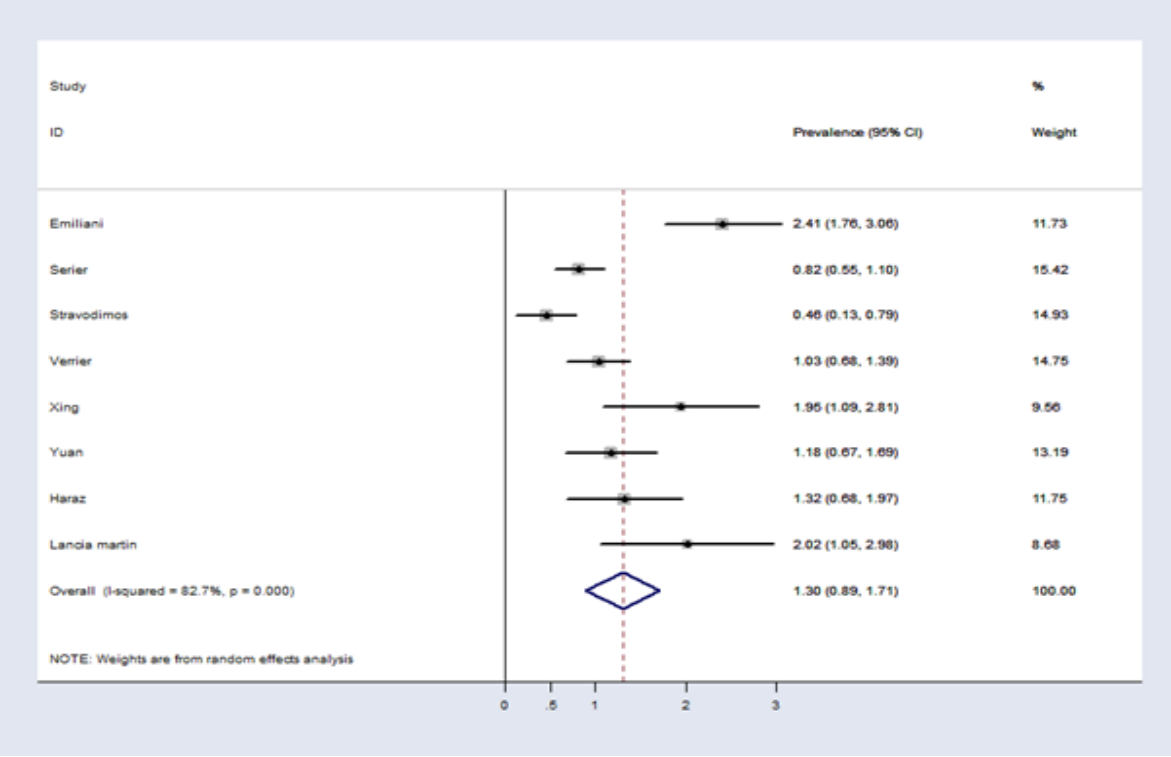

Figure 2. Forest plot for the prevalence of nephrolithiasis in kidney transplant patients.

The mean stone size in patients treated conservatively was not reported in five studies[3,4,11-13]. In the other study, this size was ranged from 0.29 cm to 1 cm[1,6,9,10].

DISCUSSION

Although many physicians use conservative treatment for urinary stones in kidney transplant recipients, a systematic review on various aspects of this method has not been performed yet. Based on our meta-analysis, of each three transplanted recipients with nephrolithiasis, one underwent conservative management. Generally, these stones were sized from 0.29 cm to 1 cm. The SFR was 100% in the majority of the studies, and no complications were reported after this management strategy.

The prevalence of nephrolithiasis in the renal graft was 1.3% in our analysis. Although this prevalence is based on studies concentrating on conservative treatment, it could be worthful due to its large sample size. Recently, Cheungpasitporn et al. performed a systematic review on 64,416 kidney transplant recipients and estimated the incidence of 1.0% for kidney stones[15].

The management of renal stones in transplanted kidneys varied from expectant management to less invasive therapies and open surgery. As a rule, in living donors, the surgeon is committed by the principle that "first no harm" to the graft[16]. Since transplanted patients are considered single-kidney and receive many immunosuppressive medications, any unnecessary intervention could cause complications. On the other hand, due to the rarity of nephrolithiasis in kidney transplantation, the evidence is not robust, and there is no clear approach protocol in this group of patients. Treatment options include expectant management, ESWL, F-URS, and PCNL. European Urology (EAU) guidelines on urolithiasis recommended shock wave lithotripsy for small caliceal stones as an option with minimal risk of complication. However, localization of the stone can be challenging, and SFRs are poor[17]. Traditionally, urology texts considered a 1.5 cm cut-off for PCNL in nephrolithiasis of renal graft[18], although recent guidelines have recommended the algorithm of stone management in native kidneys for transplanted kidneys. In non-obstructing asymptomatic stones with a size below 4 mm, observation with serial ultrasonography and serum creatinine level check is helpful. Other invasive methods are suggested when stone grows or becomes symptomatic[19].

Generally, conservative management could be divided into medical treatment and expectant management. Expectant management for small graft calculus could be done in stones less than 4 mm[20]. Yuan et al. have reported successful conservative treatment for allograft stones in 2 out of 19 patients and emphasized the central role of close follow-up to prevent complications[1].

Medical treatment for large stone burden seems potentially feasible. There are a few reports on medical therapy of graft stones due to their low prevalence. For instance, complete resolution of a staghorn stone with adequate drainage of the pyelocaliceal system using a ureteral stent and medical treatment had been demonstrated previously[20]. In another one, 19 patients with uric acid nephrolithiasis after renal transplantation treated with medical therapy, including the daily water intake above 3000 mL to maintain the urine volume in the range of 2000-3000 mL/d, urine alkalization with sodium bicarbonate, oral allopurinol, analgesic, and antispasmodic. In this study, oliguria, anuria, stone obstruction, stone length greater than 7 mm, or severe hy-

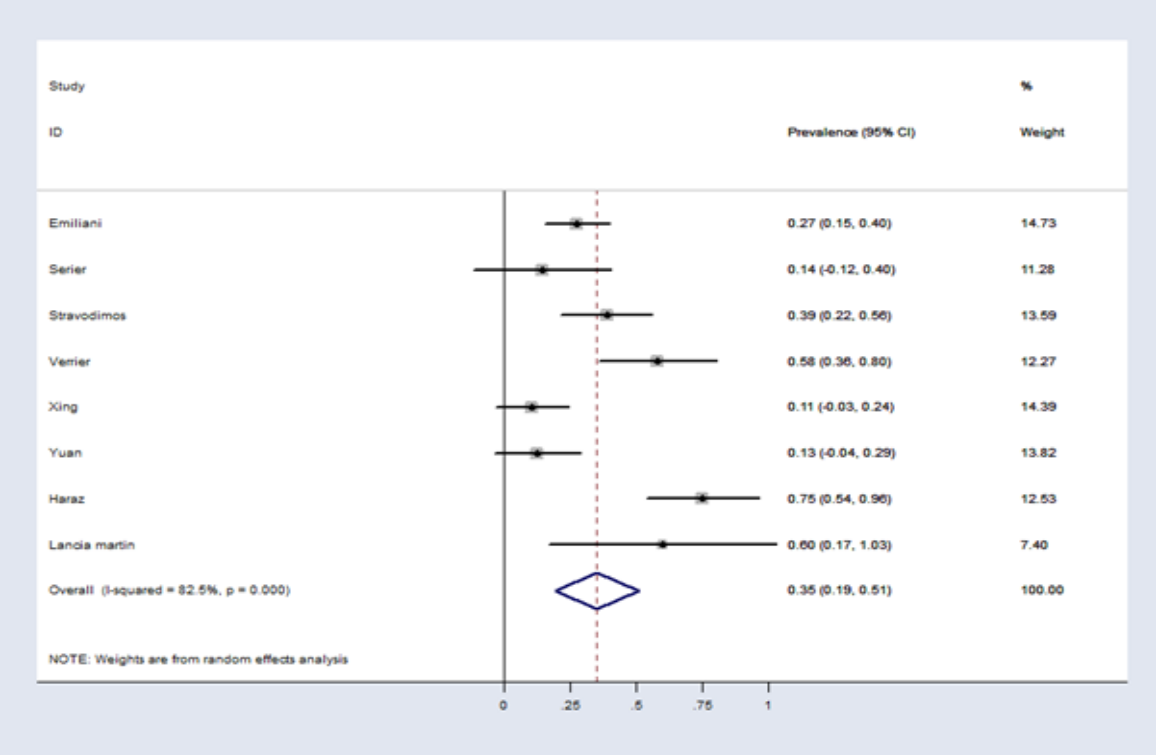

Figure 3. Forest plot for the prevalence of conservative treatment in kidney transplant patients with nephrolithiasis.

dronephrosis were indications of surgery[13].

Many factors could affect a physician's decision during expectant management in graft stone. It could be divided into stone-related and renal anatomic factors. Stone-related factors are size, number, location, and composition. Renal anatomic factors are circumstances such as obstruction or stasis, hydronephrosis, and caliceal diverticulum[18]. Most kidney transplanted recipients are considered single-kidney, and the primary recommendation for patients with single kidney and stone is an intervention. However, some researchers tried to use conservative treatment in transplanted patients. Of note, there exist several conditions, including the presence of fever, uremia, shortage of urinary output, and refractory pain, in which conservative treatment is contraindicated. These situations usually require emergent decompression of the urinary system.

Additionally, another crucial factor is the stone size or stone burden. Many studies utilized a 4 mm cut-off to manage graft stones conservatively; nevertheless, some larger stones have been successfully managed by surveillance. Emiliani et al. used active surveillance in 13 patients and urine alkalization in one. Except for two, all of these stones were smaller than 1 cm. They reported four spontaneous expulsions of stones in the active surveillance group[4]. One of the drawbacks of the study is the lack of details about the composition, location, and mean size of these stones. In another series with conservative treatment in 31 donated transplanted patients, the spontaneous passage rate of above 4 mm stones was 0% vs. 92.8% in the less than 4 mm group. It should be mention that no pretreatment was performed for donated stones[14]. Yuan et al. reported two spontaneous passages in ureteropelvic stones, with the size of 0.4 * 0.5 cm and 0.3 * 0.5 cm[1]. Harraz et al. used a watchful waiting policy with hemolysis for a 10 mm radiolucent stone with no change in size. In their series, conservative treatment was successful in two patients with the stones in kidney and ureter, and the stones passed spontaneously[10]. Nevertheless, they did not mention the size of these two stones. Devasia et al. performed expectant management in three gift-donated stones, with a mean size of 3.3 mm. During two years of follow-up, graft function remained stable, and stones were invisible in ultrasonography or X-ray. One of these cases experienced spontaneous passage[9]. Regarding other factors such as multiple stones and their composition, there is not sufficient evidence with respect to the conservative treatment.

Concerning the stone location, there is no difference between upper and lower pole stones in spontaneous passage rates. In one report, 83% and 84% of lower and mid-upper pole stones passed spontaneously (*P*-value = 0.9). This insignificant difference may be due to changing the position of calyces in transplanted kidneys [14]. For calculating SFR among studies, Clinically Insignificant Residual Fragments (CRIF) could be used, which may be a misnomer as some small residual particles eventually become symptomatic and clinically important as they can move and cause obstruction, act as niduses for stone growth, or become sources for persistent infections[18]. Unfortunately, SFR was not reported accurately in these studies. Data were extracted based on the stone passage during the follow-up period. Two studies did not report SFRs. Three studies reported 100% SFR, and the lowest rates were reported by Varrier et al., who performed active surveillance in seven post-transplant kidney stones. They reported two

spontaneous passages, and other stones were stable[12]. In case the patient selection for expectant management is performed well, and close follow-up is achieved, minimal complications would be expected. The major complication in this management is the requirement of invasive intervention. Verrier et al. performed surveillance in 12 cases, in which two of the patients passed stones spontaneously, and ten were stable during the follow-up[12]. In another study with 31 transplanted recipients, only three patients (9.6%) with a stone size of $\geq$ 4 mm required further intervention. During this time, none of the patients with stones smaller than 4 mm became symptomatic or required any intervention[14].

The duration of follow-up and its intervals were not precise in the studies, and there was no similar strategy. In these studies, the follow-up duration ranged from 24 to 96 months. In one study, patients were followed up every three months with serum creatinine levels and ultrasonography. At their last follow-up within the study period, all patients underwent non-contrast computed tomography (CT) for stone evaluation, and they were followed up for a minimum of 12 months[14]. In another one, serum concentrations of urea, creatinine and uric acid, and cyclosporine A or tacrolimus were tested every 2–3 months. The patients underwent ultrasonography every three months in the first year after the transplantation and every six months thereafter[1]. Emiliani et al. used only ultrasonography every 3–4 months in active surveillance cases[4]. For gifted stones, Devasia et al. repeated imaging every six months after transplantation over a follow-up period of two years and annually afterward[9]. Overall, there is no consensus on the follow-up protocol of kidney transplant patients with nephrolithiasis, while, in our center, we perform ultrasonography every three months.

This review revealed that our knowledge of conservative treatment of nephrolithiasis in renal transplantation is insufficient. During the last 40 years, few studies have been dedicated to this entity, and this topic was usually addressed as a part of a study, besides other modalities. Authors reported neither stone characteristics nor outcomes in this group separately. The stone size has not been mentioned in most studies, so the exact cut-off for stone-size for conservative treatment could not be advised. There were heterogeneous data of immunosuppressive regimens in the reviewed studies, and most of them did not specialize the regimen in the conservative group. We suggest further multi-central studies on conservative treatment modality in transplanted patients to assess stone characteristics, SFR, and outcomes.

CONCLUSIONS

Approximately 35% of nephrolithiasis was conservatively managed in transplanted patients. There are few articles regarding this treatment option in kidney transplant patients with incomplete data in the literature. Conservative treatment could be utilized in stones less than 4 mm in size with high SFR and low rate of complications. Further studies are required to explore the SFR, complications, and follow-up of conservative management in kidney transplant recipients with nephrolithiasis.

CONFLICT OF INTEREST

All authors declare there is no conflict of interest.

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