DEVELOPMENTS IN URETEROSCOPIC STONE TREATMENT

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DEVELOPMENTS IN URETEROSCOPIC STONE TREATMENT

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REVIEW
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Prevention and Management of Infectious Complications of Retrograde Intrarenal Surgery

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Kidney stone disease (KSD) is a commonly encountered ailment in urologic practice. Urinary tract infection (UTI) is commonly associated with KSD, both as an etiology (e.g., struvite and carbonate apatite stones), and as a complication (i.e., obstructive pyelonephritis and post-operative UTI). Indeed, a significant portion of the economic burden of KSD is skewed toward stones associated with infection. UTI is the most common post-operative complication related to stone intervention with progression to urosepsis as a rare but serious consequence. Risk for infection is influenced by a variety of factors including co-morbid conditions, anatomic abnormalities, prior surgical procedures, and local anti-microbial susceptibility. Understanding these risks and the proper steps to mitigate them is an essential component in reducing post-operative morbidity and mortality. Retrograde intrarenal surgery is routinely used for the treatment of KSD. The objective of this review article is to examine the current literature and guidelines for the prevention and management of stone-related infectious complications associated with retrograde intrarenal surgery. Special attention will be given to the incidence, etiology, and antibiotic prophylaxis choice in the management of stone-related infections. Intraoperative risk mitigation techniques will be discussed in conjunction with the management of post-operative infections. Antibiotic stewardship and the potential benefits of reduced empiric antibiotic treatment will also be discussed.

Keywords: infection, ureteroscopy, nephrolithiasis, urology, sepsis

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INTRODUCTION

Kidney stone disease (KSD) is a commonly encountered ailment in urologic practice, with an estimated incidence and prevalence in the United States of 0.9 and 8.8%, respectively (1, 2). The prevalence of KSD has been trending upwards in recent years in both population-based and large-scale studies (1, 3). While the increasing rates of KSD can be partly attributed to improvements in imaging technology and detection, the increasing obesity rates in the United States are another likely contributing factor (1, 3).

Urinary tract infections (UTI) are commonly associated with KSD as both an etiology and complication. Kidney stones that form secondary to infection with urease producing bacteria are often referred to as infection stones and common causative organisms include *Proteus, Klebsiella,* and *Staphylococcus* species (4). However, one recent study by Parkhomenko et al. evaluated the urine and stone cultures in a 1,191 patient cohort and found the bacteriology of struvite stones had shifted toward non-traditional urea-splitting microorganisms such as *Enterococcus* species (5). Infection stones often consists of magnesium ammonium phosphate (struvite) or carbonate apatite (6). These stones form from the breakdown of urea into ammonia and carbon dioxide (CO_2) by urease (6). The increased concentration of ammonia (and later ammonium) creates a locally alkaline environment that facilitates stone formation (6). The increased concentration of CO_2 drives in the conversion of CO_2 to carbonate which in turn results in the formation of carbonate apatite (6). Notably, infection stones can be polymicrobial with the incorporation of the non-urease producing bacteria as well (4). Infection stones are more likely to occur in patients with indwelling catheters, neurogenic bladders, or other medical comorbidities that may result in urinary tract microbial colonization (6).

Distinct from *infection stones (IN stones)* are *infected stones (ID stones)* (6). ID stones are colonized kidney stones in which stone genesis and growth is not driven by urease production (6). For example, a kidney stone may form by other metabolic processes (i.e., hypercalciuria) and subsequently become colonized by urinary tract bacteria (6). Another proposed mechanism for the genesis of ID stones is that urinary tract bacteria themselves serve as a stone nidus and host metabolic abnormalities subsequently drive stone growth (6). ID stones are more likely than IN stones to exhibit discordance between stone cultures and urine cultures (6). Contrarily, given that IN stones are often a sequalae of a preceding UTI, stone cultures and urine cultures are often concordant (6). Importantly, IN stones pose a clinical challenge because antibiotics are unable to penetrate the matrix of the stone, making complete surgical extraction crucial (6). If possible, stone fragments should be collected under sterile conditions to be sent for stone culture (7). Stone cultures are not only a better predictor of serious postoperative infectious complications, but they can also provide essential information to guide antimicrobial treatment if a patient develops sepsis (7).

The management of KSD is multimodal, with retrograde intrarenal surgery (RIRS) as a mainstay surgical management option (8). According to current American Urologic Association (AUA) guidelines, patients with a stone burden of <20 mm (or <10 mm for lower pole stones) can be offered RIRS as a first line surgical treatment with excellent stone free rates (9). Other options for surgical management of nephrolithiasis include shock wave lithotripsy (SWL) and percutaneous nephrolithotomy (PCNL) (8). However due to improvements in ureteroscope technology such reduction in scope size and increased laser efficacy, RIRS has become the most commonly utilized surgical management tool for KSD (8, 10).

Though generally safe, important, and potentially morbid complications of RIRS include urinary tract infections and urosepsis. Infectious complications can occur when treating all types of kidney stones including infected, infection, and metabolic stones. Several large collaborative groups have studied infectious complications associated with RIRS. The Clinical Research Office of the Endourology Society (CROES) evaluated 11,885 patients undergoing ureteroscopy and found that postoperative fever occurred in 1.8% of patients with 1.0% of patients developing a UTI and 0.3% of patients becoming septic (10). The Reducing Operative Complications from Kidney Stones (ROCKS) collaborative reported that in 1,817 ureteroscopy procedures, 2.4% of patients were hospitalized secondary to an infectious complication (11). In addition to potential patient morbidity, postoperative sepsis represents a large financial burden on the healthcare system. Although cost calculations can vary widely, Arefian et al. reported that the management of a septic patient incurs a mean total hospital costs upwards of $30,000 per patient (12). Minimizing postoperative infectious complications after RIRS is an important potential avenue for much needed cost-saving as the overall estimated economic impact of nephrolithiasis was 4.5 billion dollars in the employed population of the United States in the year 2000 (13). Given the medical and economic burden produced by infectious complications of RIRS, the aim of this Review is to summarize the literature on infectious complications of RIRS and provide up-to-date clinical mitigation strategies involving pre-operative, intra-operative, and post-operative care.

PRE-OPERATIVE CONSIDERATIONS

The preoperative workup for a patient undergoing RIRS for KSD should include a thorough history and physical exam, basic preoperative bloodwork including basic metabolic panel (BMP) and a complete blood count (CBC), and in most patients, preoperative evaluation by a general medical doctor. Additionally, the AUA guidelines recommend obtaining a urinalysis in all patients, and urine culture in patients in whom there is clinical or laboratory signs of infection (14). The European Association of Urology (EAU) recommends that a preoperative urine culture be obtained for all patients undergoing a procedure for stone removal (15). While positive nitrites on a urinalysis are specific for the presence of bacteria, many uropathogens do not produce nitrates, such as *Enterococcus* (14, 16). Furthermore, many patients with nephrolithiasis have sterile pyuria due to local inflammation and trauma from the stone. Given these pragmatic challenges with using urinalysis alone, in clinical practice, obtaining a urine culture prior to endourologic intervention in all patients is non-controversial (17).

Preoperative urine cultures are an important predictor of infectious complications following RIRS (18–20). Blackmur et al. reported a significant relationship between pre-operative positive mid-stream specimen urine (MSSU) and the incidence of urosepsis, even despite antibiotic prophylaxis (21). A recent meta-analysis conducted by Sun et al. that included 14 studies with 9,532 total patients evaluating potential risk factors for infectious complications following ureteroscopy reported positive pre-operative urine culture to be the most significant predisposing factor for infectious complications (19). **The compilation of evidence makes the use of routine pre-operative urine cultures in all patients strongly encouraged** (7, 22). Routine preoperative urine culture in all patients already appears to be widespread and its value in outcomes prediction for infectious complications support its continued practice.

Urine culture results can fall into one of three general categories: negative, positive, and contaminated. For patients with negative urine cultures, preoperative antibiotic prophylaxis beyond the standard perioperative antibiotic dosing on the day of surgery is generally not indicated. Indeed, the current AUA best practice statement states, "There is no high-level evidence to support the use of multiple doses of antimicrobials in the absence of preoperative symptomatic infection" (14). For patients with positive urine cultures, treatment with culture specific antibiotics should be initiated and follow up urine culture should be obtained. The literature suggests that that RIRS should only be carried out in the presence of a negative follow up culture for patients with a positive preoperative culture (20, 22–24). For patients with persistent positive cultures, practitioners should consider obtaining an infectious disease consultation. For patients with contaminated urine cultures, a repeat sample should be obtained. Contaminated cultures may be reported by the microscopy lab as such, but are also suggested by the presence of epithelial cells on urine microscopy (25). Indeed, the AUA best practice statement recommends that additional samples be obtained from the patient as a midstream sample or *via* catherization for repeat urine studies (14).

Escherichia coli, a gram negative rod is, one of the most commonly encountered infectious organisms in the genitourinary system (7, 26, 27). Senocak et al. found in their retrospective review that *E.coli* was not only responsible for the majority of positive overall positive cultures, but also the highest proportion of multi-drug resistant cultures as well (28). Other commonly encountered gram negative organisms include *Proteus mirabilis*, *Klebsiella* and *Pseudomonas aeruginosa* (4, 7, 26). *E.coli*, *Proteus* and *Pseudomonas* are known gram negative biofilm formers as well (26). Gram positive organisms tend to consist of *Enterococcus* species and *Staphylococcus aureus* (7, 26) *Enterococcus* species and *Staphylococcus aureus* have also been isolated from biofilms found on catheters of the urinary tract (26). Gram positive bacteria can make up as much as 40% of encountered UTIs in an inpatient setting, with *Enterococcus* making up the majority of these specimens (29). *E.coli* and *Proetus* are of particular interest because they tend to cause infection as a consequence of overgrowth of endogenous flora rather than as foreign invaders (4). Proteus is typically found as part of the gut flora with occasional cross-over to the urethra, but it usually does not cause UTIs in patients with unobstructed urinary tracts (4). The presence of an indwelling catheter allows for ascension of the organisms into the upper urinary tract via unique "swarming" motility (4). Proteus also is a model urease producing organism and is commonly associated with struvite and staghorn calculi (4).

The rise of MDR bacteria is a cause for significant concern and has the potential to increase morbidity and mortality of RIRS. Senocak et al. reported a prevalence of 32.3% for MDR bacteria in pre-operative urine cultures for patients undergoing RIRS for KSD (28). Additionally they found on multi-variate analysis the presence of MDR organisms to be a strong predictor for infectious complications, with an odds ratio of 4.75 after controlling for other patient factors (28). This is despite the use of appropriate preoperative antibiotic therapy (28). Patel et al. reported similar results for PCNL (30). This highlights the importance of antibiotic stewardship and limited use of empiric therapy and preferred use of direct, targeted definitive therapy in the face of a known infection.

Another crucial entity for the urologic practitioner to be aware of prior to RIRS is funguria. Funguria most often is due to *Candida* species and is known as candiduria (31). Although other fungal species such as *Cryptococcus* or *Aspergillus* can infect the kidney, they typically only do so when part of a disseminated infection and rarely cause isolated urinary tract symptoms (31). Funguria often presents as sterile pyuria on urinalysis. Urine cultures are routinely used to diagnose fungal infections with similar efficacy as bacterial infection (31). Like bacterial infections, susceptibility to antifungal agents should be determined and treatment tailored if those services are available. Other routine laboratory tests are less useful in the management of a fungal infection (31). Patients with asymptomatic candiduria are typically not treated unless the patient is scheduled to undergo a urologic procedure (31). Patients with candiduria should be treated with oral fluconazole or IV amphotericin B for several days prior to and following RIRS (14). A longer course of antifungal treatment is recommended in neutropenic patients who present with an obstructive uropathy and are undergoing genitourinary tract surgery such as RIRS (14). Additionally, diabetic patients are more likely to present with candiduria, so a higher degree of clinical susception should be used when treating diabetics (31). Furthermore, a detailed history of recent antibiotic use should be obtained as the loss of saprophytic flora with prolonged use of common antibiotics such as fluroquinolones, third generation cephalosporins, and clindamycin is associated with an increased risk of fungal infections (32). While rare, fungal infections following RIRS have been reported in patients on prolonged antibiotic therapy (33).

In urologic practice, indwelling urinary tract drains are commonly utilized. These include bladder catheters, ureteral stents, and percutaneous nephrostomy tubes. The presence of preexisting drains at the time of RIRS has been found to be associated with post-operative infectious complications (7, 34). The presence of a foreign body in the genitourinary system essentially provides a scaffold for microorganisms to colonize and form a biofilm, acting as nidus for infection (22). In short, a biofilm is a matrix of extracellular material excreted by microorganisms, typically bacterium, that form a film or coat on the surface of a foreign body and allows for the adhesion and further colonization (22, 35). This is particularly relevant for the urologist as many common uropathogens are adept at biofilm formation (26). The manipulation of a foreign body with biofilm during RIRS could seed bacteria throughout the genitourinary track (22).

Indwelling bladder catheters (aka Foley catheters) are commonly encountered in urologic practice and often lead to nosocomial infections called catheter-associated urinary tract infections (CAUTI) (26). A CAUTI is the most commonly encountered hospital-acquired infection in clinical practice (26). Unsurprisingly, indwelling bladder catheters have been shown to be associated with increased risk for infection following RIRS (36, 37). Additionally, indwelling bladder catheters have also found to be strongly associated with pre-operative funguria and the development of SIRS following RIRS (38). Urinary catheters are quickly colonized by bacteria after insertion, and ascent to the bladder takes only 1–3 days (39). The duration of catherization is greatest risk factor for infection (39). Almost all patients with an indwelling catheter for longer than 1 month will have bacteriuria (40). Keeping this in mind, catheters would ideally be changed as close to the procedure as possible. Patients with indwelling catheters with asymptomatic bacteriuria should be treated prior to the procedure (39). Furthermore, obtaining a urine culture from a "freshly" exchanged catheter may help better tailor antimicrobial prophylaxis during RIRS. Biofilms formed on catheters tend to be polymicrobial if they have been in place for more than a few days (40). A "freshly" exchanged sample could avoid contamination and may give more relevant clinical data.

Several studies have established an association between the presence of pre-operative stents and infection following RIRS (19, 34, 36). The recent meta-analysis by Sun et al. found that pre-operative ureteral stents are significantly associated with the development of infectious complications following RIRS with an odds ratio of 1.53 (19). Like indwelling bladder catheters, ureteral stents are rapidly colonized and subject to biofilm formation shortly after they are placed (23). Importantly, stent related infection can occur in the absence of biofilm formation, indicating that other mechanisms also mediate the relationship between pre-operative ureteral stents and the development of sepsis after RIRS (22). Urine cultures are often discordant with stent cultures, making antibiotic selection challenging (23). Nevo et al. found 11% of patients had positive stent cultures despite a sterile urine culture, and 26.4% patients with positive urine and stent cultures had discordant cultures (23). The same study also demonstrated an association between positive stent cultures and post-procedure sepsis (23). Nevo et al. found a significant relationship between prolonged stent dwelling time and postoperative sepsis in patients who underwent ureteroscopy after stent insertion (35). Indeed, Nevo et al. reported a fivefold increase in urosepsis risk for patients with indwelling stent times longer than 30 days as compared to patients with indwelling stent times shorter than 30 days (35). An increase in sepsis rates were also observed at 2, 3 and >3 months of stent dwell time (35). Though these findings suggest that stent exchange prior to RIRS should be considered for patients with longer indwelling stent times, there are currently no prospective randomized controlled trials on which to base definitive recommendations. These studies suggest that in patients with indwelling stents, a higher degree of suspicion for infectious complications should be maintained despite sterile preoperative urine cultures and sending stent cultures should be considered intraoperatively. Pragmatically speaking, unlike foley catheters, stents cannot be routinely exchanged prior to RIRS, given that stent exchanges are usually performed in the operating room. "In-office" stenting has be adapted by some urologists and if office-based stenting were to gain widespread adaptation, routine stent exchange prior to RIRS may be a potential avenue for minimizing complications from RIRS in the future (41). Drug-eluting and anti-microbial coated stents have been explored as a means to address infection concerns, but currently there is no widely adapted drug eluting or coated ureteral stent (22, 26). This represents another important avenue for future research.

Patients may undergo percutaneous nephrostomy tube placement prior to RIRS for a variety of reasons. Most commonly, these are acutely ill patients who are too unstable to undergo retrograde ureteral stent placement or patients in whom retrograde renal access could not be established (42). Preexisting PCNs are a known risk for infectious complications following RIRS (36). However, given that patients who undergo PCN placement rather than stenting for acute obstruction are often sicker, it is unclear if the higher sepsis rates at the time of RIRS are related to the actual PCN, or to severity of illness at the time of initial decompression (42). Like ureteral stents, PCNs cannot be pragmatically exchanged prior to RIRS in most practice setting. One systematic review concluded that PCN urine cultures can help guide antibiotic selection when selecting antibiotics for the treatment of sepsis in the context of upper urinary tract obstruction (43). Ideally these cultures should be drawn at the time of decompression, and a general rule, cultures should be taken from the drain and never from the collection bag. This applies to foley catheters as well. Of note, though PCN cultures can help guide antibiotic selection, there is little utility in treating to sterility as there were no differences in infectious complication outcomes for patients who waited to have urine from their PCN sterilized before undergoing upper tract stone surgery (43). For patients who present septic and undergo emergent decompression, either with a stent or PCN, there is no well-established, evidence-based guideline for how much time should elapse prior to undergoing definitive RIRS. However, it is reasonable and intuitive to allow for completion of treatment course of antibiotics for a complex urinary tract infection, which is at least 7 days (44).

The risk factors for developing infectious complications following RIRS have been extensively studied and several at risk populations have been identified. In addition to positive pre-operative urine culture and indwelling urinary tract drains, these risk factors include female gender, diabetes, renal abnormalities, ischemic heart disease, advanced age, history of recurrent UTI, previous incomplete stone removal, urinary diversion, paraplegia, and a higher Charleston comorbidity index (11, 18, 19, 22, 34, 45, 46). Immunosuppression, recent chemotherapy or steroid treatment, poor nutrition and prolonged hospital course are other factors that increase the risk of post-operative infectious complications, in general (47). Some of these populations require special consideration in preparation for RIRS.

Female gender is a well-established risk factor for infectious complications following RIRS (19, 37, 48). The shorter urethra puts the female urinary tract at higher risk for colonization with perineal bacteria and rectal bacteria that can cause infection (19, 39, 47). Clinicians should maintain a higher index of suspicion for infectious and infected stones in female patients. For pregnant patients, clinicians must be wary to avoid potentially teratogenic antibiotics such as fluoroquinolones and aminoglycosides (49). Although ureteroscopy is considered safe, pregnant patients are maintained as a high risk population by the AUA (50, 51). One meta-analysis reported that there were no increased rates of complications following RIRS for pregnant patients, and complications were typically minor when encountered (50). A second retrospective review also noted no difference in complication rates between pregnant and non-pregnant patients (52). Pregnant patients may see a delay in diagnosis of KSD in favor of other medical or obstetric causes (50). Stenting following RIRS in a pregnant patients may be problematic because the higher concentrations of calcium and urate in the urine increase the risk of stent encrustation (53). Stents are also more prone to migrate in pregnant patients (53). If the pregnancy is considered high risk or there are unique obstetric concerns, consider an OB/GYN consult prior to surgery and/or fetal heart monitoring with an OB/GYN present during surgery.

Sun et al. that reported that diabetes mellitus was among the most clinically relevant pre-operative risk factors for infectious complications after undergoing ureteroscopy (19). Li et al. also found diabetes mellitus to be an independent predictor of infection following RIRS (45). Patients with diabetes mellitus are more susceptible to infection for several reasons (19). Higher glucose in the urine may act to facilitate bacterial survival and proliferation within genitourinary system although evidence supporting a direct relationship is lacking (54). Furthermore, impaired immune function secondary to incomplete phagocytosis and diminished function of granulocytes in diabetic patients can leave them more prone to infections (54). Additionally, diabetic patients are prone to developing diabetic cystopathy which may result in recurrent UTIs secondary to incomplete bladder emptying (55). Patients with diabetes mellitus as also at a higher likelihood of developing a UTI compared to the general population outside the context of post-surgical complications (54).

Prior to surgery, known diabetic patients should be evaluated with an HbA1c, as those with higher HbA1c levels could be at higher risk for complications and longer hospital stays (51). One might consider delaying elective RIRS if blood glucose exceeds 400 mg/dL preoperatively (51). Patients should be counseled on how their diabetic medications regime should be altered on the day of surgery (51). Overall, a higher degree of suspicion should be maintained for infectious complications postoperatively for diabetic patients. If blood glucose remains uncontrolled or the patient's medication regime is complex, consider an endocrinology consultation.

Patients artificial joints placed within 2 years of the procedure should be considered for antibiotic prophylaxis for procedures that can cause bacteremia such as RIRS, however they are not considered independently high risk for infectious complications by the AUA (14). Other comorbidities such as advanced age, ischemic heart disease, and higher Charleston comorbidity index have been associated with greater risk of post-operative infectious complications after RIRS (11, 18, 22, 34). For elderly patients, preoperative evaluation by a geriatrician should be considered and for patients with abnormal cardiac histories, preoperative evaluation by a cardiologist should be considered. As a general rule of thumb, a multidisciplinary approach with specialist consultation should be utilized for the preoperative optimization of patients with multiple co-morbidities. Pre-operative recommendations are summarized in **Table 1**.

TABLE 1 | Summary of pre-operative considerations.

Risk factor	Mitigation strategy
Positive preoperative urine culture (bacteria)	Culture specific antibiotics
Positive preoperative funguria	Oral fluconazole or IV antifungal for several days prior to RIRS (14). Extended therapy in neutropenic patients (14).
Presence of indwelling drain	• **Foley**: Asymptomatic bacteriuria treated prior to RIRS, cultures obtained ideally from a recently exchanged catheter (39). Ensure that the culture is drawn directly from the drain and not the collection bag. • **Ureteral stent**: Limit dwell time to one month if possible, consider exchange if lengthy time to definitive therapy anticipated (35). • **PCN**: Obtain renal pelvis culture to guide antibiotic selection (43). Ensure that the culture is drawn directly from the drain and not the collection bag.
Diabetic patient	Preoperative HbA1c and blood glucose (51). Delay RIRS if blood glucose exceeds 400 mg/dL (51).
Artificial joints	If placed within 2 years, consider antibiotic prophylaxis for several days prior to RIRS (14)
Patients with other known risk factors for infectious complications following RIRS and complex patients with multiple comorbidities	Employ a multidisciplinary approach with input from the appropriate medical/surgical services on how to best manage the unique risk factors

INTRA-OPERATIVE CONSIDERATIONS

The current AUA guidelines recommend antibiotic prophylaxis for gram-negative rods and *Enterococci* species for patients undergoing upper urinary tract endoscopic procedures (14). Per the AUA, the perioperative antimicrobials of choice for RIRS are trimethoprim-sulfamethoxazole (TMP-SMX) or a 1st/2nd generation cephalosporin. Alternative antibiotic regiments are an aminoglycoside +/− ampicillin, aztreonam +/− ampicillin, or amoxicillin/clavulanate (14). The EAU guidelines are similar in their recommendation of TMP-SMX, an aminopenicillin plus a beta-lactamase inhibitor, or a 2nd/3rd generation cephalosporin (56). TMP-SMX should be avoided in the pregnant patient and aztreonam should be reserved for patients with renal insufficiency and penicillin allergies (14, 49). Parenteral antibiotic prophylaxis should be administered within I h of the procedure, or 2 h if vancomycin is used (14). Contrary to these recommendations, Deng et al. found there to be no difference in the rates of post-operative febrile UTI with or without antibiotic prophylaxis for patients with negative urine cultures undergoing ureteroscopic lithotripsy in their meta-analysis of 4,591 patients across 11 different studies (57). However, there was a significantly lower risk of post-operative pyuria and bacteriuria with patients receiving a single dose of antibiotics prior to the procedure, with no difference between oral or IV agents (57). Similarly to this later finding, Knopf et al., that found a single dose of levofloxacin reduce the risk of post-operative bacteriuria from 12.5 to 1.8% (58).

This controversy is not new, and while the AUA guidelines are in favor of antibiotic prophylaxis, the European Association of Urology does not take a hardline stance on their use for all patients (57). Antibiotic stewardship is critical as we have already begun to see the rise of common uropathogens such as *E.coli* with resistance patterns to fluoroquinolones and TMP-SMX (28). This is a growing body of evidence that favors the limiting the use of empiric antibiotic therapies both in an effort to limit the proliferation of resistance but also with potentially lowering rates of sepsis (27). Zisman et al. found in their retrospective study that a significant portion of patients with a positive urine culture prior to RIRS contained ciprofloxacin resistant pathogens (27). They aimed to tailor antibiotic prophylaxis with two agents based on their hospital's local resistance patterns, and found a decreased risk of septic events when compared with typical prophylaxis (27). Additionally, Schnabel et al. came to a similar conclusion during their literature review of antibiotic prophylaxis in urolithiasis, with moderate benefit to single dose prophylaxis in patients undergoing RIRS (59). This would suggest that perioperative antibiotics be given based on local sensitivities if they are known. Lastly, for fungal prophylaxis, the AUA best practice statement notes: "Single-dose antifungal prophylaxis is recommended for patients with asymptomatic funguria undergoing endoscopic, robotic, or open surgery on the urinary tract." (14). Otherwise, there are no guidelines suggesting patients with specific risk factors received perioperative antifungal prophylaxis.

Maintaining low irrigation pressures during RIRS is key for reducing infectious complications. Pressure increases in the collecting system can impair renal filtration and even result in retrograde flow from the collecting system, known as "pyelovenous backflow" in which there is communication of urine and renal venous blood (60). Theoretically, this would allow for the communication of bacterial products and inflammatory mediators from the urinary tract to enter systemic circulation (45). This notion is supported by the fact that high intra-renal pressures experienced during RIRS has been found to be associated with post-operative fevers (60). Additionally, one *ex-vivo* study of simulated ureteroscopy found a link between high intra-renal pressures and histologic changes as well as fluid extravasation in a porcine model (60). Normal intrapelvic pressure are approximately 5 mmHg, and the threshold for pyelovenous reflux is approximately 35 mmHg (61). Intraoperatively, pressures can reach up to 328 mmHg during forced irrigation, almost 10 times the reflux threshold (61).

A commonly used method for maintaining low intrapelvic pressure and reducing the risk of infectious complications is the use of a ureteral access sheath (UAS) (61). A UAS is an instrument originally conceived as a "guide tube" used during ureteroscopy for repeated entry to the ureter and renal collecting system while maintaining lower irrigations pressures (61). A UAS facilitates low irrigation pressures because it creates a channel from the collection system to outside of the body. This channel allows for irrigation outflow and equilibration with atmospheric pressure. Notably, these effects are most pronounced when a large diameter sheath is used and instruments are not obstructing the lumen (61). UAS have been shown to reduce intrapelvic pressure by up to 75% and large diameter sheaths can maintain pressures below the reflux threshold for the duration of the procedure (61). When using a UAS during RIRS, intrapelvic pressure is inversely related to UAS and directly related to ureteroscope size (61).

UAS may also reduce infection risk by minimizing operative time. Kim et al. found operative time to be an independent risk factor for the development of a febrile UTI following RIRS on multivariate analysis (62). This could be related to several factors, namely stone burden, irrigation pressure and irrigation volume (45, 62). Reasonably, increased operating time require the use of a larger amount of irrigation volume when compared to shorter procedures. A higher stone burden would also necessitate more operative time and provide more nidi for infection (45, 62). The continued introduction of foreign fluid into the genitourinary system, coupled with the repeated exposure of the internal matrix of the stone would provide an avenue for infection (45). If this were done under high pressure, the likelihood of the patient experiencing the movement of infectious material into other systems via pyelovenous reflux also would increase (45). One method that has been shown to reduce operative time is the use of an UAS secondary to the reduce time for repeated entry into the collecting system (61). However, the use of a UAS is not without its own risks, as their use can cause independent damage to the ureters ranging from superficial lesions of the mucosa to circumferential perforations (61).

Another method for maintaining low irrigation pressures is the use of gravity irrigation. A retrospective study by Farag et al. suggested that the use of fixed pressurized bag gravity irrigation was associated with less infectious complications when compared to the use of hand-syringe irrigation during RIRS (63). Gravity irrigation is "natural irrigation based on the height from the tip of the ureteroscope to the surface of saline" (64). With gravity irrigation, the saline flow rate depends on the height that the irrigation bag is hung, the height of the operating room table, and the size of the instrument that occupies the working channel (64). Smaller working channel diameters and shorter heights tend to lead to lower irrigation flow rates (64). One issue with the use of gravity irrigation is that a constant flowrate cannot be maintained as the pressure decreases as the bag empties and collecting system fills.

There are a variety of methods beings trialed allow for adequate flow rate while maintaining low collecting system pressures. These include automatic pumps, hand controlled syringes, and foot pedal controlled devices that seek to provide at constant flow rate at lower pressures (64). Inoue et al. sought to explore this further, and compared two novel automatic irrigation pumps to gravity irrigation in terms of flow rates at similar pressures (64). They found that with and without instruments gravity irrigation was had consistently lower flow rates compared to one of the two automatic pumps in this *ex vivo* study (64). Hendlin et al. found in their *ex-vivo* study that gravity irrigation exerted less force than both hand and foot controlled pump devices (65). Ultimately, when selecting irrigation methodology, one should aim to use the minimum pressure that provides adequate visualization.

Intraoperative stone cultures are another tool used in the management of infectious complications. Retrieval of a stone for culture during RIRS under sterile conditions can provide vital information for future infectious complications (7). Bacteria can be situated within the matrix of the stone and therefore not be sample on preoperative urine cultures or be targeted by antibiotic prophylaxis (6, 7). Evidence to suggests that positive stone cultures are important predictors of infectious complications (7). If a patient develops post-operative infectious complications, stone culture results may help guide targeted antimicrobial therapy. For this reason we recommend sending stone cultures intraoperatively when there is suspicion that the stone may be an infection stone or infected stone. One should be aware that there is often discordance between preoperative cultures and stone cultures (66). Korets et al. aimed to determine the concordance between preoperative bladder cultures and intraoperative stone and renal pelvis cultures as well as infectious complications (66). This prospective study found that in patients with a positive preoperative bladder culture and a positive renal pelvis culture, concordance was 64.3% (66). Stone cultures were concordant with preoperative bladder cultures in 70.6% of patients with a positive result for both (66). In patients with a positive stone culture and renal pelvic culture there was 75% concordance (66).

Forced diuresis is another method that can be employed and may reduce the risk of infectious complications following RIRS (7). The main concept is that administering a diuretic agent such as furosemide intravenously while in the operating room may help to prevent pyelovenous reflux by increasing urine production and improving outflow during the procedure, though the evidence supporting this practice is relatively weak (7). As a final note on intraoperative management, when performing RIRS, it is important to maintain open lines of communication with the anesthesiology team. Often times anesthesiologists will be the first to see physiologic signs of impending sepsis which may require prompt termination of the procedure. This applied to all types of surgery, not just RIRS, as a team-based approach has been shown to improve outcomes for all surgical procedures (67). If there is intraoperative suspicion that an infectious complication may be developing or that the patient is at high risk, placement of a foley catheter and ureteral stent should be strongly considered for maximum urinary tract decompression. As a final note, when performing RIRS for nephrolithiasis, two common strategies for stone destruction are stone dusting and stone fragmenting. Currently, there are no high-quality prospective randomized studies comparing stone dusting to stone fragmenting in regards to infectious complications (most such comparative studies evaluate stone free rate as a primary outcome), and this represents an important avenue for future research. Intra-operative recommendations are summarized in **Table 2**.

TABLE 2 | Summary of intra-operative considerations.

Intervention	Mitigation strategy
Perioperative antibiotic therapy	**AUA Guidelines** (14): Within 1 h of procedure, • TMP-SMX or a 1st/2nd generation cephalosporin. Alternatives: • aminoglycoside +/– ampicillin or • aztreonam +/– ampicillin or • amoxicillin/clavulanate. **EAU Guidelines** (56): • TMP • TMP-SMX • 2nd or 3rd generation cephalosporin • Aminopenicillin + beta-lactamase inhibitor
Maintaining low intra-renal pressures to minimize pyelovenous backflow	• Ureteral access sheath (UAS) (61). • Gravity irrigation (63–65). • Low irrigation pressures when employing hand/foot-controlled systems (64)
Other intraoperative techniques	• Obtaining stone cultures to guide post-operative antibiotics (7). • Forced diuresis (7)

POST-OPERATIVE CONSIDERATIONS

Even with optimal preoperative and intraoperative strategies, the development of infectious complications after RIRS in some patients is inevitable, and early recognition and treatment is crucial to minimize morbidity (7). Patients should be monitored in the recovery room and for patients with known risk factors for infectious complications, a prolonged recovery room stay may be warranted with possible admission for observation to monitor for postoperative sepsis (11). Sepsis is defined by the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) as "life-threatening organ dysfunction resulting from dysregulated host responses to infection" (68). Urosepsis is sepsis originating from the urinary tract (69). Clinical criteria for the diagnosis of sepsis is quantified by the sequential organ failure assessment (SOFA) scoring system (70). This system assigns a score from 0–4 to each of the six major organ systems, including respiratory, coagulation, hepatic, cardiovascular, central nervous and renal systems with a higher score indicating worse function (70). Sepsis is identified in patients with an acute change in SOFA score of 2 or greater in the presence of infection, typically in an intensive care setting (70). Outside of an ICU setting, the quick SOFA (qSOFA) is used for risk stratification for patients at risk for sepsis (70). This tool is comprised of three criteria: alteration in mental status (Glasgow coma scale), systolic blood pressure of $<$100 mmHg, and a respiratory rate of $\geq$22 breaths per minute (70). Patients are considered high risk if two or more criteria are met (70). In the context of stone disease, an inflammatory reaction can develop from the release of endotoxin secondary to stone fragmentation or from the release of bacteria. Bacteria and their surface molecules act as pathogen associated molecular patterns (PAMPs) that bind receptors on the surfaces of the innate immune system (69, 71). This stimulates a local immune reaction as well as the induction of the transcription of various inflammatory mediators (71). In the genitourinary system and elsewhere, this can lead to an initial overwhelming cascade of inflammation as more immune cells are recruited, local tissues are damages, and mediators such as nitrous oxide cause local edema (71).

TABLE 3 | Summary of post-operative considerations.

Risk factor/intervention	Mitigation strategy
Urosepsis (Bacterial)	Early recognition with qSOFA and SOFA scores (68, 70)
	Urine and Blood cultures
	Empiric therapy covering gram positive and gram negative pathogens (69) **One or more of the following:** ampicillin, gentamicin, piperacillin/tazobactam*, carbapenems, cefepime, and vancomycin *Poor efficacy for ESBL bacteremia (72)
	Obtain prompt infectious disease consult
	Early escalation of care to ICU
Sepsis (Fungal)	Suspect in critically ill patients with known risk factors and no other cause of symptoms (73)
	Start empiric therapy when there is any clinical suspicion of fungal sepsis as the associated morbidity and mortality is high (73)
	Empiric therapy with echinocandins in anticipation of azole resistance (73)
	Obtain prompt infectious disease consult
	Early escalation of care to ICU

If impending urosepsis is suspected, urine and blood cultures should be obtained, and antibiotics should be promptly initiated. Culture directed treatment is ideal, but antibiotics should not be delayed for culture results. Delayed antibiotic treatment is associated with increased mortality in patients with severe sepsis, so empiric therapy with broad-spectrum antibiotics should be started as soon as possible (66). Though most uropathogens are gram negative, gram positive bacteria are becoming an increasingly important source of urologic infections (29). Empiric antibiotics should cover both gram negative and gram-positive bacteria and options include various combinations of the following: ampicillin, gentamicin, piperacillin/tazobactam, carbapenems, cefepime, and vancomycin. However, in selecting antibiotics, special consideration must be given to extended spectrum beta-lactamase (ESBL) producing bacteria. One randomized clinical trial by Harris et al. found a higher 30-day mortality rate for ESBL bacteremic patients treated with piperacillin-tazobactam compared to patients treated with meropenem (12.3 vs 3.7%) (72). Options for treating ESBL include carbapenems alone or in combination with Fosfomycin or tigecycline (69).

Another important etiology of post-operative sepsis is a fungal infection. The criteria for initiating fungal treatment is vague, and is generally to initiate therapy in critically ill patients with known risk factors and no other cause of fever (73). Using an arbitrary cut off of greater than a 10% risk of infection to start antifungal therapy has been suggested in the literature (73). However, as a general rule, given the morbidity and mortality associated with fungal sepsis initiation of antifungal therapy should be strongly considered upon early clinical suspicion (73). Echinocandins may be considered for empiric therapy because of azole resistant organisms in patients with recent azole exposure or suspected *Candida glabrata* infection (73). Fluconazole may be considered in non-critically ill patients (73). Ultimately when a patient is suspecting of having post-operative urosepsis from RIRS, early consultation by infectious disease specialist should be obtained to determine the optimal empiric regiment based on local resistance patterns. Switching antibiotic therapy from empiric to therapy based sensitivities should be done as soon as the information becomes available (22). In addition to prompt initiation of antimicrobial therapy and infectious disease consultation, the diagnosis of urosepsis following RIRS should prompt an early escalation of care to an ICU setting (74). Patients should receive proper hemodynamic and respiratory support if their clinical condition necessitates it (69). Elimination of any nidus for infection should be done, if possible (69). Additionally, patients who do not have a foley catheter in place should have to catheter placed for maximum urinary tract decompression.

Urosepsis secondary to KSD carries a high risk of morbidity and mortality (12, 22, 69, 71) and accordingly routine use of postoperative antibiotics to minimize infectious complications has been an active area of discussion. The current guidelines state that there is no evidence to continue antibiotic therapy after 24 h in the absence of other factors (14). However, some centers continue antibiotic therapy anywhere from 3 to 5 days postoperatively even in patients with negative cultures (74). Given the rise in MDR bacteria, the use of postoperative antibiotics in patients without risk factors or evidence of postoperative infection should be limited. Post-operative recommendations are summarized in **Table 3**.

CONCLUSION

KSD remains a common medical ailment effectively treated by urologists with RIRS. While adverse events are rare, infectious complications can produce serious consequences. It is vital for clinicians to understand which patients are at risk for infectious complications and the steps that can be taken to minimize such complications. Furthermore, understanding and recognizing the warning signs of a serious infection postoperatively coupled with knowledge of current guidelines and the most effective treatments are critical to addressing these complications when they arise.

AUTHOR CONTRIBUTIONS

JK: conception and design, analysis and interpretation of data, drafting of manuscript, and supervision. JH: acquisition of data, analysis and interpretation of data, and drafting of manuscript. AS: conception and design, analysis and interpretation of data, and critical revision of manuscript for important intellectual content. WA and MG: conception and design, analysis and interpretation of data, critical revision of manuscript for important intellectual content, and supervision. All authors contributed to the article and approved the submitted version.

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Comparison of the Efficacy of ShuoTong Ureteroscopy and Simple Flexible Ureteroscopy in the Treatment of Unilateral Upper Ureteral Calculi

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Background: ShuoTong ureteroscopy (Sotn-ureteroscopy, ST-URS), a new lithotripsy operation method developed on the basis of ureteroscopy, is widely used to treat ureteral stones in China. Its composition includes rigid ureteral access sheath, standard mirror, lithotripsy mirror, and ShuoTong perfusion aspirator (ST-APM). Here, we compared the efficacy and safety of the ST-URS and the flexible ureteroscope (F-URS) holmium laser lithotripsy in the treatment of unilateral upper ureteral calculi.

Methods: Retrospective analysis was conducted on the clinical data of 280 patients who met the inclusion 1) urinary tract CT was diagnosed with unilateral single upper ureteral calculi above the L4 lumbar spine; 2) patient age was from 18 to 80 years old; 3) patients were informed and consented to this study; and 4) patients were approved by the hospital ethics committee (proof number: KY-2019-020) and the exclusion criteria for unilateral upper ureteral calculi in the First Affiliated Hospital of Xiamen University from January 2018 to November 2020, and they were divided into the ST-URS group and the flexible ureteroscopy (F-URS) group.

Results: The stone-free rate of 1 day after operation of the ST-URS group was significantly higher than the F-URS group (63.71 vs. 34.62%, $P < 0.0001$). The operative time (38.45 vs. 46.18 min, $P = 0.005$) and hospitalization cost (27,203 vs. 33,220 Yuan, $P < 0.0001$) of the ST-URS group were significantly lower than the F-URS group. There were no significant differences in the success rate of ureteral access sheath placement, operative blood loss, stone-free rate of 1 month after operation, postoperative complications, postoperative hospital stay, and postoperative visual analog scale (VAS) pain score between the two groups ($P > 0.05$). In subgroups

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of a diameter of calculi ≥ 1.5 cm, calculi CT numerical value ≥ 1,000 Hounsfield unit and the preoperative hydronephrosis range ≥ 3.0 cm, ST-URS shows more advantages in the operative time, stone-free rate of 1 day after the operation, the hospitalization cost, and the incidence of postoperative complications.

Conclusion: In unilateral upper ureteral stones treated with a holmium laser, compared with the simple F-URS, the ST-URS has a shorter operative time, lower hospitalization cost, and a higher stone-free rate of 1 day after the operation, suggesting that the ST-URS could be more widely applied in clinics.

Keywords: unilateral upper ureteral calculi, ShuoTong ureteroscopy, flexible ureteroscopy, efficacy and safety, stone-free rate

INTRODUCTION

Urolithiasis is a common disease in urology with an incidence rate of 1–5%, and the recurrence rate in 10 years can reach 50% (1, 2). Recently, the incidence rate of urolithiasis has been increasing year by year (3). Upper ureteral calculus is one of the main types of urinary calculi and its main clinical characteristics are renal colic and hematuria. While the diameter of a stone is more than 1 cm, it can easily cause obvious urinary tract obstruction, resulting in kidney function damage in a short time and seriously affecting the clinical prognosis (4). Clinically, the treatment of upper urinary tract stones depends on the surgery. Hospitalization and postoperative morbidity of the traditional open surgery are significantly higher than shock wave lithotripsy and endourological procedures (5). Currently, indications for traditional open stone surgery are rare, so it is less used in clinical practice (6). At present, the common methods for clinical treatment of upper ureteral calculi include extracorporeal shock wave lithotripsy, rigid ureteroscopy, flexible ureteroscopy (F-URS), and percutaneous nephrolithotripsy (PCNL) (7). The treatment of ureteral calculi with the ureteroscopy has many advantages, such as smaller trauma, quick recovery, and high stone clearance rate, and is considered as the first choice for the treatment of upper ureteral calculi by many authors (8–11). Negative pressure combined with ureteroscopy, also called ShuoTong ureteroscopy (Sotn-ureteroscopy, ST-URS), is a new type of stone removal surgery in China in recent years. ST-URS can suck out larger stones while crushing the stones, reduce the residual stone fragments and the residual stone rate, and the risk of postoperative stone-street formation. In addition, ST-URS can maintain the renal pelvis at low pressure by its vacuum suction to reduce the risk of infection and bleeding caused by prolonged surgery. Importantly, the flexible ureteroscope can be inserted through a rigid ureteral access sheath (UAS) to treat kidney stones and residual stones, thereby increasing the stone-free rate (SFR). In this study, the clinical application effects of two surgical methods for treating unilateral upper ureteral calculi were compared between ST-URS and simple F-URS and these findings provide a theoretical basis for the clinical treatment of upper ureteral calculi.

MATERIALS AND METHODS

Clinical Information

Retrospectively, analysis was conducted on the clinical data of patients who were diagnosed with unilateral upper ureteral calculi and treated with ST-URS and F-URS in the First Affiliated Hospital of Xiamen University from January 2018 to November 2020. The inclusion and exclusion criteria were listed as shown in **Table 1**. Inclusion criteria: 1) urinary tract CT [noncontrast computed tomography (NCCT)] was diagnosed with unilateral single upper ureteral calculi above the L4 lumbar spine; 2) patient age was from 18 to 80 years old; 3) patients were informed and consented to this study; and 4) patients were approved with the hospital ethics committee (proof number: KY-2019-020). Exclusion criteria: 1) patients were with complex kidney stones, bladder stones, renal tuberculosis, renal tumors, renal dysfunction, acute or chronic nephritis, and nephrotic syndrome; 2) patients were with severe urethral stricture and other urinary malformation; 3) patients have cardiopulmonary dysfunction and cannot tolerate surgical treatment; 4) patients have abnormal coagulation function; 5) patients were with a positive culture of urine bacteria; and 6) the preoperative urine white blood cell count was more than 500/μl. A total of 280 patients were enrolled according to the aforementioned criteria. According to the surgical methods, the patients were divided into the ST-URS group (124 cases) and the F-URS group (156 cases).

Main Surgical Instruments and Materials

The following instruments were used in this study: a URF-P5 flexible ureteroscope (Olympus, Tokyo, Japan), flexible laser (200 pm, holmium laser fiber, Lumenis, Beijing, China), a 0.035-foot nickel-titanium super smooth guide wire (0.888 mm × 150 cm, C.R. Bard Inc., Murray Hill, NJ, USA), a 1.7-Fr basket catheter (Zero tipped, Boston Scientific Corp, Natick, MA, USA), an 8.5/9.8 rigid ureteroscope and ST-URS (Jiangmen, China), namely, a standard ureteroscope (F7.5/11.5), a gravel ureteroscope (F4.5/6.5), a rigid ureteral channel sheath (F11.5/13.5), and a ShuoTong perfusion aspirator (ST-APM).

TABLE 1 | Inclusion criteria and Exclusion criteria.

Inclusion criteria	Exclusion criteria
Urinary tract CT (non-contrast Computed tomography) was diagnosed with unilateral single upper ureteral calculi above the L4 lumbar spine	Patients were with complex kidney stones, bladder stones, renal tuberculosis, renal tumors, renal dysfunction, acute or chronic nephritis and nephrotic syndrome
Patient age was from 18 to 80 years old	Patients were with severe ureteral stricture and other urinary malformation
Patients were informed and consented to this study	Patients have cardiopulmonary dysfunction and cannot tolerate surgical treatment
Patients were approved with the hospital ethics committee (proof number: KY-2019-020)	Patients have abnormal coagulation function
	Patients were with positive culture of urine bacteria
	The preoperative urine white blood cell count was more than 500/μL

Surgical Procedure

For the ST-URS group, after general anesthesia, the patients were placed in the lithotomy position while and the device was connected. A standard mirror (F7.5/11.5) was combined with a rigid UAS (F11.5/13.5), and the F11.5/13.5 rigid UAS was inserted into the urethra under direct vision under the guidance of a super smooth guidewire. Then, the UAS was inserted into the interureteric ridge and was fixed at the position where the ureteral calculus is located on the affected side. Subsequently, the rigid UAS was left in place, and the ShuoTong standard mirror was removed. Next, a special vacuum suction device was connected to the end of the rigid UAS, which was connected with the mastering perfusion aspirator so that the collection system and negative pressure system formed a closed loop, thus establishing a working channel. Then, the gravel mirror is placed in the rigid UAS with a perfusion aspirator, and a 200 μm holmium laser fiber was placed in the operation channel of the gravel mirror. A holmium laser with a power of 8–30 W (0.4–1.0 J/20∼30 Hz) was used to crush the stone into pieces or powder. In the gravel process, the interspace between the shaft of the gravel mirror and the rigid UAS allowed continuous outflow by vacuum suctioning, and stone fragments flow out from this interspace. The operator can regulate the negative pressure of the suctioning system through the negative pressure adjustment button at the end of the rigid UAS. If the stone moved up to the lower calyx during surgery, exit the gravel mirror, and the flexible ureteroscope was placed into the outer sheath. Stones in the lower calyx were moved into the renal pelvis or upper calyx by using a 1.7-Fr basket catheter and the flexible ureteroscope was replace with a gravel mirror to clear stones. After the ureter and the renal pelvis were viewed and no obvious stone fragments were observed, perfusion and vacuum suction was stopped. The gravel mirror was then removed, and a standard mirror was put in its place and was fastened to the rigid outer sheath. The standard mirror and the rigid outer sheath are exited simultaneously under visual vision. The renal pelvis region and ureteral mucosal damage were observed when the standard mirror was removed. Then, an F7 D-J tube was inserted, and an F20 three-chamber catheter was inserted. We also made a video to show the surgical procedure of ST-URS as shown on the website of *Frontiers in Surgery*. For the F-URS group, the operation was performed as described previously (12).

Observation Index

It includes operative time, operative blood loss, SFR of 1 day after the operation, SFR of 1 month after the operation, the incidence of postoperative complications, the success rate of UAS placement, creatinine level, hospitalization cost, postoperative hospital stay, postoperative catheter extraction time, and postoperative visual analog scale (VAS) pain score.

Judgment Standard

Complications were classified according to the modified Clavien classification system and the infectious complications were classified according to the standardized classification system of Francesco Berardinelli (13, 14). The occurrence of fever postoperatively was defined as an increase in the body temperature to > 38°C, which persisted for 48 h (15). The stone size was measured based on the maximal diameter of the stone by three-dimensional reconstruction NCCT is used as the size of the stone. The SFR was defined as the presence of no stones or only residual stone fragments of < 4 mm in diameter (16–18). The CT scan was re-examined 1 month after the operation and there were no residual stones or clinically meaningless stones suggesting the operation was successful. The hospitalization cost was calculated with the sum of all examinations, medicines, surgical consumables, and surgical operation expenses during the hospitalization period.

Statistical Analysis

SPSS 23.0 software (IBM SPSS; Armonk, NY, USA) was used for the statistical analysis. Measurement data are presented as the means ± SD, Student's t-test was applied to continuous data with normal distribution, and the Mann–Whitney rank-sum test was applied to continuous data with the nonnormal distribution. For data presented as percentages (%), the χ^2-test was applied for group comparisons. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Compositions and Surgical Procedures of ST-URS

ShuoTong ureteroscopy is a new lithotripsy operation method developed on the basis of ureteroscopy in China in recent years. It is a system that combines lithotripsy and stone removal. Its composition includes rigid UAS, standard mirror, lithotripsy mirror, and ST-APM. Compared with the F-URS, the biggest characteristic and advantage of the ST-URS is the negative pressure perfusion aspirator (**Figure 1**).

Efficacy and Safety Analysis of ST-URS and F-URS

In the ST-URS group, there were 82 men and 42 women, their age was from 24 to 79 (average: 49.4 ± 12.8) years old, the average diameter of ureteral stones was 1.37 ± 0.49 cm, the CT numerical value of calculus was 1,003.1 ± 332.7 Hounsfield unit (HU), and the preoperative hydronephrosis range was 2.9 ± 1.2 cm. In the F-URS group, there were 104 men and 52 women, their age was from 22 to 79 (average: 49.7 ± 13.2) years old, the average diameter of ureteral stones was 1.35 ± 0.43 cm, the stone CT numerical value was 1,055.5 ± 341.6 HU, and the preoperative hydronephrosis range was 2.7 ± 1.1 cm. There was no significant difference between the two groups of patients in general information such as age, body mass index, preoperative white blood cell count, preoperative blood neutrophil ratio, the diameter of calculus, the CT numerical value of calculus, and preoperative hydronephrosis range statistically ($P > 0.05$, **Table 2**).

The operation time of the ST-URS group was shorter (38.45 vs. 46.18 min, $P = 0.005$) and the SFR of 1 day after the operation was higher (63.71 vs. 34.62%, $P < 0.0001$) than that of the F-URS group as shown in **Table 2**. However, there were no statistically significant differences between the two groups in operative blood loss, SFR of 1 month after the operation, the incidence of postoperative complications, and the success rate of UAS placement ($P > 0.05$, **Table 2**). In addition, we analyzed the hospitalization cost of these two groups and found that the ST-URS group was significantly less than that of the F-URS group ($P < 0.0001$, **Table 2**). There were no statistically significant differences in the postoperative hospital stay, postoperative catheter removal time, and postoperative VAS pain score between the two groups ($P > 0.05$, **Table 2**).

In addition, we analyzed the creatinine level between these two groups and found that there was no statistical significance in the comparison of creatinine level before and 1 day after the surgery between the two groups ($P > 0.05$), while the creatinine level of 1 day after the surgery in these two groups is significantly lower than that of before the surgery ($P < 0.0001$, **Table 2**).

In the F-URS group, Clavien I complications were noted in six cases, namely, fever in three cases and hematuria in three cases. Clavien II complications were noted in 14 cases, namely, ureteral injury in 2 cases, urinary tract infection in 11 cases, and systemic inflammatory response syndrome (SIRS) in 1 case. Clavien IV complications were noted in one case with septic shock. In the ST-URS group, Clavien I complications were noted in three cases with fever. Clavien II complications were noted in six cases with urinary tract infection. No Clavien III–V complications were noted. The incidence of surgical complications of the ST-URS group was lower than the F-URS group (7.26 vs. 13.46%, $P = 0.095$, **Table 3**).

Subgroup Analysis of ST-URS and F-URS

Furthermore, we analyzed the operation time of these two groups and found when the diameter of calculi ≥ 1.5 cm, the operation time of the ST-URS group was shorter than that of the F-URS group (42.87 vs. 52.41 min, $P = 0.01$). The SFR of 1 day after the surgery was 51.06% in the ST-URS group and that was 20.41% in the F-URS group, and the difference was statistically significant ($P = 0.002$). The hospitalization cost analysis found ST-URS group was significantly less than that of the F-URS group ($P < 0.0001$). The incidence of surgical complications was 6.38% in the ST-URS group and that was 18.37% in the F-URS group ($P = 0.076$). There were no significant differences between these two groups in the operative blood loss and the SFR of 1 month after operation ($P > 0.05$, **Table 4**). When the calculi CT numerical value ≥ 1,000 HU, the operation time of the ST-URS group was shorter than that of the F-URS group (40.10 vs. 49.43 min, $P = 0.01$). The SFR of 1 day after the surgery was 60.66% in the ST-URS group and that was 25.29% in the F-URS group ($P < 0.0001$). The incidence of surgical complications (3.28%) in the ST-URS group was dramatically decreased than that of the F-URS group (13.79%, $P = 0.031$). The hospitalization cost analysis of these two groups found that the ST-URS group was significantly less than that of the F-URS group ($P < 0.0001$). However, there were no significant differences between the two groups in the operative blood loss and the SFR of 1 month after operation ($P > 0.05$, **Table 5**).

When the preoperative hydronephrosis range ≥ 3.0 cm, compared with the F-URS group, the operation time was shorter (40.38 vs. 52.24 min, $P = 0.025$) and the SFR of 1 day after the surgery was higher in the ST-URS group (66.67 vs. 34.78%, $P = 0.002$, **Table 6**). The hospitalization cost analysis of these two groups found that ST-URS group was significantly less than that of the F-URS group ($P < 0.0001$). In addition, the incidence of surgical complications in ST-URS group was lower than F-URS group (4.17 vs 13.04%, $P = 0.241$). However, there were no significant differences between the two groups in the operative blood loss, the SFR of 1 month after surgery, and the incidence of surgical complications ($P > 0.05$, **Table 6**).

DISCUSSION

Ureteral calculi frequently cause renal colic and lead to obstructive urinary tract disease without treatment. Given the development of natural endoscopic instruments and techniques, URS is considered one of the most important methods for the primary treatment of > 10 mm proximal ureteral stones (6). Rigid ureteroscopy is considered to be a preferred operation method for the treatment of the middle and lower ureteral stones (19), but it may be ineffective for treating upper large ureteral stones (19–21). F-URS has excellent SFRs in treating patients harboring proximal ureteral stones smaller than 2 cm (22). Despite the increasing popularity of F-URS, the management of high intrarenal pressure during F-URS has been a clinical dilemma because of its difficulty. While the renal pelvic pressure is high, this may cause the high probability of absorption of liquid, bacteria, and endotoxin into the blood resulting in

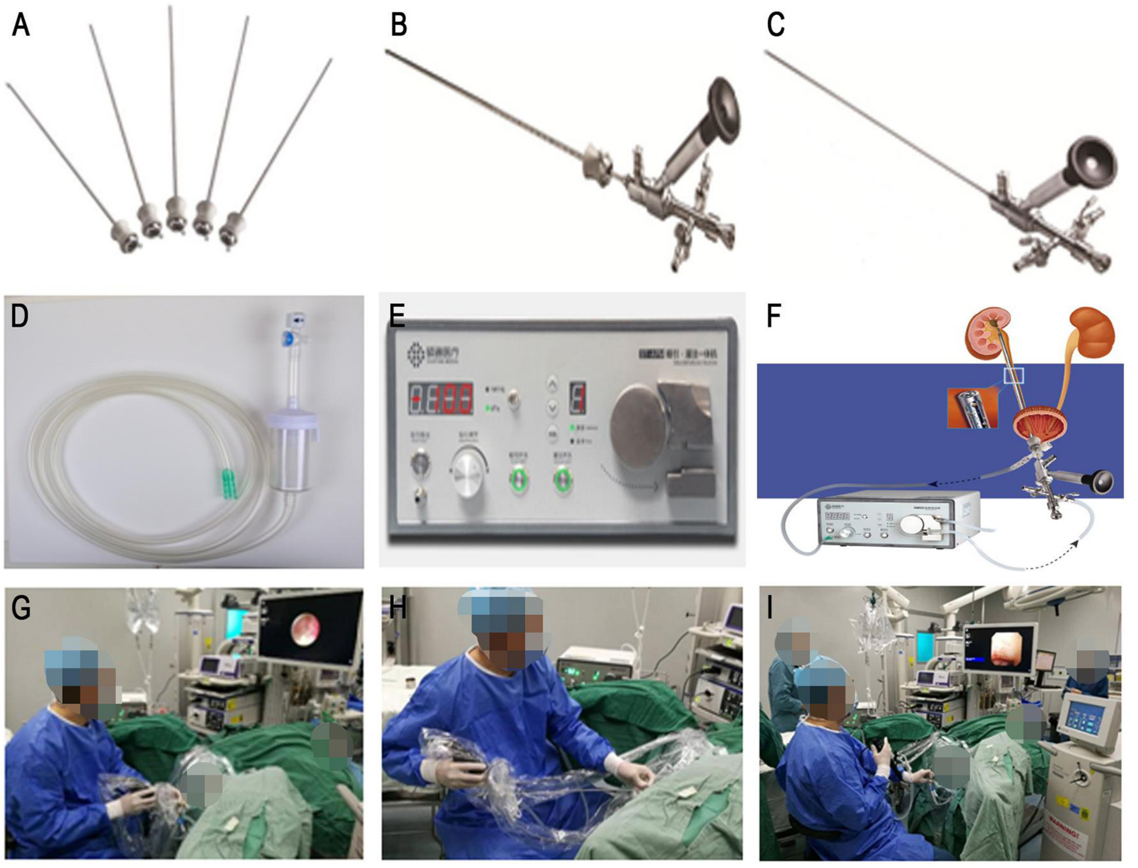

FIGURE 1 | ShuoTong mirror compositions and surgical procedures. **(A)** The mirror sheath portion of the standard mirror. **(B)** Standard mirror. **(C)** Gravel mirror. **(D)** Adjustable negative pressure suction device and stone collector. **(E)** Vacuum suction system, perfusion system. **(F)** Connection diagram. **(G)** Use of the gravel mirror. **(H)** Use of vacuum suction to remove stone fragments and powder. **(I)** The rigid outer sheath is inserted into the flexible ureteroscope for examination.

short-term complications such as SIRS, sepsis, and long-term complication of renal function impairment (23, 24). However, decreasing the perfusion flow to avoid high intrarenal pressure will directly affect the surgical visualization and result in low lithotripsy efficacy. For reducing the renal pelvic pressure, there are many methods such as adding isoproterenol to the surgical perfusion solution using a dual-channel continuous-flow URS and a traditional UAS for F-URS (25–28). In addition, studies have shown that vacuum suctioning can reduce renal pelvic pressure efficiently and significantly increase the safety and efficacy of minimally invasive suctioning PCNL (29–31). Consistent with this, another study showed that a ureteroscopy featuring a vacuum suction system is effective and safe for treating upper urinary tract calculi (32). Despite the acceptance of ureteroscopy with vacuum suction system in urological clinical practice; however, robust comparative data comparing ureteroscopy with suction system and F-URS are lacking. Therefore, we conducted a retrospective study to explore the effects of a novel semirigid ureteroscopy named ST-URS that has an irrigation and vacuum suction platform functioned by its UAS.

Recently, ST-URS, a new lithotripsy operation method in China is widely used in the treatment of ureteral stones. During the operation, the surgeon can adjust the rotary knob to control the negative pressure and actively control the pressure of the suction of stones for simultaneous reduction of the renal pelvic pressure and active suction of the stones (33). Therefore, ST-URS can bring the following surgical effects: 1) at the same time as lithotripsy, the broken stone particles and powder are directly sucked out through the ureteral inlet sheath, thus realizing the integration of crushing and removing stones. 2) By adjusting the pressure of the negative pressure suction valve, the intraoperative pressure in the ureter can be controlled, reducing the possibility of stone escape. 3) The negative pressure suction can suck out the air bubbles, blood clots, and gravel generated during the lithotripsy process so that the surgical vision is clear. 4) The negative pressure suction produces continuous convective water circulation, reducing thermal damage to the ureteral wall caused by the holmium laser. 5) The negative pressure suction can keep the low pressure of the renal pelvis, reducing the risk of infection and bleeding from prolonged surgery and improving surgical visualization (34). In addition, the way of UAS placement is also different between the ST-URS and the flexible ureteroscope. The flexible ureteral sheath is a blind placement method that mainly depends on the experience and feel of the operator or is

TABLE 2 | Comparison of the basic information and Surgical effect in the two groups.

Variables	Total	ST-URS	F-URS	*P*
Cases	280	124	156	-
Sex (M/F)	186/94	82/42	104/52	-
Age (years)	49.6 ± 13.0	49.4 ± 12.8	49.7 ± 13.2	0.886^{t}
BMI	24.3 ± 3.3	24.5 ± 3.0	24.0 ± 3.6	0.206^{t}
Stone size (cm)	1.36 ± 0.46	1.37 ± 0.49	1.35 ± 0.43	0.946^{u}
Stone CT numerical value (Hu)	1032.3 ± 338.1	1003.1 ± 332.7	1055.5 ± 341.6	0.189^{u}
Hydronephrosis (cm)	2.8 ± 1.2	2.9 ± 1.2	2.7 ± 1.1	0.195^{u}
Preoperative white blood cell count ($\times 10^9$/L)	6.72 ± 1.70	6.73 ± 1.52	6.72 ± 1.84	0.614^{u}
Preoperative bloodneutrophil ratio (%)	58.6 ± 8.5	59.5 ± 8.2	57.8 ± 8.6	0.099^{t}
Operative time (min)	42.76 ± 23.29	38.45 ± 21.09	46.18 ± 24.42	0.005^{u}
Operative blood loss (ml)	4.24 ± 6.65	4.22 ± 7.86	4.26 ± 5.51	0.361^{u}
Success rate ofUAS placement	97.14% (272/280)	97.58%(121/124)	96.79%(151/156)	0.975$^{\chi}$
SFR of 1 dayafter operation	47.50% (133/280)	63.71%(79/124)	34.62% (54/156)	< 0.0001$^{\chi}$
SFR of 1 monthafter operation	83.93% (235/280)	87.10%(108/124)	81.41%(127/156)	0.198$^{\chi}$
Hospitalization cost(Yuan)	30,556 ± 7,077	27,203 ± 7,134	33,220 ± 5,798	< 0.0001^{t}
Postoperative hospital stay (day)	2.46 ± 1.08	2.49 ± 1.20	2.44 ± 0.98	0.939^{u}
Postoperative catheter extraction time (day)	1.56 ± 0.81	1.49 ± 0.71	1.61 ± 0.83	0.138^{u}
Postoperative VAS pain score	1.00 ± 0.33	0.98 ± 0.41	1.02 ± 0.24	0.300^{t}
Creatinine before the operation (μmol/l)	80.7 ± 24.3	80.6 ± 20.6	80.8 ± 27.0	0.954^{t}
Creatinine 1 day after the operation (μmol/l)	75.2 ± 21.7	74.3 ± 17.4	75.9 ± 24.5	0.546^{t}
P	< 0.0001^{t}	< 0.0001^{t}	< 0.0001^{t}	-

ST-URS, negative pressure combined ureteroscopy (Sotn-ureteroscopy); F-URS, flexible ureteroscopy; BMI, Body Mass Index; UAS, ureteral access sheath; SFR, stone-free rate; VAS, visual analogue scale; $P < 0.05$ as statistically significant; ^{t}Using the Student's t test; $^{\chi}$Using the Chi-squared test; ^{u}Using the Mann-Whitney U-test.

TABLE 3 | Comparison of the Surgical complication in the two groups.

	Total, N (280)	ST-URS, N (124)	F-URS, N (156)	*P*
Clavien Grade I				
Hematuria	3(1.07%)	0	3(1.92%)	0.333$^{\chi}$
Clavien Grade II				
Ureteral injury	2(0.71%)	0	2(1.28%)	0.505$^{\chi}$
Clavien Grade III				
Urethral stricture	0	0	0	-
Infection	25(8.93%)	9(7.26%)	16(10.26%)	0.382$^{\chi}$
Fever (> 38°C) (G I)	6(2.14%)	3(2.42%)	3(1.92%)	1.000$^{\chi}$
Urinary tract infection (GII)	17(6.07%)	6(4.83%)	11(7.69%)	0.4410$^{\chi}$
SIRS/Sepsis (GII)	1(0.36%)	0	1	1.000$^{\chi}$
Septic shock (GIV)	1(0.36%)	0	1	1.000$^{\chi}$
Total	30(10.71%)	9(7.26%)	21(13.46%)	0.095$^{\chi}$

$P < 0.05$ as statistically significant; $^{\chi}$Using the Chi-squared test.

placed under x-ray fluoroscopy. It may lead to accidental ureteral injury or radiation injury. When the ureter is constricted or twisted, blind placement results in a greater risk of accidental ureteral injury and greater difficulty in operation. Compared with the blind placement method of the flexible ureteral sheath, the rigid UAS of the ST-URS is placed simultaneously under the direct vision and the standard mirror. It is easy for beginners to use and is not easy to damage the ureter, which shortens the learning curve. Therefore, the vision of the whole ST-URS lithotripsy process is clear, and it realizes the integration of crushing and removing stones, which made up for the drawback of ureteroscopy that "only lithotripsy but cannot remove stones at the same time."

This study compared the clinical efficacy of ST-URS and simple flexible ureteroscope in the treatment of unilateral upper ureteral calculi. Our research suggests that ST-URS has the following advantages in the treatment of upper ureteral calculi: 1) higher SFR of 1 day postoperatively and shorter operative

TABLE 4 | Comparison of Surgical effect in the two groups while the diameter of calculi ≥ 1.5 cm.

Variables	Total	ST-URS	F-URS	P
Cases	96	47	49	-
Sex (M/F)	75/21	39/8	36/13	-
Age (years)	49.3 ± 13.3	48.6 ± 13.4	50.0 ± 13.4	0.593^{t}
BMI	24.6 ± 3.2	24.8 ± 3.0	24.4 ± 3.3	0.603^{t}
Stone size (cm)	1.87 ± 0.32	1.89 ± 0.32	1.85 ± 0.32	0.412^{u}
Stone CT numerical value (Hu)	1108.8 ± 305.0	1113.7 ± 301.8	1104.1 ± 311.0	0.878^{t}
Hydronephrosis (cm)	2.9 ± 1.3	3.0 ± 1.2	2.8 ± 1.3	0.418^{t}
Operative time (min)	49.20 ± 20.62	42.87 ± 15.73	52.41 ± 19.49	0.010^{t}
Operative blood loss (ml)	4.44 ± 6.71	4.85 ± 8.24	4.04 ± 4.87	0.904^{u}
SFR of 1 dayafter operation	35.42% (34/96)	51.06%(24/47)	20.41% (10/49)	0.002^{x}
SFR of 1 monthafter operation	81.25% (78/96)	85.11%(40/47)	77.55% (38/49)	0.343^{x}
Hospitalization cost(yuan)	29,698 ± 5,560	26,842 ± 4,285	32,439 ± 5,285	< 0.0001^{t}
Total complication rate	12.50%(12/96)	6.38%(3/47)	18.37%(9/49)	0.076^{x}

ST-URS, negative pressure combined ureteroscopy (Sotn-ureteroscopy); F-URS, flexible ureteroscopy; BMI, Body Mass Index; SFR, stone-free rate; P < 0.05 as statistically significant; ^{t}*Using the Student's t test;* ^{x}*Using the Chi-squared test;* ^{u}*Using the Mann-Whitney U-test.*

TABLE 5 | Comparison of Surgical effect in the two groups while the calculi CT numerical value ≥ 1,000 Hu.

Variables	Total	ST-URS	F-URS	P
Cases	148	61	87	-
Sex (M/F)	103/45	45/16	58/29	-
Age (years)	48.4 ± 12.8	48.3 ± 12.7	48.5 ± 13.0	0.917^{t}
BMI	24.4 ± 3.4	24.7 ± 2.7	24.1 ± 3.8	0.262^{t}
Stone size (cm)	1.47 ± 0.42	1.50 ± 0.45	1.45 ± 0.40	0.530^{u}
Stone CT numerical value (Hu)	1302.0 ± 184.6	1288.8 ± 179.0	1311.3 ± 188.9	0.466^{t}
Hydronephrosis (cm)	2.9 ± 1.2	2.9 ± 1.3	2.8 ± 1.2	0.739^{t}
Preoperative white blood cell count ($\times 10^{9}$/L)	6.71 ± 1.73	6.75 ± 1.75	6.69 ± 1.73	0.835^{t}
Preoperative bloodneutrophil ratio (%)	59.0 ± 8.4	59.5 ± 7.9	58.6 ± 8.8	0.495^{t}
Operative time (min)	45.58 ± 24.03	40.10 ± 20.01	49.43 ± 25.92	0.010^{t}
Operative blood loss (ml)	4.35 ± 7.65	4.92 ± 9.51	3.95 ± 6.04	0.364^{u}
Success rate ofUAS placement	96.62% (143/148)	96.72%(59/61)	96.55% (84/87)	1.000^{x}
SFR of 1 dayafter operation	39.86% (59/148)	60.66%(37/61)	25.29% (22/87)	< 0.0001^{x}
SFR of 1 monthafter operation	78.38% (116/148)	81.97%(50/61)	75.86% (66/87)	0.375^{x}
Hospitalization cost(yuan)	30,387 ± 7,502	27,686 ± 9,120	32,281 ± 5,420	< 0.0001^{t}
Total complication rate	9.46% (14/148)	3.28%(2/61)	13.79%(12/87)	0.031^{x}

ST-URS, negative pressure combined ureteroscopy (Sotn-ureteroscopy); F-URS, flexible ureteroscopy; BMI, Body Mass Index; UAS, ureteral access sheath; SFR, stone-free rate; P < 0.05 as statistically significant; ^{t}*Using the Student's t test;* ^{x}*Using the Chi-squared test;* ^{u}*Using the Mann-Whitney U-test.*

time. In our study, the SFR of 1 day after the operation of the ST-URS group was significantly higher than the F-URS group (63.71 vs. 34.62%, $P < 0.0001$), but the SFR of 1 month after the operation was comparable in the two groups (87.10 vs. 81.41%, $P = 0.198$). Consistent with our results, the study of Zewu Zhu also shows that the suctioning UAS group had a significantly higher SFR of 1 day postoperatively and a significantly shorter operative time in the treatment of renal stones (35). Compared to other studies of patients with similar stone burdens, our SFR result of 1 day postoperatively was superior to that reported in studies in which F-URS was used (36, 37). This is because the negative pressure attraction effect of the ST-URS can suck out larger stones when crushing the stones, reducing the residual stone fragments and stone escape, thus improving the SFR and stone removal efficiency and reducing the operative time. In addition, stone basketing used in the traditional F-URS is time-consuming with incomplete clearance carrying a risk of stone-street formation (38). The use of a suction device had the advantage of removing all stone fragments without requiring a stone basket and thus shortened the operation time. The direct aspiration of small fragments in the ST-URS group would provide better surgical vision and thus lead to higher lithotripsy efficiency. 2) Lower hospitalization costs. In our study, the total hospitalization cost of the ST-URS group was significantly lower than the F-URS group (27,203 vs. 33,220 Yuan, $P <$ 0.0001). Compared with the F-URS, ST-URS does not require the

TABLE 6 | Comparison of Surgical effect in the two groups while the preoperative hydronephrosis range ≥ 3.0 cm.

Variables	Total	ST-URS	F-URS	*P*
Cases	94	48	46	-
Sex (M/F)	73/21	37/11	36/10	-
Age (years)	48.5 ± 13.3	48.9 ± 13.7	48.1 ± 13.0	0.770^{t}
BMI	25.2 ± 3.3	25.1 ± 3.1	25.3 ± 3.5	0.865^{t}
Stone size (cm)	1.44 ± 0.47	1.44 ± 0.52	1.44 ± 0.41	0.942^{t}
Stone CT numerical value (Hu)	1086.3 ± 329.8	1073.7 ± 352.4	1099.5 ± 307.8	0.707^{t}
Hydronephrosis (cm)	4.1 ± 1.0	4.1 ± 1.0	4.0 ± 1.0	0.578^{u}
Operative time (min)	46.18 ± 25.98	40.38 ± 22.97	52.24 ± 27.76	0.025^{u}
Operative blood loss (ml)	4.77 ± 8.77	4.44 ± 10.58	5.11 ± 6.46	0.114^{u}
SFR of 1 dayafter operation	51.06% (48/94)	66.67%(32/48)	34.78% (16/46)	0.002$^{\chi}$
SFR of 1 monthafter operation	79.79% (75/94)	85.42%(41/48)	73.91% (34/46)	0.165$^{\chi}$
Hospitalization cost(yuan)	29,297 ± 5,468	26,819 ± 4,180	31,881 ± 5,492	< 0.0001^{t}
Total complication rate	8.51% (8/94)	4.17%(2/48)	13.04%(6/46)	0.241$^{\chi}$

ST-URS, negative pressure combined ureteroscopy (Sotn-ureteroscopy); F-URS, flexible ureteroscopy; BMI, Body Mass Index; SFR, stone-free rate; P < 0.05 as statistically significant; ^{t}Using the Student's t test; $^{\chi}$Using the Chi-squared test; ^{u}Using the Mann-Whitney U-test.

insertion of a ureteral stent tube 2 weeks before the operation and does not require the use of a disposable ureteral soft sheath. In addition, the ST-URS reduces the use of flexible ureteroscope and the use of disposables, such as a disposable ureteral soft sheath and the 1.7-Fr basket catheter reducing the medical cost (39). 3) Fewer postoperative complications. In our study, the incidence of infectious complications of the ST-URS group (7.26%) was lower than the F-URS group (10.26%). Zhu et al. also found the incidence of infectious complications was 7.90% in the suctioning UAS group vs. 22.4% in the traditional UAS group and both higher than our results (35). This may be because the average stone size is larger in their study (18.2 and 17.4 vs. 13.7 and 13.5 mm). Both our results suggested the ureteroscopy with a suction device can reduce infectious complications. ST-URS adopts an adjustable negative pressure suction device, the surgeon can actively control the size of the attraction, maintain the low pressure of the renal pelvis, thus significantly decrease perioperative infectious complications (39, 40). Instead of F-URS, the ST-URS is placed under direct vision, which may reduce the damage of the ureter during the insertion process (33). In this study, three patients in the F-URS group had postoperative hematuria while there were no patients with postoperative hematuria or postoperative ureteral injury in the ST-URS group. Consistent with our results, there were no complications of the ureteral mucosa stripping, perforations, and avulsions founded in other studies (33, 39, 40). A study showed that high-power laser lithotripsy settings fired in long bursts with low irrigation flow rates can generate high fluid temperatures in the process of holmium laser lithotripsy (41). In addition, the negative pressure suction produces continuous convective water circulation and higher irrigation flow rates and can take away the heat generated by the holmium laser in time, which may reduce thermal damage to the ureteral wall. Although the incidence of surgical complications in the ST-URS group (7.3%) was lower than the F-URS group (13.5%), but the difference was not statistically significant. This may be related to the small sample size in this study and the results need to be confirmed by a large sample study in the future. Our study combined with these published results showed that the ST-URS with negative pressure suction device has the advantages of high lithotripsy efficacy, fewer complications, more safety, and treating the upper ureteral calculi effectively (33, 35, 39, 40).

Ito et al. reported that the CT value of stones is significantly related to the efficiency of lithotripsy (42). Consistent with their results, we found that when the calculi CT numerical value ≥ 1,000 HU, the operation time of the ST-URS group was shorter than that of the F-URS group ($P = 0.01$) and the incidence of surgical complications of the ST-URS group dramatically decreased than that of the F-URS group (3.28 vs. 13.79%, $P = 0.031$). This reveals that ST-URS also has the advantages of shorter operation time and fewer complications for the treatment of stones with high CT values.

This study has also certain limitations, such as the case number of both the groups in our retrospective study is relatively small. Furthermore, the study was based on the data extracted from a single center. For better validating of the clinical outcomes, we require a multicenter study with a large size sample. Finally, the developed ST-URS cannot achieve real-time monitoring of the actual renal pelvic pressure and should be further improved in the future.

In conclusion, compared with the F-URS, the ST-URS has a shorter operation time, lower hospitalization cost, and higher SFR, especially the SFR of 1 day after the operation. Moreover, the ST-URS has lower postoperative complications in the treatment of ureteral calculi with a CT numerical value ≥ 1,000 HU, so it is a good surgical method for the treatment of upper ureteral calculi.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the First Affiliated Hospital of Xiamen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BC, HC, and YH designed the study. LL, WZ, FZ, TW, and PB collected the clinical data. ZL, JZ, ZS, BD, HW, and JX analyzed the clinical data. LL and TW wrote and revised the manuscript. All authors approved the final version and agreed to publish the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.707022/full#supplementary-material

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Comparison Between Single-Use Flexible Ureteroscope and Reusable Flexible Ureteroscope for Upper Urinary Calculi: A Systematic Review and Meta-Analysis

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Objective: This article explores the differences in the effectiveness and safety of the treatment of the upper urinary calculi between single-use flexible ureteroscope (su-fURS) and reusable flexible ureteroscope (ru-fURS).

Methods: We systematically searched PubMed, Embase, Cochrane Library, Scopus database, and CNKI databases within a period from the date of database establishment to November 2020. Stata 16 was used for calculation and statistical analyses.

Results: A total of 1,020 patients were included in the seven studies. The statistical differences were only found in the Clavien–Dindo grade II postoperative complication [odds ratio (OR) 0.47; 95% CI 0.23–0.98; $p = 0.04$]. No significant statistical differences were observed in operative time (OT), estimated blood loss (EBL), length of hospital stay (LOS), and stone-free rate (SFR).

Conclusion: Our meta-analysis results demonstrate that su-fURS, compared with ru-fURS, has similar effectiveness and better security for treating upper urinary calculi.

Keywords: upper urinary calculi, flexible ureteroscope, single-use, reusable, meta-analysis

INTRODUCTION

Urolithiasis is one of the most common diseases in urology, which has a high incidence in the world. Its incidence rate varies, among which North America has the highest incidence rate of 7–13%, Europe has the highest incidence rate of 5–9%, and Asia has a relatively low incidence rate of 1–5% (1). Kidney stones can lead to renal colic, urinary tract infection, and obstruction and are also risk factors for chronic kidney disease (2). The treatment of upper urinary calculi has always been the focal point of medical research. Surgical treatment was the main treatment method of the upper urinary tract stone. Open surgery was highly traumatic and could only be used for some special patients. Percutaneous nephrolithotomy has the highest rate of surgical exclusion for large stones and multiple kidney stones. Tubeless minimally invasive percutaneous nephrolithotomy may be a probable choice for strictly chosen patients (3). The flexible ureteroscopes (f-URSs) were taking an essential role in recent years and the new thulium laser system during ureteroscope was giving interesting results (4).

In the recent revision of the European guidelines on the management of urolithiasis, ureteroscope was recommended as a first-line management option, especially for stones measuring between 10 and 20 mm. Moreover, for stones > 1.5 cm in the lower pole, a flexible ureteroscope is also one of the recommendations (5).

However, the existing limitations on reusable flexible ureteroscope (ru-fURS) include a high initial purchase cost, high expenditures for repair, and a risk of cross-infection (6). Studies have shown that even when ru-fURS was cleaned manually and disinfected by hydrogen peroxide gas, contamination could still be found (7, 8). For solving these problems with existing ru-fURS, a single-use flexible ureteroscope (su-fURS) has been proposed and has recently come to gain achievements (9, 10).

In fact, for su-fURS, there is still a lack of high-level evidence to compare its safety and efficiency with that of ru-fURS. Therefore, the purpose of this meta-analysis is to compare the clinical efficacy and safety of the treatment of the patients with upper urinary calculi between the two types of scopes.

METHODS

Literature Search and Eligible Criteria

A systematic search in PubMed, Embase, Cochrane Library, Scopus database, and CNKI databases was performed to identify the studies published from the date of database establishment to November 2020. Search terms included: "ureteroscope," "flexible ureteroscope," "single-use," "disposable," "reusable," "upper urinary calculi," "kidney stone," "ureteral calculi," and the search was not restricted by language. Besides, manual retrieval from the references of subject-related studies was performed to broaden the search.

Studies meeting the following inclusion criteria were listed as follows: (1) patients diagnosed as upper urinary calculi by a urologist; (2) comparison of su-fURS with ru-fURS; (3) any size of the stones and a similar number of surgeries; (4) full papers containing at least one outcome parameters such as operative time (OT), estimated blood loss (EBL), length of hospital stay (LOS), stone-free rate (SFR), and complications; and (5) the type of articles should be a prospective controlled study, cohort study, retrospective study, or randomized controlled study. Duplicate studies, reviews, case reports, letters, irrelevant studies about our topic, and studies from which available data could not be extracted were excluded. OT, SFR, and complications were the primary outcomes. The secondary outcomes were EBL and LOS.

This process was independently performed by the two authors (JZL and LP) and the differences between the authors were settled by consultation. The third reviewer (YXL) was involved in the judgment if an agreement could not be reached.

Data Extraction

We extracted the following data from each study into the meta-analysis: author, publication year, study design, sample size, detailed information of ureteroscopes, OT, EBL, LOS, SFR, and complications. When continuous variables were reported as median and range in the main literature, we calculated the mean and SD (11).

Study Quality Assessment

Based on the results available, we used the Jadad scale (12) to assess the randomized controlled trials (RCTs) and the Newcastle–Ottawa Scale (NOS) scoring rules (13) for non-randomized controlled studies. The Jadad score ranges from zero to seven points. A score lower than four should be considered to indicate a low-quality study; else, it should be considered a high-quality study. The NOS scale is a total of nine stars and more than six stars should be considered as high-quality research.

Risk of Bias Assessments

Not only using ROBINS-I tool for non-randomized studies but also using ROB2 for RCTs to evaluate a risk of bias. The ROBINS-I tool included seven domains: confounding bias, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported result (14). The ROB2 tool contained a randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (15).

Statistical Analysis

This meta-analysis was performed by using Stata 16 for the statistical analysis. The odds ratio (OR) and mean difference (MD) were used to evaluate the dichotomous and continuous data, respectively, and a 95% CI and p-value were calculated. $p < 0.05$ was considered as statistically significant. I-square tests were used to verify the heterogeneity between the included studies. Meanwhile, we performed a sensitivity analysis to interpret the potential source of heterogeneity, if the heterogeneity is more than 50%.

Registration

This study registered on the PROSPERO and the registration number was CRD42021230884.

RESULTS

Description of Studies

A total of 287 studies were identified, out of which 28 studies were full-text reviewed and seven studies were eventually selected (16–22). The screening process is shown in **Figure 1**. **Table 1** lists the characteristics of the included studies. The seven included studies were published between 2015 and 2020 and a total of 1,020 patients and the sample size of the studies ranged from 61 to 360. Among them, four studies had a prospective design and three studies had the RCTs.

Quality Assessment

Based on the Jadad scale and the NOS scoring rules, we have listed the final study quality scores in **Table 1**.

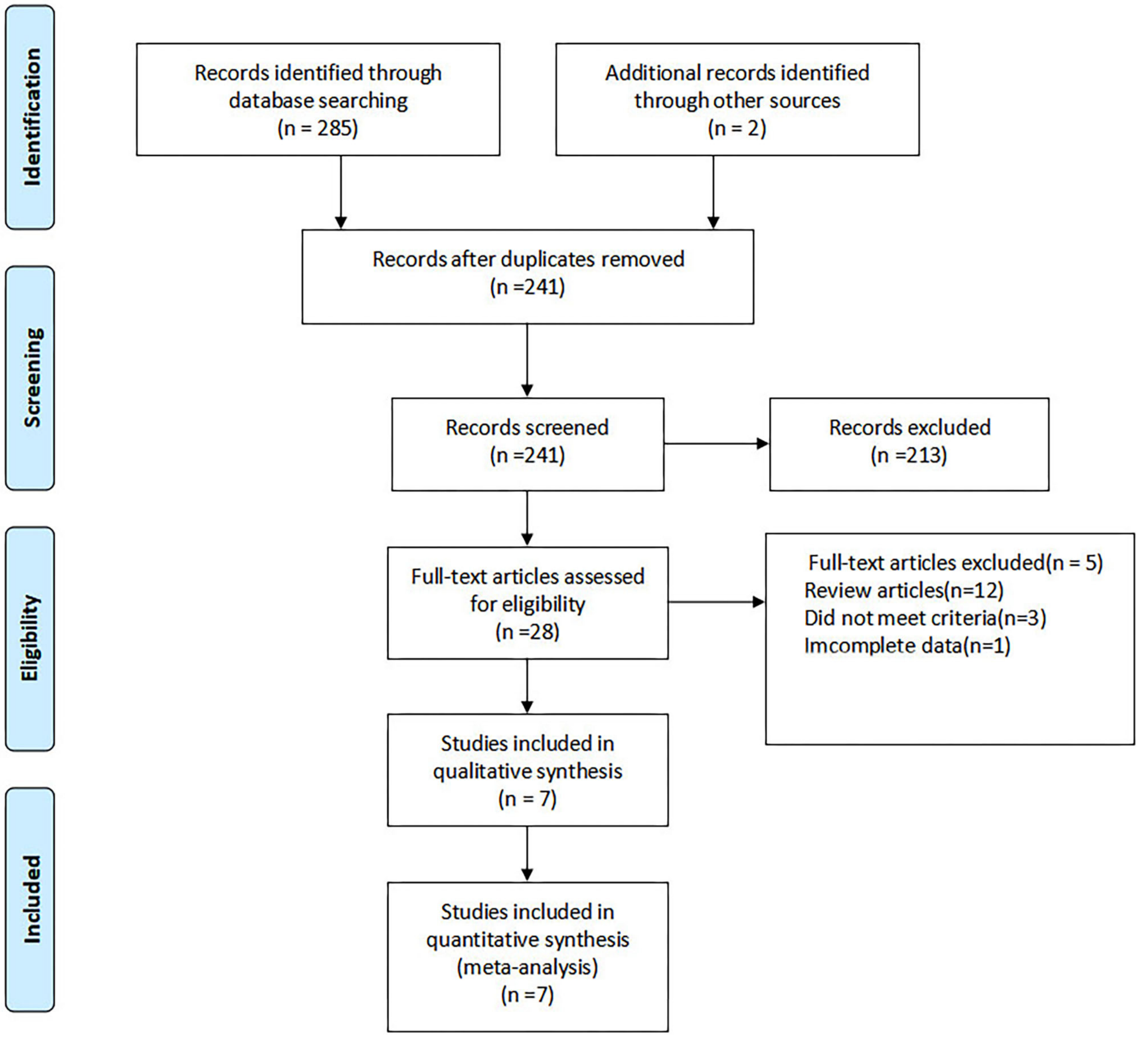

FIGURE 1 | Flow diagram of studies selection process.

Risk of Bias of Included RCTs

The ROB2 tool was performed to evaluate the risk of bias and the major weakness was in the domains of deviations from intended interventions. The final results were upload to **Supplementary Materials**.

Risk of Bias of Included Non-randomized Studies

The ROBINS-I tool was used to assess the risk of bias and the main weakness was in the selection bias. The final results suggested that all the comparative studies had a moderate risk of bias.

PERIOPERATIVE OUTCOMES

Operative Time

Data of OT were reported in six studies (16–21) including 930 patients. The heterogeneity test results suggested that the heterogeneity among studies is high ($I^2 > 50\%$) and a random effects model was used. The final meta-analysis showed no statistical difference between the su-fURS and ru-fURS (MD: 0.64; 95% CI 9.48–8.19; $p = 0.886$; **Figure 2A**).

Estimated Blood Loss

A total of two studies related to EBL (19, 22) after the operation, including 1,287 patients, and a fixed effects model was used

TABLE 1 | Baseline characteristic of included studies.

Studies, year	Country	Intervention su-fURS/ru-fURS	No.of patients	Age (year)	Number of stones	Stone size (mm)	Study design	Quality score
Zhu (2020)	China	PU3022A Flex-X2	45 45	45.1 ± 9.3 44.5 ± 8.5	NA	11.6 ± 5.0 8.7 ± 3.0	RCT	7[a]
Qi (2019)	China	ZebraScope URF-V	63 63	51.84 ± 13.16 53.25 ± 12.11	1.17 ± 0.92 1.95 ± 1.02	NA NA	RCT	6[a]
Mager (2018)	Germany	Lithovue Flex-X2S, Flex-XC	60 62	54 ± 17 59 ± 16	NA	NA NA	prospective	8[b]
Kam (2019)	Australia	Lithovue URF-V2	55 64	53.5 (46.2–60.7)[c] 53.3 (47.6–59.0)[c]	2.3 (1.6–2.9)[c] 2.0 (1.7–2.4)[c]	14.7 (11.2–18.1)[c] 13.3 (11.0–15.6)[c]	prospective	7[b]
Usawachintachit (2017)	U.S.A	Lithovue URF-P6	92 50	55.8 ± 15.1 50.5 ± 12.6	2.0 ± 1.7 1.6 ± 1.3	14.7 ± 9.9 16.3 ± 12.2	prospective	8[b]
Ding (2015)	China	PolyScope URF-P5	180 180	50.5 ± 12.8 51.1 ± 13.7	1.53 ± 0.7 1.58 ± 0.94	NA NA	RCT	6[a]
Salvado (2019)	Chile	Uscope3022 Cobra	31 30	50.4 ± 13.8 49.9 ± 16.5	NA	10.8 ± 5.0 9.0 ± 3.3	prospective	7[b]

su-fURS, single-use flexible ureteroscope; ru-fURS, reusable flexible ureteroscope; NA, not available; ±, refers to standard deviation.
[a]using Jadad scale; [b]using NOS scoring rule; [c]mean (95%CI).

according to the results of heterogeneity analysis ($I^2 = 0\%$). The last result showed that the difference was not statistically significant between the su-fURS and ru-fURS (MD: 0.42; 95% CI 2.07–2.92; $p = 0.74$; **Figure 2B**).

PROGNOSTIC OUTCOMES

Length of Hospital Stay

Among the two studies (16, 19) on the LOS, there was no obvious heterogeneity and we used a fixed effects model for meta-analysis. The final outcomes indicated the absence of statistically significant difference between the su-fURS and ru-fURS (MD: 0.11; 95% CI 0.13–0.34; $p = 0.371$; **Figure 2C**).

Stone-Free Rate

The SFR was recorded in five out of seven studies (16, 18, 19, 21, 22) containing 840 patients. Since there was no outcome of the heterogeneity test ($I^2 = 32.8\%$), a fixed effects model was used. No statistical differences were observed between the su-fURS and ru-fURS (MD: 1.01; 95% CI 0.70–1.46; $p = 0.948$; **Figure 2D**).

Complications

We performed a meta-analysis of the complication after surgery and based on the heterogeneity test, a fixed effects model was used. The final results indicated that there was no statistically significant difference between the su-fURS and ru-fURS (OR 0.93; 95% CI 0.66–1.29; $p = 0.646$; **Table 2**).

Furthermore, based on the Clavien–Dindo grades for the postoperative complications, we also performed subgroup analysis. The results of the subgroup analysis interpreted that significant differences were only observed in the Clavien–Dindo grade II postoperative complication: Clavien–Dindo grade I (OR 1.05; 95% CI 0.72–1.55; $p = 0.79$), Clavien–Dindo grade II (OR 0.47; 95% CI 0.23–0.98; $p = 0.04$), Clavien–Dindo grades III–V (OR 1.11; 95% CI 0.52–2.36; $p = 0.79$; **Table 2**).

DISCUSSION

The f-URS has been used in the field of urology for more than 40 years and the development of f-URS is perfectly in accordance with the concept of urology in the field of minimally invasive surgery. In recent decades, the studies reported on f-URS have increased (23). A meta-analysis has shown that, compared with extracorporeal shock wave lithotripsy (ESWL), f-URS could successfully treat the patients with stones < 2 cm, with a higher SFR, especially 1–2 cm in the lower pole (24).

However, the limitations in conventional f-URS, i.e., ru-fURS, contain a high initial purchase cost, expensive repair, a risk of cross-infection, and durability at a later stage. To overcome some limitations of ru-fURS, the conception of su-fURS has been proposed (25). It is, particularly, important to discuss the difference between the su-fURS and ru-fURS. As far as we know, this is the first meta-analysis to explore the differences between the two f-URS that aimed to provide medical evidence for clinicians to choose the appropriate approach.

After a sensitivity analysis (**Figure 3**), this meta-analysis of OT was eventually included in six studies. The final result indicated that no significant differences exist between the two f-URS. It could be seen that the OT of su-fURS procedure was more than ru-fURS in Ding et al. study (16). Professor Ding et al. used a kind of su-fURS, which was named Polyscope and developed in 2011. The surgeon adjusted the degree of deflection of the Polyscope by the force to squeeze the handle constantly and become fatigued during prolonged operation, especially for stones in the lower calyces (16). In addition, the Polyscope lacked two-way deflection, which could not only increase the difficulty in operation but also cause, sometimes, loss of navigation control (26). These causes all bring out increased OT of su-fURS. On the contrary, Salvado et al. reported the use of su-fURS that was the Uscope (PU3022), which was developed in 2017. It has a special self-locking technology that could reduce the fatigue of the surgeon (27). We speculate that the difference between su-fURS themselves was the main reason. Different definitions of time and technical proficiency of the surgeon are also important factors affecting the time of OT.

In terms of EBL, LOS, and SFR, our meta-analysis showed that no significant statistical difference. Since the introduction of su-fURS, it has undergone an evaluation of a series of *in vitro* experiments. Several studies have indicated that there were no remarkable differences in image quality and deflection ability between the su-fURS and ru-fURS (28, 29). Different stone locations, calyceal structures, long learning curves, and surgeon proficiency are all probable reasons.

The previous study (30), which compared the su-fURS and ru-fURS for the renal stones, was different from our study results, especially in terms of OT and SFR. Sometimes, the SDs are not presented in the article and researchers need to estimate SDs from other related information such as standard errors, confidence intervals, *p*-values, and *t*-values. Different calculation methods may be the reasons. In addition, the sensitivity analysis results of their study are not stable, which means that results were greatly affected by bias and should be very careful when concluding results.

Our final meta-analysis results about complications and demonstrates that no statistical difference exists between the su-fURS and ru-fURS. In addition, we did subgroup analysis according to the Clavien–Dindo grades, and the statistical difference can only be found in the Clavien–Dindo grade II (OR 0.47; 95% CI 0.23–0.98; $p = 0.04$; **Table 2**). According to the existing studies, most complications were grade I–III (98%) and the most common complication in grade II is urinary tract infection (31). Studies have shown that even when ru-fURS was cleaned manually and disinfected by hydrogen peroxide gas, contamination could still be found (7, 8). This may lead to cross-infection between the patients (32). The amount of cleaning and disinfection could also affect the service life of the extremely fragile equipment. On the other hand, the su-fURS automatically eliminates the risk of contamination (25). However, many factors could affect the occurrence of postoperative infections and the definition of urinary tract infection also was the influencing factor. Generally speaking, the outcome needs to be with respect to caution.

The greatest advantage of su-fURS is its cost-effectiveness, which means lower price, no maintenance, and is ready to use. Professor Martin et al. reported a 12-month demographic-based cost-effectiveness analysis in the United States pointing out that the su-fURS and ru-fURS reached the financial breakeven point in 99 cases (33). Another study showed that if the price of su-fURS is no higher than $1,200, it would be more economical (9). One study, which included 23 cases (14 cases for URF-P6, nine cases for LithoVue) and was a small sample cost analysis, showed that compared with URF-P6, LithoVue acquisition costs were higher, but savings were achieved in the terms of labor, consumables, and repair. When these factors were taken into account, the total cost of using these two fURS per case was comparable (34). Nevertheless, these studies not only contain the treatment of the upper urinary stones, but also diagnostic and

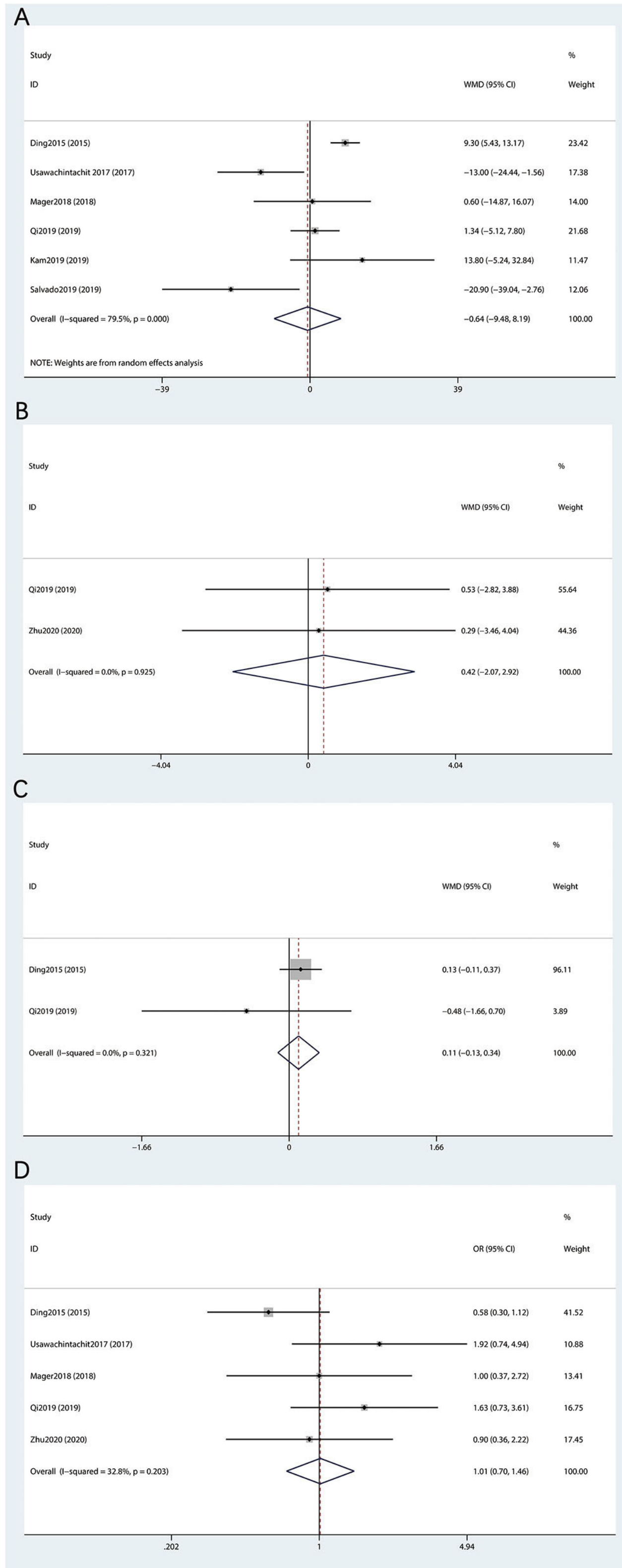

FIGURE 2 | Forest plot of perioperative outcomes between the su-fURS and ru-fURS. **(A)** operative time, **(B)** estimated blood loss, **(C)** length of hospital stay, and **(D)** stone-free rate.

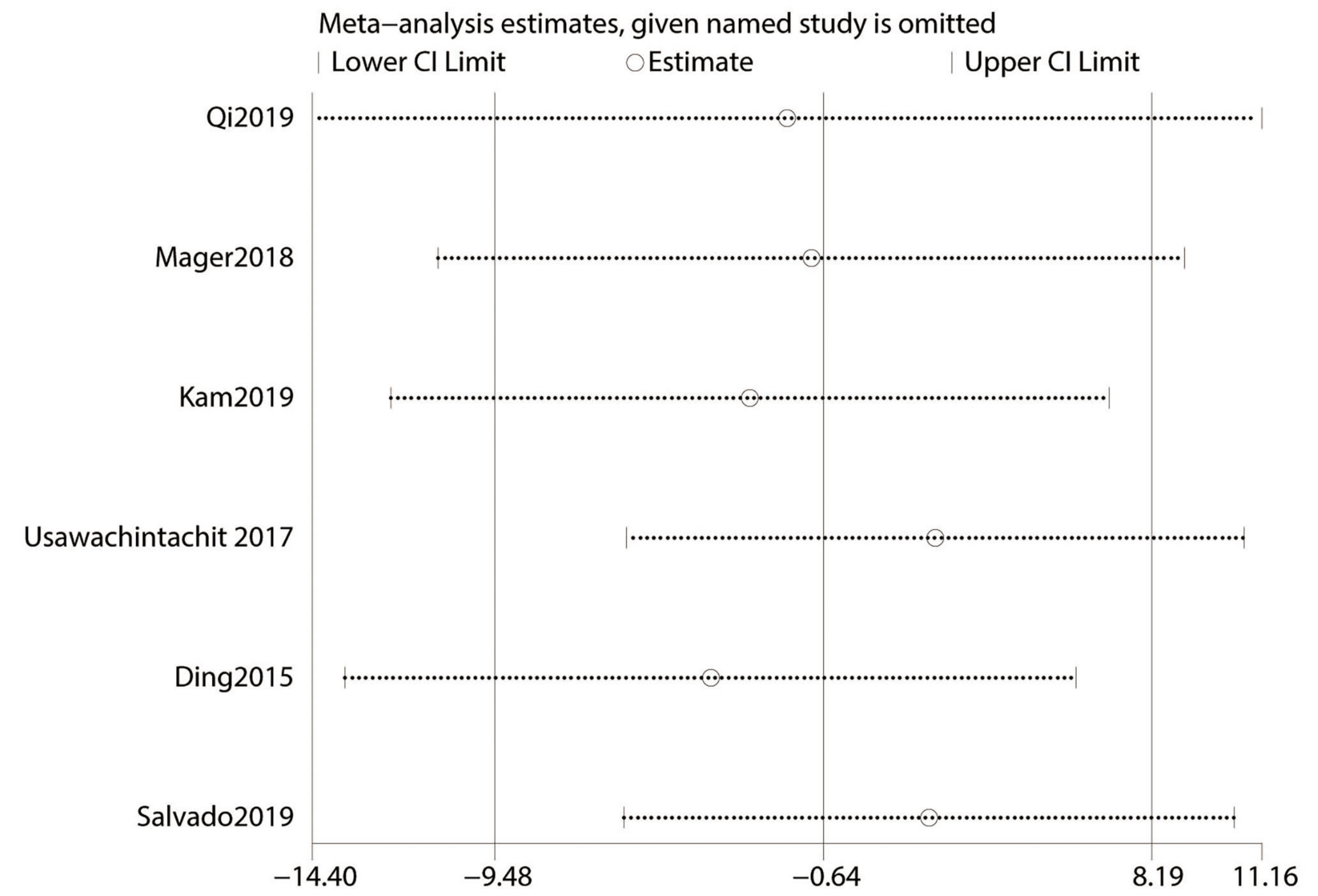

FIGURE 3 | Sensitivity analysis of operative time.

TABLE 2 | The meta-analysis of postoperative complication.

complication	No. of studies	No. of patients su-fURS /ru-fURS	OR (95% CI)	*P*-value	Heterogeneity (I^2)
Clavien–Dindo grade I	7	526/494	1.05 (0.72, 1.55)	0.79	1.7%
Clavien–Dindo grade II	5	315/284	0.47 (0.23, 0.98)	0.04	0%
Clavien–Dindo grade III–V	4	395/355	1.11 (0.52, 2.36)	0.79	0%
Total	7	526/494	0.93 (0.66, 1.29)	0.65	41.7%

OR, odds ratios; CI, confidence interval; su-fURS, single-use flexible ureteroscope; ru-fURS, reusable flexible ureteroscope.

biopsy. The aforementioned research conclusions need to be with respect to caution.

We followed the PRISMA guidelines strictly to perform this meta-analysis (35). However, some limitations cannot be avoided. First, the studies included were not all high-quality RCTs, leading to insufficient levels of evidence. Second, a limited number of clinical studies, so it is not convincing to apply it on a large scale. Third, lacking detailed date, we fail to perform a subgroup analysis of stone location and stone size. Fourth, due to the definition of expenditure and income, we failed to perform a meta-analysis on cost-effectiveness. This was an important inherent limitation of our study.

CONCLUSION

In conclusion, our meta-analysis demonstrates that su-fURS, compared with ru-fURS, has similar effectiveness and better security for patients with upper urinary calculi which provides some benefit to medical institutions of less surgical volume. A larger sample size, multicenter, and longer follow-up RCTs are still needed to support our conclusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YL conceived and designed the experiments. LP and JinzL analyzed the data. JinzL, JinmL, and JW contributed to reagents, materials, and analysis. CM and LP wrote the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.691170/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparison of the Efficacy and Safety of Extracorporeal Shock Wave Lithotripsy and Flexible Ureteroscopy for Treatment of Urolithiasis in Horseshoe Kidney Patients: A Systematic Review and Meta-Analysis

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Background: Urolithiasis is the most common complication of horseshoe kidney (HK), which can be treated by extracorporeal shock wave lithotripsy (ESWL), flexible ureteroscopy (FURS), and percutaneous nephrolithotomy (PCNL). When comparing treatments of ESWL and FURS, it is unclear which is more efficient and safe. The objective of this study was to compare the efficacy and safety of FURS and SWL for the treatment of urolithiasis in HK patients.

Methods: A systematic search of the Web of Science, PubMed, and EMBASE was performed in February 2021. Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias in each study.

Results: Five studies published between 2008 and 2018 were synthesized in the present meta-analysis. The study revealed that FURS compared with SWL had greater initial and overall stone-free rates (SFRs). Risk ratios (RRs) were 2.46 ($P < 0.00001$) in initial SFRs, 1.36 ($P = 0.02$) in overall SFRs. No differences were found in the retreatment ratio, RRs were 0.49 ($P = 0.43$). In addition, no major complications were encountered, and all the complications were mild to moderate.

Conclusion: The study demonstrated that FURS and SWL are effective and safe treatments for patients with HK with stones (<20 mm). Moreover, FURS has greater clearance rates and lower complication rates than SWL.

Keywords: horseshoe kidney, urolithiasis, extracorporeal shock wave lithotripsy, flexible ureteroscopy, efficacy

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INTRODUCTION

Horseshoe kidney (HK) is the most common renal fusion anomaly, with an incidence range from 1/400 to 1/666 (1). HK occurs as a result of the abnormal fusion of the lower poles at the embryological stage. Consequently, the normal ascent and rotation of the kidneys are arrested, leading to malrotation with anterior displacement of the collecting system (2). Impaired drainage of the collecting system and ureteropelvic obstruction predispose the patients to urolithiasis and a higher incidence of infection (3, 4).

The most common complication of HK is urolithiasis, which is encountered at an incidence of 21–60% (2). For early-phase treatment of urolithiasis in HK, open-operative approaches were mainly taken. However, minimally invasive surgery and non-invasive treatment are gaining popularity for smaller incisions, fewer complications, less postoperative pain, and shorter length of hospital stay. Extracorporeal shock wave lithotripsy (ESWL), flexible ureteroscopy (FURS), and percutaneous nephrolithotomy (PCNL) are the currently available methods for treating calculi in HK. There have been no guidelines or standard criteria for the selection of the favorable approach for the treatment of calculi in HK, especially for <20 mm renal stones (5). PCNL is the first choice therapeutic option for stones larger than 2 cm (5, 6). Despite the fact that PCNL has the higher success rates, the risk of complications (complication rates 83%) cannot be neglected due to the invasive nature of PCNL (7, 8). Nevertheless, the latest study demonstrated that PCNL in patients with HSK is safe and effective with a low complication rate (17%) (9). Additionally, laparoscopic lithotripsy, including retroperitoneal and transperitoneal, seems to be safe and effective for patients with HK with a limited number ($n \leq 3$) of 20–40 mm renal stones, but these patients require prolonged hospitalization (10). Inevitably, it is a less invasive approach being more preferable. Uncomplicated and small (<15 mm) calculi can be treated non-invasively by SWL, which is a common and well-tolerated procedure for HK with stones (11–13). Additionally, with the development of technology, FURS has shown promising prospects of urolithiasis therapies with high stone-free rates (SFRs) and low complication rates, especially in moderate- or small-sized stones (14, 15). Whereas, there is no common consensus on which approach is most appropriate.

Recently, some studies reported the experience of the therapeutic effects of SWL and FURS. Accordingly, the objective of this study is to compare the efficacy and complications of FURS with SWL in the treatment of HK with stones. Ultimately, we can provide guide treatment selection for the treatment of HK with stones.

METHODS

Literature Search and Data Extraction

This systematic review of the literature was performed in February 2021 using the Web of Science, PubMed, and EMBASE. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed. The comprehensive search of the studies was carried out independently by two investigators using the following string terms: ("HK" OR "fused kidney") AND ("stone" OR "calculus" OR "calculi"). The search was limited to English-language literature, and no date restrictions were applied.

The population, intervention, comparator, outcome, and study design (PICOS) approach was used to define the study eligibility. Inclusion criteria were (P) patients were diagnosed as HK with urolithiasis (the diameter of the stone is <2.0 cm); (I) undergoing FURS; (C) in which SWL was performed as a comparator; (O) evaluating the following outcomes: initial SFRs, overall SFRs, retreatment ratio, and complication; (S) randomized controlled trials (RCTs), non-zRCTs, prospective observational studies, or retrospective observational studies. The exclusion criteria include the following: <2 treatment arms; non-English publications without an English abstract; and studies with unavailable or incomplete outcome data. Meanwhile, editorial comments, letters to the editor, case reports, and meeting abstracts were also excluded.

All database results were imported into an EndNote X7 reference manager prior to screening, and then duplications were removed. Titles, abstracts, and full-text articles were screened by two authors. Additionally, data extraction was carried out by the reviewers independently. The data we extracted included the following: setting, date, study design, participant demographics, baseline characteristics, intervention details, and outcomes.

Quality Assessment

The studies we included were assessed by Newcastle-Ottawa Scale (NOS). Studies with NOS scores <5 were considered as low-quality studies, 6–7 were considered intermediate-quality studies, and 8–9 were considered as high-quality studies.

Statistical Analysis

Meta-analysis was conducted with Cochrane Collaboration Review Manager software (RevMan v.5.3.0). Continuous variables were presented as mean ± SD or the minimum-to-maximum range, whereas categorical variables were expressed as percentage or number of individuals. Treatment results were calculated using the Mantel-Haenszel method and evaluated by risk ratios (RRs) and 95% CIs. When RR is more than 1.0, it indicates a greater likelihood of SFR in the FURS group. The two-tailed test was used to assessed statistical significance (test level $\alpha = 0.05$), and $P < 0.05$ was considered significant.

Assessment of heterogeneity will be assessed by chi-squared test and I^2 test, $P < 0.1$ and $I^2 > 50\%$ indicated heterogeneity. The fixed-effects models were used for calculation when no significant heterogeneity was observed. Sensitivity analysis was conducted by excluding studies from the analysis one by one, and a random-effects model instead of a fixed-effects model was also used to test the robustness of the meta-analysis results. A formal assessment of publication bias was unable to be evaluated due to the limited number of included studies.

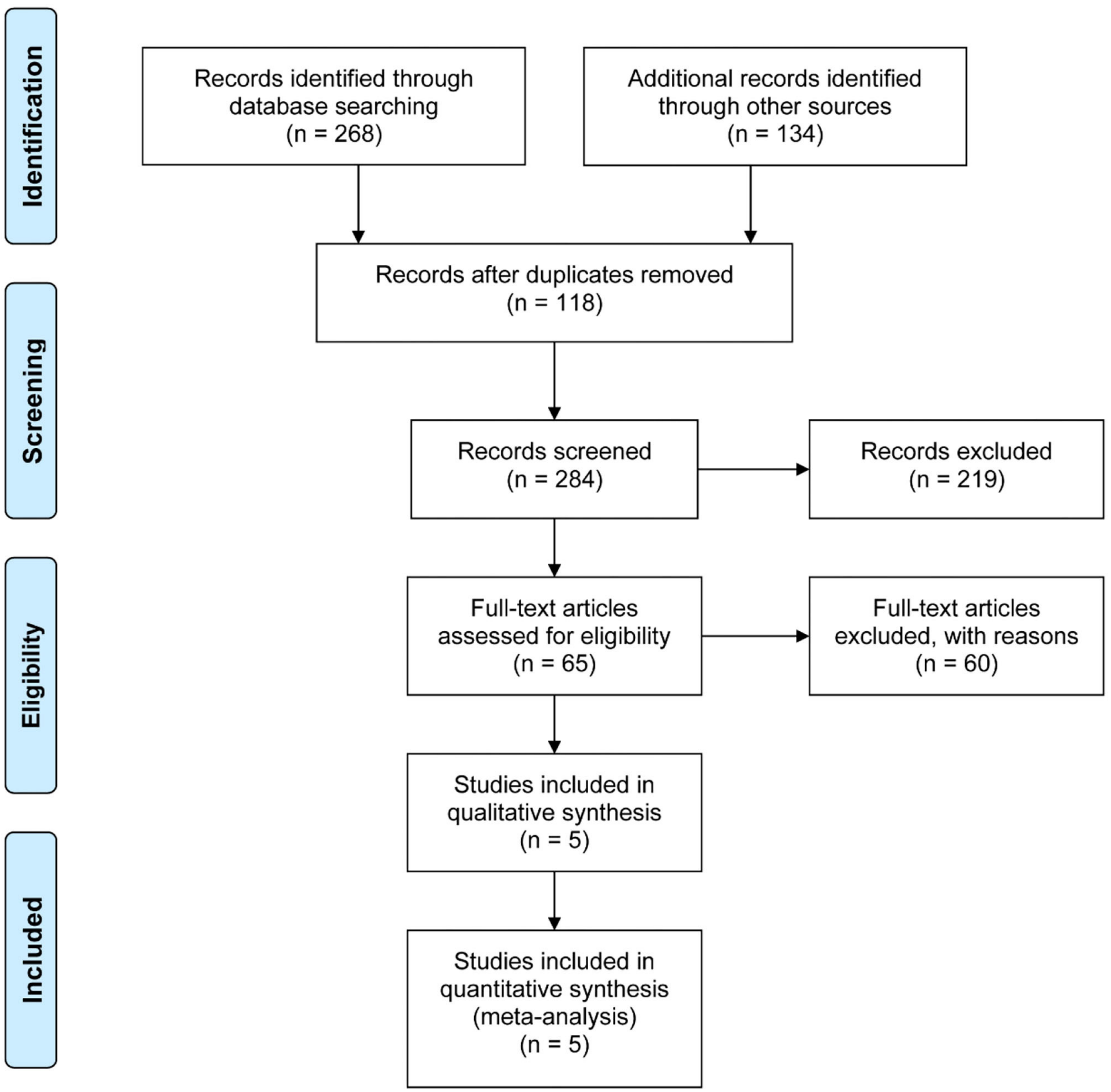

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analysis flowchart.

RESULTS

Characteristics of Eligible Trials

The search strategy identified 284 records and 65 remained eligible for inclusion based on screening. Of the 65 full-text articles assessed for eligibility, a total of five cohorts were invited to participate (**Figure 1**) (16–20). Sixty studies were excluded for the following reasons: 38 studies were excluded because of unavailability of data for statistics, five studies because of the study design, and 17 studies because they were single-arm studies. These included studies were published from five countries between 2008 and 2018.

The characteristics of the five studies were summarized in **Table 1**. All of the studies were retrospective, single-center studies. Patients were recruited from July 1991 to May 2015. As shown in **Table 1**, five studies get a 6–7 NOS, which means all studies we included were considered intermediate-quality studies and low risk of bias. A total of 134 patients were included in our study (87 males (65%) and 47 females (35%), and 66 in the FURS group vs. 68 in the SWL group). The mean stone size of

TABLE 1 | Characteristics of included studies.

Study	Country	Study location	Period	Definition of SFR	NOS
Al Otay et al. (16)	Saudi Arabia	Single center	2000–2012	No residual stones left behind on CT scan	6
Blackburne et al. (17)	US	Single center	2002–2015	No residual fragments noted on KUB, nephrostogram, or CT scan	7
Ding et al. (18)	China	Single center	2005–2014	No residual fragments noted on plain film and ultrasound	7
Gokce et al. (19)	Turkey	Single center	2003–2014	No residual fragments≥3mm in size in plain radiography, ultrasound and CT	7
Symons et al. (20)	India	Single center	1991–2008	No residual stones noted on follow-up imaging	6

Study	Treatment	Median Age, yr (range)	Gender (M/F)	Patient number	Numbers of renal moieties	Median Stone size, (range)	Stone location	Median duration of follow-up, (range)	Initial SFR	Overall SFR
Al Otay et al. (16)	FURS	37 (2–78)	16/9	1	-	<10 mm	-	31.6 ± 24.1* months (12–76)	-	-
	SWL			6	-	(10-20) mm	-		-	-
Blackburne et al. (17)	FURS	48.1 (29–28)	13/7	22	25	8.4 (2–25) mm	lower pole	20.5 months (0–118)	84%	100%
	SWL	32.5 (23–42)	0/2	2	2	4.5 (4–5) mm	-		50%	100%
Ding et al. (18)	FURS	42.9 ± 11.6*	14/4	18	20	18.9 ± 3.6 (339.6 ± 103.9 mm^2)*	-	4 weeks	55.6%	88.9%
	SWL	36.6 ± 8.2*	9/2	11	12	11.9 ± 2.0 (110.6 ± 44.5* (range, 63–205) mm^2)	-	-	27.7%	72.7%
Gokce et al. (19)	FURS	44.2 ± 9.9*	18/5	23	-	17.1 ± 5.1* mm	Lower pole 6; Pelvis and upper pole 17	(2–6) weeks	73.9%	73.9%
	SWL	42.8 ± 8.4*	32/12	44	-	16.8 ± 4.4* mm	Lower pole 12; Pelvis and upper pole 32	(1–6) weeks	22.7%	47.7%
Symons et al. (20)	FURS	36.5 (7–60)	49/6	2	5	172 (63–281) mm^2	Pelvis 1, multiple (in the pelvis, superior calyx, middle calyx and isthmus) 1	1 month	100%	100%
	SWL			5	6	149.2 (50–225) mm^2	Upper calyx 1; Pelvis 3; Lower calyx 1		60%	80%

FURS, flexible ureteroscopy; SWL, extracorporeal shock wave lithotripsy; SFR, stone-free rate.
**Mean ± SD.*

patients was <20 mm. Moreover, calcium oxalate was the most common stone type, although it was not described in the studies of Gokce et al. (19) and Al Otay et al. (16). The definition of SFR was concordant in most of the studies we included, what are no residual fragments noted on follow-up imaging.

Efficacy of Treatment

Results of the efficacy of surgery are based on all 134 patients from FURS and SWL. The rates of initial SFRs were ranged from 55.6 to 100% and 22.7 to 60% in FURS and SWL groups (**Table 1**). Additionally, there were statistically significant differences between the two groups overall, and RRs were 2.46 (95% CI 1.59, 3.81, $P < 0.0001$, $I^2 = 0$; **Figure 2A**). Repetitive treatment was used in some patients with low stone clearance rates. Moreover, the rates of overall SFRs were ranged from 73.9 to 100% and 47.7 to 100% in FURS and SWL groups, respectively. Similarly, the overall SFRs of the FURS group were significantly better than that of the SWL group (RR = 1.36, 95% CI 1.06–1.76, $P = 0.02$, $I^2 = 0$; **Figure 2B**). Nevertheless, there was no evidence that the retreatment ratio of the two groups was different (RR = 0.49, 95% CI 0.22–1.08, $P = 0.11$, $I^2 = 54\%$; **Figure 2C**). A sensitivity analysis of all studies indicated consistent results (**Supplementary Figures 1–4**).

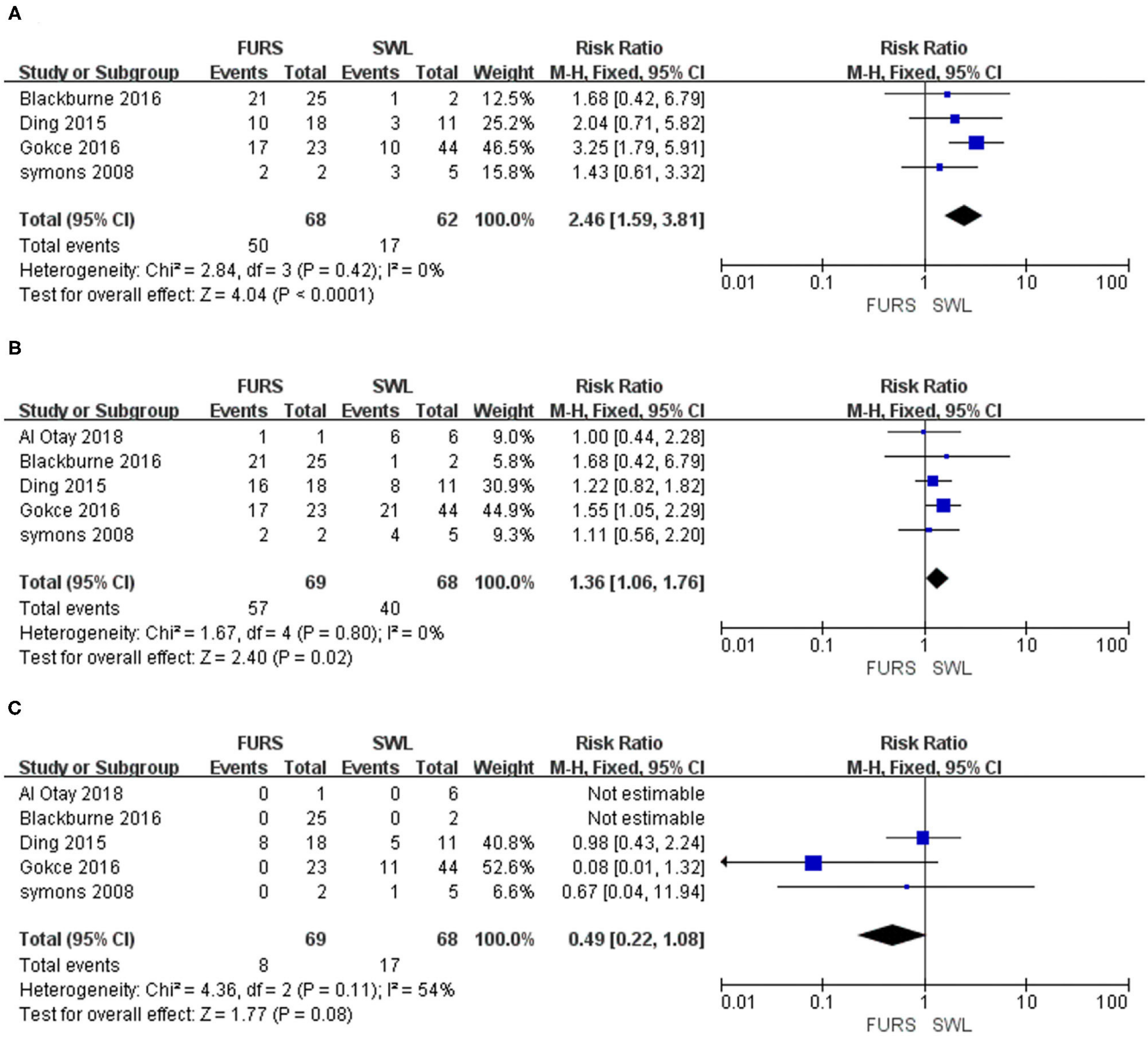

FIGURE 2 | (A) Forest plot of initial stone-free rates for SWL vs. FURS. **(B)** Forest plot of overall stone-free rates for SWL vs. FURS. **(C)** Forest plot of retreatment ratios for SWL vs. FURS. SWL, extracorporeal shock wave lithotripsy; FURS, flexible ureteroscopy; CI, confidence interval; M–H, Mantel-Haenszel.

Complications

In total, 41 patients developed complications after FURS and SWL. The renal colic episode, which was the most common complication encountered, was presented in 20 patients; patients in the FURS group accounted for most of the total number. Five patients had a fever, and six patients had hydronephrosis. While hematuria was observed in nine patients, and the perirenal hematoma was observed in one patient. Additionally, no serious complications have been reported in the studies we included. On the whole, the rate of complications among patients of the SWL group was higher as compared to FURS groups (36.8 vs. 24.2%; **Table 2**). Whereas complications of FURS and SWL were not reported in the studies by Al Otay et al. (16), Gokce et al. (19), and Symons et al. (20), we failed to perform a further meta-analysis.

DISCUSSION

In this meta-analysis, we compared the efficacy and complications between FURS and SWL in HK stones. Our findings suggested that patients with HK treated with FURS showed higher SFRs and lower complication rates than SWL. However, no statistical differences in terms of retreatment ratio were observed between the two groups.

To our knowledge, unique anatomical features of the HKs lead to impaired renal pelvic drainage, which accelerates the

TABLE 2 | Complications of FURS and SWL.

Complication	FURS ($n = 66$)	SWL ($n = 68$)
Renal colic episode	3	17
Fever	4	1
Hydronephrosis	6	0
Hematuria	3	6
Perirenal hematoma	0	1
Total	16 (24.2%)	25 (36.8%)

FURS, flexible ureteroscopy; SWL, extracorporeal shock wave lithotripsy.

formation of stones. Moreover, patients with HK with stones may be troubled with some complications, such as pyelonephritis, hydronephrosis, and pyonephrosis. The therapy of HK stone is more difficult than the stone in a normal anatomical kidney. Published data have clearly shown that PCNL was an efficient mini-invasive stone removal procedure for patients with HK, particularly in the case of large stones (with a diameter larger than 2 cm) (9, 21, 22). However, since the high risk of complication associated with PCNL was performed for HK stone, SWL and FURS have great application prospects for relatively efficient and safe (8, 20).

Currently, SWL is one of the most commonly used treatments for urolithiasis, and stones smaller than 1.5 cm in patients with HK without ureteropelvic junction obstruction could be removed successfully with SWL (usually need repeat sessions) (23). Aside from this, Kirkali et al. (13) and Serrate et al. (24) reported that SFRs of SWL were between 28 and 80%, which was lower when compared to patients with normal kidneys. FURS was gradually applied to the management of renal stones in HSKs since 2005, and 75% (three of four) patients were complete stone clearance in the report of Weizer et al. (15). Breda et al. (25) demonstrated that the SFR is not the same across the size of the stone, and the SFR was higher in patients whose intrarenal stone burden <2 cm. Likewise, Molimard et al. (26) found that SFR was 53% after one session of FURS, and it rose to 88% after an average of 1.5 sessions (the mean stone size was 16 mm). Surprisingly, not only no complications were observed, but also the efficacy of FURS was similar to PNCL. Lavan et al. (27) published a more recent review on the outcomes of ureteroscopy for stone disease in anomalous kidneys, and they reported that patients who underwent FURS got good stone-free rates with a low risk of major complications, although the technic is challenging. This evidence indicated that SWL and FURS could be a feasible and safe alternative in patients with HK with calculus. As state in the latest European Association of Urology (EAU) guidelines, SWL can be used in patients with HK with stones, but the passage of fragments might be poor, while FURS can achieve acceptable SFRs (28). Furthermore, there is a debate about which therapy is more favorable for patients with HK with stones.

In our study, the SFRs of FURS and SWL were similar results to previous studies. As for the stone size of small to moderate, the removal of stone had an obvious effect. Nevertheless, both initial and overall SFRs were lower in the group of SWL, perhaps owing to the anatomic constraints of the HK, which makes stone fragments pass pelvis and ureter difficult. Compared with FURS, the main advantages of SWL are that general anesthesia does not require, and it is less expensive. Although the effect of FURS was stronger and statistically significant, the surgical procedure is complicated for flatter renal pelvis and narrower intrarenal space of HK kidney, which increases the difficulty of navigating and deflecting ureteroscope inside the kidney (29). Atis et al. (30) reported that the location in the lower pole was one of the factors for clearance failure of FURS in HK. Blackburne et al. (17) also arrived at similar conclusions. The SFR was lower for HK stones located in the lower pole. However, the clearance of stones at different locations was not clear in the other studies we included. Moreover, some patients receipted reoperation after an initial failed procedure and achieved the stone-free status, but there were no statistically significant differences between the two treatments.

As for complications, we found that the complication rates were comparable to previous studies. The abnormal anatomical kidney increases the difficulty of operation as well as prolongs the procedure time, which may lead to a higher rate of complications. Fortunately, no major complications were encountered, and all the complications were mild to moderate. Still, the different follow-up duration of studies should be taken into account, and long-term efficacy requires further investigation. Importantly, there were only two studies that reported complications, and the complications were not standardized by the Clavien-Dindo classification. Thus, more studies are required to confirm the safety of SWL and FURS.

This study has some limitations. All included studies were retrospective single-center studies, and the number of included patients was relatively small. Additionally, for the individual studies, baseline differences of each study might confound the results, especially the age of patients. The definition of SFR was different in included studies, as does the imaging tools used to assess SFR. However, there was no significant heterogeneity in this study, and our findings are reliable. And sensitivity analyses indicated that these pooled results were robust. Further, additional larger-scale studies are needed to confirm the findings of the present study.

CONCLUSION

This study indicates that FURS and SWL are effective and safe treatments for patients with HK with stones. Moreover, FURS has greater clearance rates and lower complication rates than SWL. However, large- and high-quality RCTs are warranted to confirm the results of this study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JA, LY, and XY conceived the project and drafted the manuscript. XY and GP searched the databases. TJ, DC, XZ,

and HX analyzed data. PY, QW, HL, XZ, and JA revised the manuscript. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.726233/full#supplementary-material

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Safety During Ureteroscopy: Radiation, Eyes, and Ergonomics

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It is known that urologic surgeons are at risk of work-place injury due to the physical requirements of operating and exposure to hazards. These hazards include radiation, exposure to body fluids, use of laser energy, and orthopedic injury due to the physical nature of operating. The risks that these hazards present can be mitigated by implementing several evidence-based safety measures. The methods to protect against radiation exposure include keeping radiation usage in the operating room as low as reasonably achievable, donning lead aprons, and wearing protective glasses. Additionally, protective glasses decrease the risk of eye injury from laser injury and exposure to body fluids. Finally, practicing sound surgical ergonomics is essential to minimize the risk of orthopedic injury and promote career longevity. The interventions discussed herein are simple and easy to implement in one's daily practice of urology.

Keywords: endourologic surgery, surgical ergonomics, radiation safety, ureteroscopy (URS), nephrolithiasis

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INTRODUCTION

Safety in the operating room is of paramount importance to the patient, but also to the surgeon and staff in the room. Here we discuss evidence-based solutions to minimize risk to the surgeon and operating room staff. We concentrate on the areas of minimizing radiation exposure, use of eye protection, and practicing sound ergonomics to improve safety in the operating room.

REDUCING RADIATION EXPOSURE

Radiation mitigation is at the forefront of efforts to improve both patient and medical staff safety. The use of radiation to aid in the diagnosis, treatment, and follow up of stone disease is, for now, unavoidable. Endourologists who regularly perform fluoroscopically-guided procedures are at risk for higher levels of radiation exposure.

Radiation has side effects on the human body and are divided into 2 categories: stochastic and deterministic. Deterministic effects occur after an acute exposure over a specific threshold of radiation dosage. Examples include hair loss, cataracts and dermal burns (1). These effects are not typically seen by the urologic surgeon as these radiation thresholds are not reached in the treatment of stone disease. Of more relevance to the urologist is the risk of secondary malignancy due to radiation exposure, which is a stochastic effect. "Stochastic" meaning that it occurs in a linear fashion with dose, age, and gender-dependent factors playing a role. The evidence for this mechanism is derived from studies reporting on increased risk of secondary malignancy seen in patients with exposure to nuclear explosions, nuclear powerplant workers, and patients with conditions requiring repeated computed tomography (CT) scans (2–5).

The stochastic effects of radiation exposure are of significance particularly for the operating urologist. Traditionally, ureteroscopy has always been fluoroscopically guided. The maximum 1-year allowable radiation dosage is 50 or 20 mSv per year over a 5-year period per International Commission on Radiologic Protection (ICRP) Occupational guidelines (1). Fortunately, there is no existing evidence of increased risk of secondary malignancy in urologists due to occupational radiation exposure. There has been historical evidence of increased risk of leukemia RR 3.86 (1.21–12.3) among interventional cardiologists and radiologists who graduated medical school before 1940, but these authors did not find an increased risk of mortality in physicians who graduated in the following decades (6). This is likely due, in part, to a continued decrease in the estimated annual radiation exposure for radiation technologists from 710 mSv in the 1930s down to 5.5 mSv in the 1990s (6). There have been 2 studies that have recently quantified this exposure for percutaneous nephrolithotomy (PCNL) and they report that the mean exposure by operating surgeons is around 0.05–0.21 mSv per case, as measured by dosimeters worn within lead aprons (7). This is notably well within safety parameters. Overall, it is difficult to accurately report exposure because studies often extrapolate data from a single or small number of surgeons with varying experiences. With significant practice volume and case complexity variation, generalizability is challenging. However, while dosage per case can be low, additional exposure received over the course of a career may add up. The Committee on the Biological Effects of Ionizing Radiation reports that, if following the linear-no-threshold theory, a dose of about 37.3 mSv carries a lifetime attributable risk of secondary malignancy ranging from 0.40% in young females to 0.065% in older men (8).

Easy to implement interventions have been shown to reduce fluoroscopy time by up to 80%. These include radiation safety training, wearing dosimeters, and instituting formal radiation reduction protocols with pre-operative checklists (9–12). Further techniques to decrease fluoroscopy time include using radiology technicians familiar with urologic procedures, collimation, using the C-arm laser beam to target organ location without image exposure, using markings on the drape to guide the laser to the organ of interest, and using last image hold functions to avoid unnecessary duplicate fluoroscopic image acquisition (13). Also, setting the C-arm to low dose and using pulsed fluoroscopy has resulted in significantly decreased radiation dosages. Switching to the low dose setting has been shown to decrease radiation dosage per case by 57% (14). Limiting pulses to 4 frames per second has decreased total fluoroscopy time for ureteroscopy from 109.1 to 44.1 s ($P < 0.001$) (15). Even using 1 frame per second is feasible and results in significantly decreased radiation exposure (16). Unsurprisingly, switching to lower frames per second also reduced surgeon radiation dosimeter measurements by 60% (17). In addition, we encourage foot pedal control by the surgeon, establishing a common terminology with the radiation technologist pre-operatively, and having the technologist mark the floor to demonstrate the appropriate C-arm position for bladder and kidney images. We find these steps minimize fluoroscopy usage when transitioning between kidney and bladder images and facilitates seamless turnover between technologists during the case.

Steps have been taken to further eliminate fluoroscopy in ureteroscopy altogether. A group from Turkey published their outcomes performing retrograde ureteroscopy without the use of fluoroscopy, instead utilizing semi-rigid ureteroscopy to verify access to the renal pelvis. They found that without fluoroscopy there was no difference in operative times, complications, or stone-free rates. These authors advocate eliminating the use of fluoroscopy especially in cases when accessing the renal pelvis can first be achieved with direct visualization (18). Ultrasonography has also been shown to be efficacious to help guide ureteroscopy. Deters et al. performed a randomized controlled trial comparing use of fluoroscopic vs. ultrasound guided ureteroscopy. They reported no difference in complication or stone free rates between the 2 groups (19). Additionally, Olgin et al. conducted a small, randomized controlled trial comparing the outcomes of fluoro-less ureteroscopy with the use of fluoroscopy, and found that in non-complex cases, forgoing the use of fluoroscopy was safe and efficacious (20).

Lastly, wearing protective equipment such as lead aprons, thyroid shields, and lead glasses is the most obvious way to protect oneself from radiation exposure. However, numerous studies have shown surprisingly variable and, in some cases, very poor compliance with shielding. As few as 50% of surgeons wear thyroid shields in some surveys and no survey has shown higher than 50% of lead eyewear use. Also worrisome is that most endourologists do not even wear a dosimeter to track their exposure to ensure they are within safe exposure ranges (21–23).

PROTECTING YOUR EYES

The eye is a key organ to protect with 3 potential risks during ureteroscopy. First, the eye is especially radiosensitive with one of the known deterministic effects of radiation being the formation of cataracts. Second, the use of laser energy could cause injury. And, finally, there is risk to the eye of exposure to bodily fluids. In a large review of the existing literature Doizi et al. reported that surgeon eye lens radiation dose ranged from 2.97 to 100 uSv per ureteroscopy. The reported long-term doses of radiation that lead to cataract formation range from 2,500 to 6,500 mSv (24). Over the entirety of a career assuming a mean dose of 0.208 mSv per case, averaging 20 cases per month, it would take about 50 years to reach the minimum threshold for cataract formation (25). Thus, the threshold for cataract formation is not likely to be reached over the career of the general urologist. However, high volume endourologists could be at risk. Lead glasses reduce this exposure by up to 95% and, also protect against other exposures which will be subsequently discussed (26).

Second, the safety of the use of laser energy to treat urolithiasis has been looked at extensively. Althunayan et al. report that eye injuries account for 37.9% of all adverse events related to laser usage. It should be noted that the degree of these injuries ranges from mild corneal abrasions to complete vision loss, with no reported eye injuries when eye protection was worn (27). Villa et al. studied the effect of holmium laser on eyes using an *ex vivo* animal model on pig eyes with various laser settings. The authors reported no injuries >5 cm from cornea (regardless of settings and time of lasering), and no injuries with laser safety glasses or with regular eyeglasses. They concluded regular

TABLE 1 | Depth of tissue penetration by type of laser (29–34).

Type of laser	Depth of tissue penetration (mm)	Wavelength (nm)
Thulium:YAG	0.5–2	1,910
Holmium:YAG	0.5–1	2,100
KTP:YAG	1	532
ND:YAG	5–6	1,064
Diode	8–9	810–830

TABLE 2 | Ergonomic recommendations by body region (35, 36).

Head	Monitors should be placed at eye level directly in front of the surgeon
Upper body	Elbows should be bent between 90 and 120 degrees with the arms abducted no further than 30 degrees away from the body
Hands	Finger grip of ureteroscope is preferrable to a "palm" grip with the wrist and finger muscles primarily used to maneuver the scope
Lower body	Distribute weight evenly and dorsiflex no >25 degrees when using foot pedals

eyeglasses are as effective as laser safety glasses for protecting eyes from holmium laser exposures (28). There are no reported eye injuries with holmium or thulium lasers. However, it is recommended to wear eye protection to cover the adequate wavelength with neodymium-doped yttrium aluminum garnet (Nd:YAG), potassium titanyl phosphate (KTP), and diode lasers as there has been reported eye injuries with these modalities due to their depth of tissue penetration and shorter wavelength (**Table 1**) (27). Lasers with shorter wavelengths, specifically near that of visible light (400–780 nm), can cause more damage such as thermal retinal injury and photokeratitis, than those with longer wavelengths (37).

Third, is the risk of surgeon exposure to bodily fluids. Wines et al. found that surgeon eye exposure to patient blood droplets is as high as 50% during ureteroscopy (38). Fortunately, the risk of infectious disease from this degree of exposure is very low and limited to a few case reports. Strikingly, on a recent survey by Paterson, nearly 28% of urologists do not wear eye protection during ureteroscopy, while 40% wear laser goggles and 23% wear regular eyeglasses (39). It should be noted that this study was conducted in the pre-COVID era.

In summary, eye protection should be worn during ureteroscopy. The degree of eye protection varies depending on the case being performed. Plastic face-shields or glasses are appropriate for cystoscopy and holmium laser usage. However, when using lasers such as the diode, KTP, NG:YAG specialized glasses to cover that laser's wavelength should be considered. For high volume endourologists using extensive fluoroscopy for >20 cases per month, lead glasses should be considered to decrease the risk of long-term cataract formation.

IMPROVING SURGICAL ERGONOMICS

Surgeons maintain prolonged static postures and place their body under various biomechanical stresses to operate. This stress leads to fatigue, discomfort, and in the worst cases, injury. Across all specialties roughly half of all surgeons will develop injuries significant enough to seek medical care, 1 in 3 will decrease case volume, and 1 in 5 will miss work due to an injury (40, 41). In a study by Elkoushy et al., 64% of endourologists reported orthopedic related discomfort, with greatest prevalence in endourologists 40 years of age and older who had practiced for >10 years. The most common complaints were back problems (38.1%), neck problems (27.6%), hand problems (17.2%), and hip/knee problems (14.2%) (42). These complaints occur at an increased rate compared to our non-procedural peers. Healy et al. found that 32% of endourologists had hand/wrist complaints compared with only 19% of psychiatrists. The authors also report that surgeons who used counterintuitive ureteroscope deflection were significantly more likely to have complaints (56%) compared with those who used intuitive deflection (27%) (43). Unfortunately, 1 in 10 urologists reports ultimately needing corrective surgery to address these issues (44). Past research has shown it takes ∼5 years among workers with highly repetitive hand activities to develop problems like tendonitis (44). Awareness is key to preventing long term disabilities.

Certainly, more ergonomic platforms such as the Avicenna Roboflex™ would help with these issues but they are not currently widely available (45). However, use of various types of endoscopes and their effect on ergonomics has been researched. Ludwig et al. measured surgeon biomechanics via EMG placement on 7 different upper extremity muscle beds and compared the differences in muscle activation when using 3 different ureteroscopes: Lithovue, Flex-X^C, Flex-X^2. The most highly activated muscles were the thenar groups and the extensor carpi ulnaris; overuse of the latter can result in the common condition of tennis elbow. They reported that digital ureteroscopes resulted in less muscle activation and therefore less surgeon fatigue and better ergonomics, likely attributable to the decreased weight of these scopes (46).

Ultimately, surgeons have control over their own body positioning in addition to the position of the patient and can take steps to improve their own ergonomics (**Table 2**). It is important to be comfortable. In an excellent review, Gabrielson et al. details the ideal ergonomics during ureteroscopy. The display monitors should be positioned directly in front of the surgeon at eye level to allow for <30 degrees of neck angulation and at a distance of 80–120 cm away. The upper body should be in a neutral position, with elbows bent between 90 and 120 degrees with the arms abducted no more than 30 degrees (35). A finger grip of the ureteroscope is preferable to a palm grip (36). The surgeon should then primarily engage wrist and finger muscles to maneuver the scope and avoid large inefficient movements of the shoulders or elbows. Additionally, dorsiflexion during foot pedal use should be limited to <25 degrees (35). It is important to distribute weight evenly when using a foot pedal.

Alternating feet throughout the case can ease stress as well. If lead aprons must be used >10 h per week then 2-piece lead aprons are recommended and have been shown to improve weight distribution (47).

LIMITATIONS

There are several limitations of this review. First, adverse events are known to be underreported due to the voluntary nature of reporting thus it is difficult to characterize the true magnitude of the risks posed by these hazards. Second, many of the studies cited were conducted at a single institution thus, their results may not be generalizable due to unique practice environments. Finally, studies seeking to assess and quantify the degree of orthopedic and other issues that arise from posture issues are subjective, survey based, and thus inherently fail to capture the entire cohort that authors seek to characterize. Despite these limitations we sought to describe several known work-place hazards for the urologist, the degree of potential risk of these hazards, and provide easy to implement solutions to mitigate these hazards.

CONCLUSION

Urologists are at risk for occupational radiation exposure and bodily injury. Procedures to mitigate this risk should be undertaken at all times including donning of lead aprons, eye protection, and maintaining ergonomic posture. In addition, keeping radiation use as low as reasonably achievable "ALARA" improves safety not only for the urologist but also for our patients and support staff.

AUTHOR CONTRIBUTIONS

DM and MS: manuscript writing and literature review. All authors contributed to the article and approved the submitted version.

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Developments in Ureteral Stent Technology

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Ureteral stents have been utilized for decades in maintaining ureteral patency, most commonly after ureteroscopy in the treatment of urolithiasis. Since their initial development, ureteral stents have had many technological advances that have allowed for better patient outcomes with improvements in comfort, durability, patency, encrustation resistance, biocompatibility, ease of insertion, migration, and biofilm development. Several new ureteral stents enter the market every year, each with their own touted benefits. It is essential to understand the different advantages for each ureteral stent to provide the best available care to patients when possible. The purpose of this review is to give a brief history of ureteral stent development and summarize the recent developments in ureteral stent designs. We aim to review the data supporting the clinical advantages of the latest ureteral stents available for use by urologists.

Keywords: ureteral stent, silicone, ureteroscopy, urolithiasis, kidney stones

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INTRODUCTION

Ureteral pigtail stents were first introduced in 1978 and have been in use for decades to maintain ureteral patency (1). They are frequently used peri-operatively in the management of urolithiasis, as well as other ureteral conditions, to prevent or treat ureteral obstruction. While stents have known side effects including patient discomfort, biofilm and encrustation, urologists continue to use them routinely after upper urinary tract endoscopy to relieve and/or prevent obstruction and to cause passive dilation of the ureter. Given the frequent use of stents in endourologic practice, it is important to understand the properties of the various stents available with respect to patient discomfort, biocompatibility, migration, ease of insertion, encrustation, and biofilm development. There has been a tremendous amount of work in this space to try and create the "ideal" stent, however the holy grail of stents has still not been developed. Since the introduction of ureteral stents, several different kinds have been developed with different compositions, coatings and designs which all have different clinical impacts.

Silicone was used as the initial polymer for ureteral stents when they were first introduced. Several advantages of silicone material have been reported including its soft composition, biocompatibility (2) and lower encrustation rates (3) than other stent materials. Despite these advantages, silicone stents were previously deemed impractical due to both the high frictional coefficients making placement difficult and lower tensile strength (2). More recently, advances in technology have allowed for modern silicone stents to be developed with stronger tensile strengths, but still with softer compositions, potentially allowing for less stent-related discomfort (4). Coating of the silicone stents with hydrophilic material has allowed for easier stent placement (5). For these reasons, modern silicone stents have emerged as the latest ureteral stents which come with several significant advantages. Other new stents introduced recently include the pigtail suture stent (PSS) where the distal portion of the stent is a 0.3 Fr suture that terminates in the bladder and the Tria^{TM} stent which has a hydrophobic coating to decrease encrustation and biofilm.

The goal of this review is to discuss the latest developments in ureteral stent technology and their potential roles in clinical urologic practice.

TRIA™ STENTS

One of the new ureteral stents developed is the Tria™ stent with Percushield™ coating (Boston Scientific). The main advantage of this stent design is a novel nonionic, smooth, hydrophobic inner and outer Percushield™ coating that claims to reduce adhesion with calcium and magnesium salts to prevent stent encrustation. The initial study was done on an *in vitro* model with the Tria™ stents ($n = 15$) incubated in sterile urine baths and in *Proteus mirabilis* bacterial infection urine baths for 2 weeks. There was reportedly significantly less deposition of calcium and magnesium salts in both sterile and *Proteus* urine baths compared to competitor stents ($n = 15$) (**Table 1**) (Boston Scientific 2021). Currently, there is a lack of studies directly comparing rates of ureteral stent encrustation among various stents (6). A recent study ($n = 84$) compared the 14-day encrustation rates between Tria Ureteral Stents with Percushield™ to the Polaris Ultra ureteral stents with HydroPlus coating™ (Boston Scientific). Using micro-CT to measure encrustation rates, the Tria™ and Polaris Ultra™ stents had comparable inner encrustation volume ($p = 0.183$) and had similar outer/total surface encrustation volumes at 14 days. Interestingly, this is the first study to employ a micro-CT method in analysis of ureteral stent encrustation. One limitation of this study is the short follow-up period of 14 days as encrustation becomes more of a concern with longer dwell times. There are no other published studies examining the rates of encrustation with Tria™ stents *in vivo*. The benefit of the Tria™ stent is that it is similar to other polyurethane stents, so it is very easy to place. It also comes in two different tensile strengths as either a firm or soft stent. The firm stents are theoretically better for obstruction from extrinsic compression vs. the softer stent is theoretically more comfortable for the patient. Further long-term data is needed to determine the efficacy of the Tria™ stents in preventing encrustation compared to other ureteral stents.

PIGTAIL SUTURE STENT

More recently, a newer type of ureteral stent was developed to help with ureteral stent symptoms called a pigtail suture stent (PSS) where the distal portion of the stent is a 0.3 Fr suture that terminates in the bladder (Jfil™ stent, Rocamed). The concept of this design was derived from the theory that the distal curl in the bladder is related to stent colic, stent reflux, and irritative lower urinary tract symptoms. A prospective cohort study with 78 patients was done with JFil™ vs. a conventional hydrophilic double pigtail stent (Vortek™, Coloplast) following flexible ureteroscopy for stone treatment (7). Stents were removed 2 weeks after surgery. Ureteral stent symptom questionnaire (USSQ) pain scores were done 2 days, 2 weeks, and 6 weeks after surgery. Urinary Symptom Index USSQ scores were significantly lower in the PSS group at 2 weeks ($p = 0.022$) and 2 days ($p = 0.001$). Additionally, overall visual analog scale pain scores ($p = 0.002$), body pain scores ($p = 0.021$), and general health index score ($p = 0.036$) were significantly better in the Jfil™ group compared to the double pigtail stent group. After the 2-week scores were adjusted for baseline scores (6 week after surgery), the above scores remained statistically significant in favor of the Jfil™ group. Importantly, the patients in the Jfil™ group reported significantly lower scores for urinary frequency, sensation of incomplete emptying, and burning while voiding. There were no cases of stent dislodgement or worsening hydronephrosis reported in either group, suggesting that the Jfil™ stent was effective in preventing ureteral obstruction, despite having a suture for the distal portion of the stent.

There are two key limitations with the Bosio et al. study. One is that they used polyurethane stents as the direct comparison, while it is known that polyurethane stents are not necessarily the best stents for preventing stent related symptoms. Additionally, as pointed out by Ventimiglia et al. in a letter to the editor, the authors placed Jfil™ stents in patients after uncomplicated ureteroscopy, when in fact current EAU guidelines recommend no ureteral stent placement after uncomplicated ureteroscopy (although still commonly performed globally).

Another randomized controlled study found significantly lower pain scores and analgesic requirements in a PSS group compared to a conventional polyurethane double pigtail stent after uncomplicated URS for symptomatic ureteral stones (8). This new type of ureteral stent may be effective following flexible ureteroscopy while also reducing stent-related symptoms compared to other ureteral stents (9). They also reported clear ureteral dilation in all 28 of the patients who had PSS placed after a 1 month indwelling period. There has been one other study to date examining the effects of PSS on passive ureteral dilation. Majdalny et al. (10) placed PSS in pig ureters and found on POD13-15 that there was ureteral dilation in 5 of 6 ureters stented with PSS. This passive ureteral dilation may help facilitate access prior to ureteroscopy or postoperatively to facilitate stone fragment/dust passage after the stent is removed. Further studies are needed to definitively state whether pigtail suture stents can safely be used after ureteroscopy and if they lead to less stent related symptoms when compared to the most comfortable stents currently available.

TABLE 1 | Differences in rates of combined calcium and magnesium encrustation for Tria™ Soft (Boston Scientific) ureteral stents compared to competitor stents at 2 weeks.

	Bard Inlay Optima™	Coloplast Imajin™	Cook Black Silicone™
Sterile urine bath	−60%	−52%	−48%
Proteus urine bath	−19%	−45%	−14%

All changes were reported to be statistically significant, but p-values were not provided (Boston Scientific website 2021).

BIODEGRADABLE STENTS

One of the recent developments in ureteral stent technology is the biodegradable stent, which is designed to dissolve in urine over time. These stents have wide-ranging advantages such as avoiding a second operation or procedure to remove stents and to avoid the feared complications of a forgotten stent. Many different biodegradable stents have been developed over the past few decades with the first reported in 2002 and 2003 (11, 12), but none have been able to show consistent degradation without complication over time *in vivo*. More recently, a group in Portugal has developed the HydrUStent™, which is made from an aqueous solution of gelatin-alginic-acid sodium salt and bismuth carbonate basic. These stents have only been tested in porcine models, although they promisingly showed all stents dissolved after 10 days (13). Another model used glycomer 631 and pure polyglycolic acid in a novel stent that dissolved completely after 3–6 weeks in porcine models without any complications at 5-month follow-up (14). This year, a new stent made from biodegradable polyurethane, magnesium, and calcium were showed to dissolve completely after 4 weeks in a porcine model (15). The clinical studies surrounding these types of stents is very limited with further need for human studies before utilization of these stents can be justified. However, this is a promising technology which may have several advantageous implications in the future.

MODERN SILICONE STENTS

Modern silicone stents have been developed with properties like polyurethane stents which increase ease of placement but still with softer compositions and improved biocompatibility compared to polyurethane. The softer compositions are thought to lead to better symptomatic outcomes for patients (16). Given the recent emergence of these modern silicone stents, there is a paucity of data surrounding the clinical impact of these stents on patient outcomes compared to other stents. Wiseman and associates performed a single-blinded, randomized multicenter study examined the effects of quality of life after placement of hydrocoated silicone ureteral stents (Imajin Hydro™, Coloplast) vs. hydrocoated nonsilicone ureteral stents (Percuflex Plus™, Boston Scientific) after flexible ureteroscopy (17). In the group of 141 eligible, randomly assigned patients, the silicone group had significantly lower USSQ scores compared to the nonsilicone group (18.7 vs. 25.1, $p = 0.015$) at postoperative day 20 (POD20) (**Table 2**). After normalizing the pain scores to consider differences in score reports between men and women, the differences remained significant ($p = 0.013$). Other urinary symptom scores were also significantly lower in the silicone group at POD20 (26 vs. 31). Safety outcomes were similar between the two stent groups. Although it was a relatively small study, the results suggest the modern silicone Imajin Hydro™ stent offers a safe option with lower pain and urinary symptom scores following flexible ureteroscopy when compared to nonsilicone Percuflex Plus™ stents. One of the limitations of this study is that a standard 26 cm length was used in all patients, which may affect stent-related pain for patients with different heights or ureteral lengths. A criticism of the study was that stents were left in patients for several weeks, where the benefit was most significant, as opposed to the typical dwell times of 5–10 days following stone treatment. Similarly, Gadzhiev et al. performed a small randomized study which found that silicone stents (Black Filiform™, Cook Medical) were associated with lower visual analog scale pain scale scores at 2 weeks ($p = 0.023$) and prior to stent removal at 4 weeks ($p = 0.001$) compared to polyurethane stents (Rüsch, Teleflex) (**Table 2**) (4).

TABLE 2 | Silicone ureteral stents vs. non-silicone ureteral stents in pain scores and biofilm/encrustation formation (4, 17, 18).

Author		Silicone stents	Non-silicone stents	*p*
Wiseman et al. (17)		**Imajin Hydro™ (Coloplast)**	**Percuflex Plus™ (Boston Scientific)**	
	USSQ body pain scores @ Day 20	18.7 (11.4)	25.1 (14.2)	0.015
	Gender normalized scores	19.2 (11.9)	26.0 (15.1)	0.013
Gadzhiev et al. (4)		**Black Filiform™ (Cook Medical)**	**Polyurethane (Rüsch, Teleflex)**	
	Visual analog pain scores @ Day 14	1.1	2.4	0.0223
Barghouthy et al. (18)		**Imajin Hydro™ (Coloplast)**	**Percuflex Plus™ (Boston Scientific)**	
	Rate of surface biofilm (global) @ Day 20	0.93 (0.09)	1.24 (0.08)	0.0021
	Rate of surface encrustation (global) @ Day 20	0.78 ± 0.11	1.22 (0.10)	0.0048

Another essential aspect of stent practicality is the rate of biofilm formation and stent encrustation since they are common causes of stent obstruction and infection (19) sometimes requiring complex interventions to change or remove. Barghouthy et al. (18) underwent complex analysis of the Imajin Hydro™ (Coloplast) and Percuflex Plus™ (Boston Scientific) stents that were removed on POD20 for formation and encrustation. The rates of biofilm formation on the internal and external parts of the stent were 25% lower ($p = 0.002$) in the silicone stents. The rate of encrustation was 36% lower in the silicone group ($p = 0.004$) as well (**Table 2**). Only in the ureteral shaft portion of the stent did the two types of stents have similar rates of encrustation and biofilm formation. This study helped clearly demonstrate the advantage of silicone stents over non-silicone stents with respect to encrustation and biofilm formation rates. Interestingly, these significant differences did not translate into different rates of UTIs since they were similar in both groups (5). In another study, silicone stents were found to have significantly lower rates of encrustation and biofilm development in stone formers compared to polyurethane stents (20). In an *in vitro* model with 5 different types of stents soaked in artificial urine for 14 weeks, silicone stents were found to have significantly lower rates of encrustation with struvite and

TABLE 3 | Recommendations for different novel ureteral stent options based on various indications.

Indication	Newer stent options*	Reasoning
Stenting after ureteroscopy	Coloplast Imajin Hydro™ Cook Black™	Silicone stents offer softer compositions and potentially lower stent related symptoms, lower rates of encrustation and biofilm
	Tria Soft™	Tria Soft™ likely more comfortable than the Tria Firm™ with decreased risk of encrustation
	J-fil™	Decreased stent reflux and irritative lower urinary tract symptoms
Obstructing ureteral and/or renal stone	Coloplast Imajin Hydro™ Cook Black™	Increased comfort, decreased risk of encrustation/biofilm for longer dwell times
Pyonephrosis	Tria Soft™	
Malignant ureteral obstruction	Tria Firm™	Longer lasting with reported lower risk of encrustation. Avoid silicone as it is not rigid enough to resist severe extrinsic obstruction
Ureteral stricture	Coloplast Imajin Hydro™ Cook Black™ Tria Soft™ Tria Firm™	Longer lasting with reportedly lower encrustation rates; potential for increased comfort

**There are many current stent options that will also function in these clinical scenarios, however the focus of this table are on the newer stent technologies specifically discussed in this article.*

hydroxyapatite compared to all other stents (Polyurethane, HPU, Percuflex, Silitek) (21). This effect is thought to be due to the uniform surface. Based on the current literature, silicone stents have been associated with lower rates of encrustation and biofilm development than other stent types.

Historically silicone stents were abandoned due to the difficulty in placing the stent over a guidewire. The modern silicone stents with hydrophilic coatings are now able to be placed over a guidewire. When deploying a 6 Fr silicone stent, it is best to use a hydrophilic guidewire to enable placement, as the smaller lumen will not easily pass over PTFE-coated (polytetrafluoroethylene) or hybrid (PTFE-Nitinol) guidewires. In contrast, the 7 Fr and 8 Fr stents can be placed over a standard hybrid guidewire, but still easiest when placed over a hydrophilic guidewire. In our experience, when placing a silicone stent, it is helpful to submerge the stent in saline to optimize the hydrophilic coating and apply a small amount of lubrication to the stent and/or wire to ease the placement when using a non-hydrophilic guidewire.

HOW TO CHOOSE THE RIGHT STENT

The ideal stent is one that causes minimal to no discomfort, causes minimal urinary symptoms, has no encrustation or biofilm formation, is easy to insert, and is radiopaque. While there is currently no stent on the market that is perfect, the modern silicone stent seems to provide some of the properties of the ideal stent based on the available research. The additional newer stents require more clinical investigation but may prove to be just as useful in a urologist's armamentarium. **Table 3** shows our recommended types of newer ureteral stents based on various indications for ureteral stenting. The times in which silicone are less ideal is in cases of extrinsic compression causing obstruction or difficult strictures due to the decreased tensile strength of silicone compared to other stents. In those cases, polyurethane stents, stents with wire-reinforcement, or possibly metallic stents are better suited. In general, stents are uncomfortable and as urologists we should use strategies to optimize patient comfort and decrease the costs and decreased quality of life associated with stent bother. This includes minimizing stent dwell time, use of adjunct medication to help with stent colic, and going stent-free when safe. Patient education and setting expectations also remains a crucial component in preventing unnecessary costs from stent bother. Further research into stent technology is needed to continue to optimize the patient experience and to create the ideal stent.

AUTHOR CONTRIBUTIONS

JL and MK contributed to literature search and writing. OS contributed to conception, literature search, and writing. All authors contributed to the article and approved the submitted version.

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REVIEW
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Management of Nephrolithiasis in Pregnancy: Multi-Disciplinary Guidelines From an Academic Medical Center

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Introduction: The management of nephrolithiasis during pregnancy can be stressful for urologists due to concerns for investigations and treatments that may pose risk of fetal harm, and unfamiliarity with optimal management of these complex patients. In response, we created multi-disciplinary evidence-based guidelines to standardize the care for obstetric patients presenting with flank pain and suspicion for nephrolithiasis.

Methods: A multi-disciplinary team involving Urology, Obstetric Anesthesiology, Obstetrics and Gynecology, Diagnostic Radiology, and Interventional Radiology from a single academic medical center was assembled. A PubMed search was performed using keywords of pregnancy/antepartum, nephrolithiasis/calculi/kidney stones, ureteroscopy, non-obstetric surgery, complications, preterm delivery, MRI, computerized tomography, renal bladder ultrasound (RBUS), and anesthesia to identify relevant articles. Team members reviewed their respective areas to create a comprehensive set of guidelines. One invited external expert reviewed the guidelines for validation purposes.

Results: A total of 54 articles were reviewed for evidence synthesis. Four guideline statements were constructed to guide diagnosis and imaging, and seven statements to guide intervention. Guidelines were then used to create a diagnostic and intervention flowchart for ease of use. In summary, RBUS should be the initial diagnostic study. If diagnostic uncertainty still exists, a non-contrast CT scan should be obtained. For obstetric patients presenting with a septic obstructing stone, urgent decompression should be achieved. We recommend ureteral stent placement as the preferred intervention if local factors allow.

Conclusions: We present a standardized care pathway for the management of nephrolithiasis during pregnancy. Our aim is to standardize and simplify the clinical management of these complex scenarios for urologists.

Keywords: pregnancy, kidney stones, nephrolithiasis, obstetric, ureteroscopy

INTRODUCTION

Nephrolithiasis is the most common non-obstetric indication for hospital admission in obstetric patients (1). It is estimated to occur in 1:200 to 1:1,500 pregnancies and can cause complications for the fetus and the mother including: pre-term labor, premature delivery, infectious complications, loss of kidney, or even loss of the fetus (1–3). Due to the potential negative outcomes for the mother and fetus and fears of litigation, management of nephrolithiasis during pregnancy can be anxiety provoking for urologists.

During pregnancy there is a physiologic increase in the glomerular filtration rate as well as elevated 1, 25 Dihydroxy Vitamin D levels. These two factors result in hypercalciuria (4) and rapid encrustation of ureteral stents or percutaneous nephrostomy tubes that may be placed for obstructing upper urinary tract stones. The high rate of encrustation necessitates frequent tube exchanges and repeated exposures to anesthesia (5, 6), which carries risks of aspiration, hypotension, and pre-term labor to the mother and fetus (7). Thus, there has been increased interest in performing primary ureteroscopy, which would avoid indwelling tubes and the need for repeat anesthetic exposures.

Due to concerns of radiation exposure to the fetus, renal bladder ultrasound (RBUS) is the diagnostic modality of choice during pregnancy (8). However, during pregnancy there is a physiologic hydronephrosis that occurs secondary to progesterone induced smooth muscle relaxation and compression of the ureter by the gravid uterus (5), which reduces the diagnostic utility of RBUS. While non-contrast computed tomography (NC-CT) of the abdomen/pelvis is the gold standard for diagnosing urinary stones and can safely be obtained during pregnancy (9), many urologists are apprehensive to order tests using ionizing radiation due to fear of litigation. Thus, diagnosis of nephrolithiasis during pregnancy can be difficult.

In our institution the on-call management of the obstetric patient with acute flank pain and suspected renal colic was determined to be variable, with concern among faculty as how to manage these patients appropriately in a stepwise fashion. As a result, a multi-disciplinary team assembled with the goal to create evidence-based, comprehensive set of guidelines to guide urologists in the management of nephrolithiasis during pregnancy.

METHODS

We performed a comprehensive PubMed? search for articles published in the English language from 1990 to 2020 using keywords: pregnancy/antepartum, nephrolithiasis/calculi/kidney stones, ureteroscopy, non-obstetric surgery, complications, preterm delivery, MRI, computerized tomography, renal bladder ultrasound (RBUS), and anesthesia to identify relevant original research articles and reviews. Additional publications were identified by reviewing the reference lists of pertinent articles identified on the initial literature search. A multi-disciplinary team involving Urology, Obstetric Anesthesiology, Obstetrics and Gynecology, Diagnostic Radiology, and Interventional Radiology was assembled. Individuals of our multi-disciplinary team reviewed their areas of expertise. A total of 54 articles (listed in **Appendix A**) were reviewed in detail and 47 were included in the formation of these guidelines (shown in the references).

RESULTS

A total of 11 guideline statements were constructed; four to guide diagnosis and imaging, and seven to guide intervention.

Part 1: Initial Work Up/Imaging

Recommendation 1

The management of the gravid patient with suspected symptomatic nephrolithiasis should emphasize a multidisciplinary approach, with early involvement of obstetrics, radiology, and anesthesiology teams. The on-call urology team and the on-call obstetrics (OB) team should also be notified when the patient first presents. The OB service can make recommendations regarding need for deep vein thrombosis (DVT) prophylaxis while patients are admitted (10). *Clinical principle*.

Recommendation 2

Initial evaluation should include patient history, relevant obstetric and pregnancy history, physical exam, urinalysis with reflex urine culture, basic metabolic panel, and complete blood count (**Figure 1**). Fetal monitoring may be initiated based on gestational age as determined by the OB service. *Clinical principle*.

Recommendation 3

RBUS should be the first line imaging modality for obstetric patients presenting with renal colic suspicious for obstructing nephrolithiasis. Elements of a high-quality report include renal indices and evaluation of ureteral jets. Transvaginal ultrasound can be considered for more accurate imaging of distal ureteral stones. *Strong recommendation, Evidence Strength A*.

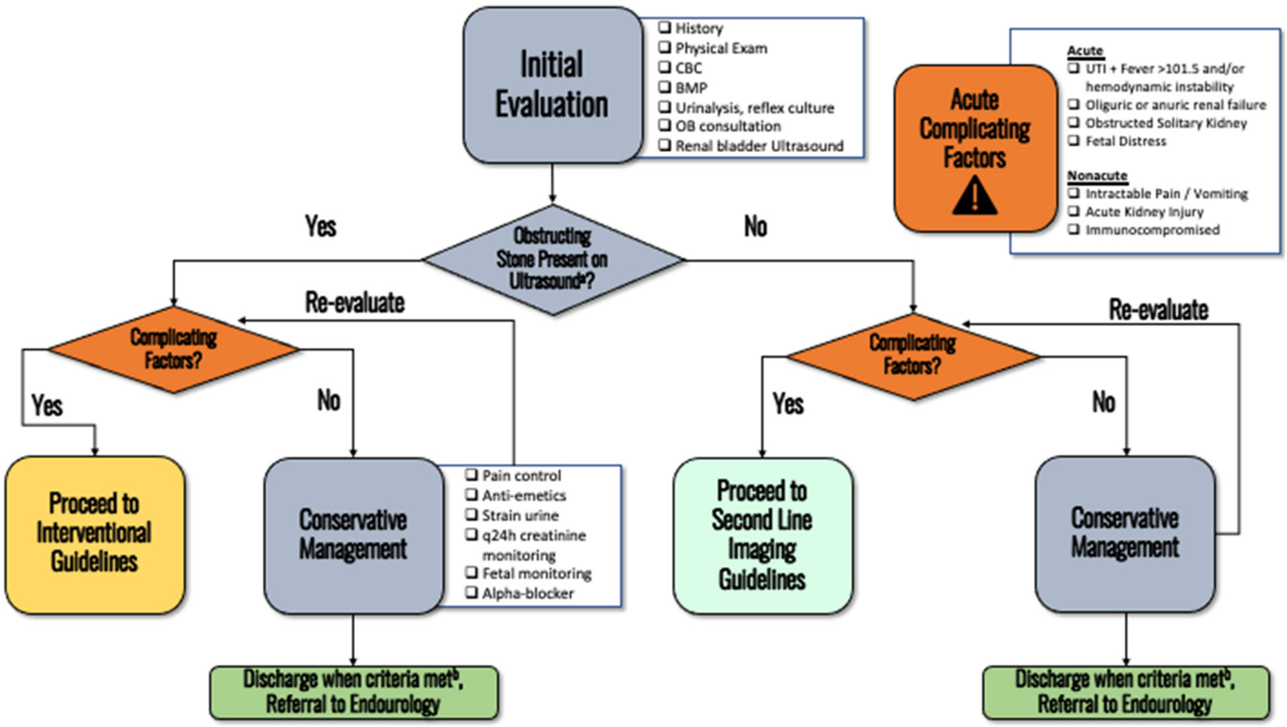

FIGURE 1 | The initial evaluation of an obstetric patients presenting with nephrolithiasis. **(a)** Pain is adequately controlled on oral pain medications, nausea well controlled and able to eat/drink, no AKI and stable creatinine, afebrile, non-concerning fetal monitoring. **(b)** When more emergent diagnosis is not needed. Consider performing doppler for RI, ureteral jets, or transvaginal ultrasonography (if distal stone suspected) if not already performed on initial ultrasound.

Recommendation 4

If the diagnosis of obstructing nephrolithiasis remains uncertain and there is a change in clinical status of the patient that would otherwise necessitate interventional management, second line imaging should be offered.

In the acute clinical setting (fever, hypotension, or considering intervention for intractable symptoms), a low dose non-contrast CT should be obtained. *Strong recommendation, Evidence Strength A*.

In the non-acute setting, repeat RBUS, non-contrast MRI with HASTE, or non-contrast CT (NC-CT) should be discussed as second-line options (see discussion–**Figure 2**). Ultimately, the next choice of imaging modality should be based on shared decision making with the patient as there are risks and benefits to each, as discussed below. If the patient has already been exposed to multiple irradiating studies throughout the pregnancy, consultation with a medical physicist from radiology (if available) to help inform the clinical decision should be considered. *Conditional recommendation, Evidence Strength C*.

Part 2: Intervention

Recommendation 5

If a patient's symptoms can be managed with analgesics and there are no complicating factors, a trial of passage with hydration and analgesia is warranted. Medical expulsive therapy appears to be safe (**Figure 1**) (11). Patients failing medical expulse therapy should follow up with the Urologist to discuss ureteroscopy. *Strong recommendation, Evidence Strength B*.

Recommendation 6

If there is **concern for a septic obstructing stone, urgent collecting system decompression is required with ureteral stent placement**, this recommendation holds regardless of gestational age (see discussion–**Figure 3**). Stenting is safer for the patient and the fetus given that percutaneous nephrostomy (PCN) placement would require prone positioning (difficult to access airway and perform fetal monitoring). Furthermore, obstetric patients are a high aspiration risk due to mechanical changes from the gravid uterus and the effects of progesterone including impaired gastric motility and lower esophageal sphincter tone. See discussion section for full details as to why we recommend first-line stenting over PCN placement. *Expert opinion*.

For obstetric patients that have been counseled by an obstetrician and recommended to have intra-operative fetal monitoring, stent placement should be performed in the proximity of specialties such as anesthesia, obstetrics, and neonatology. *Clinical principle*.

For patients with prior GU reconstruction (e.g., conduit, neobladder, transplant kidney), or a stone large enough to require future percutaneous nephrolithotomy, percutaneous nephrostomy (PCN) tube should be the first line intervention (**Figure 3**). Interventional radiology (IR) should be notified when

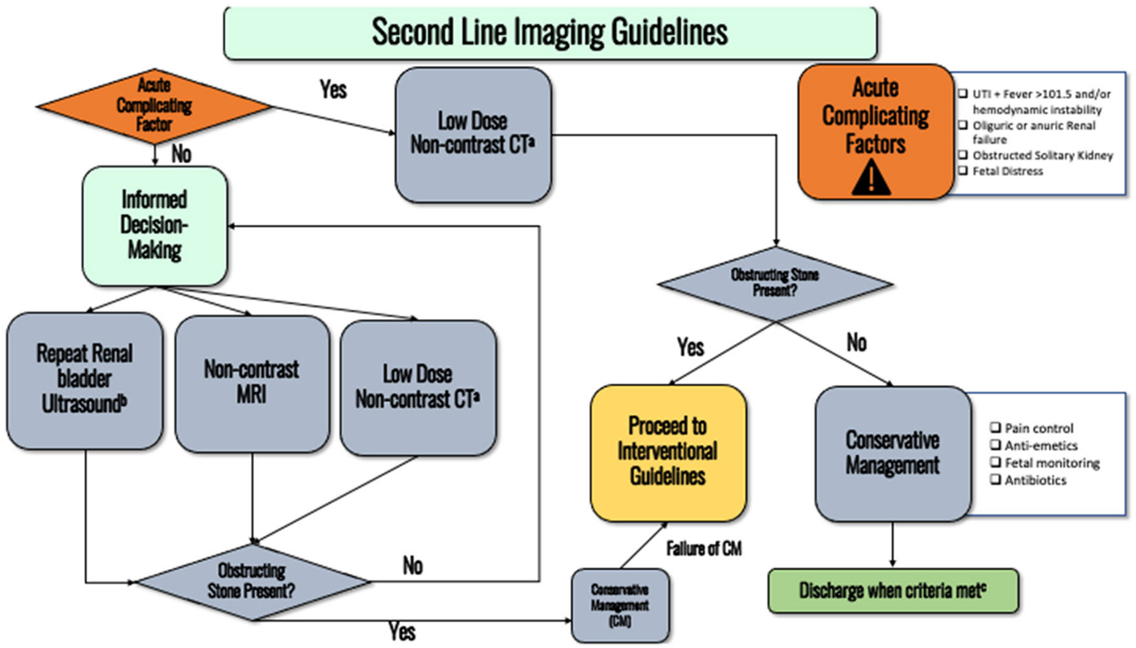

FIGURE 2 | Flowchart detailing the second-line imaging guidelines. **(a)** Consider discussing with medical physicist to ensure lowest possible radiation dose is administered. **(b)** Pain is adequately controlled on oral pain medications, nausea well controlled and able to eat/drink, no AKI and stable creatinine, afebrile, non-concerning fetal monitoring. **(c)** Transvaginal ultrasound can more accurately detect distal ureteral stones.

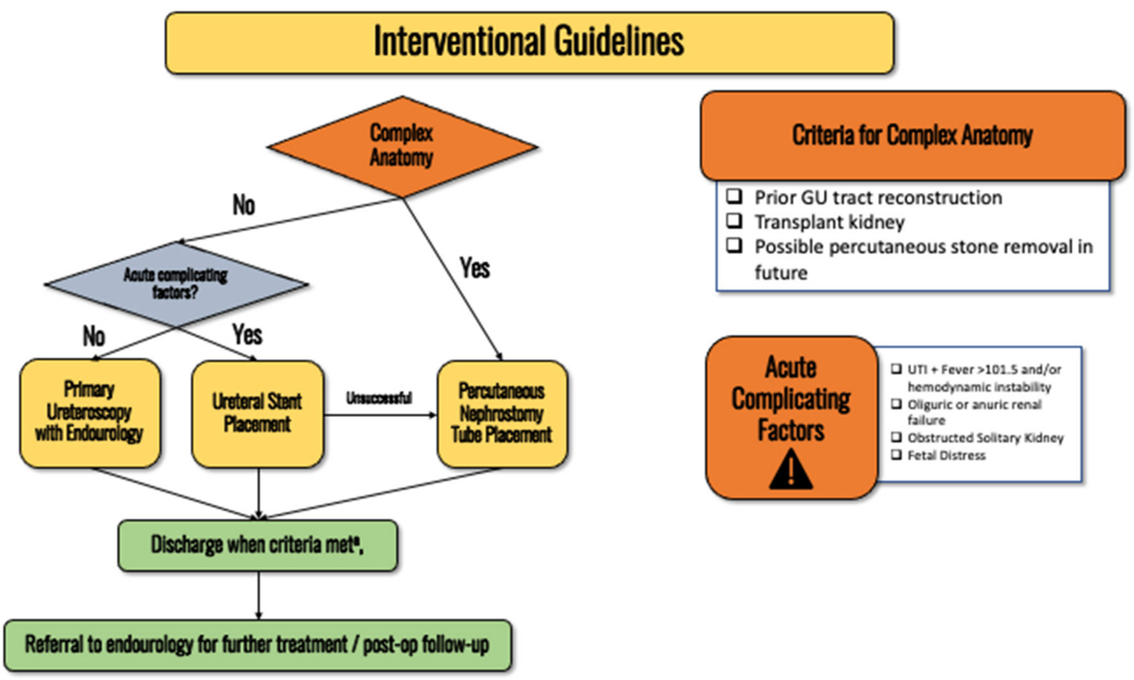

FIGURE 3 | Flowchart detailing the interventional guidelines for obstetric patients with nephrolithiasis. **(a)** Pain is adequately controlled on oral pain medications, nausea well controlled and able to eat/drink, no AKI and stable creatinine, afebrile, non-concerning fetal monitoring.

attempting ureteral stenting so that the patient can be quickly treated by IR if stenting fails. Patients should be consented for both ureteral stent and PCN placement prior to attempted stent placement so IR can proceed with the PCN placement without requiring emergence from anesthesia for the patient to obtain another consent. If the patient refuses to have radiation with fluoroscopy, PCN placement under ultrasound access is an option. *Expert opinion*.

Obstetricians will determine whether intraoperative fetal monitoring is indicated. When appropriate, the OB team will obtain informed consent for possible emergency cesarean delivery, arrange for delivery equipment, and should notify the neonatal intensive care unit. *Expert opinion*.

Recommendation 7

When placed, ureteral stents should be exchanged every 4 weeks until definitive management is performed. *Strong recommendation, Evidence Strength C*.

Recommendation 8

If conservative management fails, ureteroscopy with laser lithotripsy should be offered as a first-line treatment in non-complex scenarios (refer to interventional flowchart/discussion section for definitions of complexity–**Figure 3**). *Strong recommendation, Evidence Strength B*.

Recommendation 9

Ureteroscopy during the third trimester may be associated with higher rates of pre-term labor, however it should not be excluded as a treatment option. When clinically prudent, the decision to proceed with ureteroscopy should be determined after a discussion between the patient, urology and obstetrics teams occur. The third trimester is from 28 to 40 weeks. Once at 32 weeks gestation, risks to the fetus quickly decline as the pregnancy progresses with similar long-term outcomes as a full-term neonate. Betamethasone for fetal lung maturation may be administered as well as magnesium sulfate for fetal neuroprotection (12). A neonatology consult should be considered. *Moderate recommendation, Evidence Strength B*.

Recommendation 10

If appropriate, neuraxial anesthesia (spinal, epidural, or combined spinal-epidural) is preferred over general anesthesia in obstetric patients given that the physiologic changes of pregnancy increase the incidence of aspiration and difficult airway management. Neuraxial anesthesia also limits fetal exposure to anesthetic agents and medications. However, these considerations do not preclude a patient from receiving general anesthesia when necessary and there is no clear evidence that it poses a greater risk to the fetus. The potential for difficult airway management and aspiration should be considered and anticipated when planning for any type of anesthetic. *Moderate recommendation, Evidence Strength B*.

Recommendation 11

Patients discharged to home with indwelling ureteral stents/PCN tubes or residual stones should have established outpatient follow-up with a urology provider and their obstetric provider. Definitive treatment with ureteroscopy can then be offered as an outpatient. *Expert Opinion*.

DISCUSSION

In this section we discuss the rationale and evidence behind our guideline statements. Furthermore, several flowcharts are also included that provide an easy-to-follow flowchart to assist with diagnostic and interventional management. **Figure 1** summarizes the initial evaluation of a patient presenting with nephrolithiasis during pregnancy. **Figure 2** displays the flowchart for when diagnostic uncertainty exists after obtaining the initial work up. **Figure 3** provides the schema for interventional management.

Part 1: Initial Work Up/Imaging Guidelines

Renal Bladder Ultrasound

RBUS is the preferred first-line imaging modality for the gravid patient presenting with renal colic and suspected obstructing nephrolithiasis given it is non-invasive, widely available, lacks ionizing radiation, and is cost effective (13). Although a useful screening test, the limitations of RBUS should be discussed with the patient. Ultrasound has limited sensitivity (34–95%) and specificity (34%) for obstructive nephrolithiasis in pregnancy (14). Presence of hydronephrosis alone is often not enough to distinguish obstructing urolithiasis from physiologic hydronephrosis. In up to 90% of pregnancies, physiologic hydronephrosis can be present (15).

If not included in the initial report, other findings to discuss with radiology that can improve the discriminative capability of RBUS include the presence/absence of ureteral jets or presence of elevated resistive indices (RI). To prevent false positives, ureteral jets are best evaluated with a well hydrated patient while they are lying in the contralateral decubitus position (14). Absence of a ureteral jet unilaterally has a sensitivity of up to 100% and specificity of 91% (16). Evaluation of RI can help improve specificity of ultrasound for obstructing nephrolithiasis. Unilateral RI > 0.70 are indicative of acute obstruction within the last 6 h (sensitivity 45%, specificity 91%) and are not typically elevated with hydronephrosis of pregnancy (17). Similarly, a difference in RI between the normal and obstructed kidney of 0.06 has been shown to be 95% sensitive and 100% specific for acute ureteral obstruction in pregnancy (17). If suspecting a distal ureteral stone based on symptoms, transvaginal imaging has also been shown to be more specific for stones located in the distal ureter (18).

CT and Second-Line Imaging Studies

Due to the very low risk of adverse effects from exposure to ionizing radiation during low-dose stone CT, both the American College of Radiology (ACR) and the American College of Obstetrics and Gynecology (ACOG) support the use of abdominal/pelvic CT if medically necessary, even in the first trimester (9, 19). Thus, in scenarios where there is clinical decompensation of the patient and the diagnosis behind renal colic remains uncertain, CT should be considered as the next diagnostic study (**Figure 2**). For all patients, it is considered best practice to use as low as reasonably achievable (ALARA) ionizing radiation. This principle applies during pregnancy as well, as there are studies that suggest theoretical concerns of teratogenesis, cognitive impairment, or other fetal harm associated with using ionizing radiation in pregnancy. However, at the doses commonly prescribed for abdominal CT imaging, this risk is exceedingly low. Radiation doses common to abdominal CT imaging (<50 mGy) have not been associated with any cases of fetal harm (20). It is estimated that doses of 20 mGy increase the lifetime cancer risk to 0.8%, or 40 individuals out of 5,000 (Abdominal CT ranges from 1.5 to 35 mGy. Newer CT machines can achieve very low mGy). These risks are based upon data from animal studies, survivors of nuclear incidents, and cancer patients (9, 21).

Non-contrast CT has the highest sensitivity and specificity for detecting obstructing calculi (22). Presence of an obstructing stone on CT is also associated with highest rates of subsequent positive ureteroscopic findings (23). To adhere to the ALARA principle, low-dose NC-CT should be offered to further minimize radiation exposure. Consultation with a medical physicist (if available) can help to ensure that scans are protocoled to keep radiation doses to a minimum, while maintaining diagnostic accuracy. Consultation with medical physics should be strongly considered when the patient has already been exposed to multiple studies using ionizing radiation previously in the pregnancy.

If the clinical status of the patient does not warrant emergent diagnosis (i.e., patient is not in septic shock or in renal failure), repeat RBUS can be offered to the patient (**Figure 2**). Repeat ultrasound can occasionally identify migrating stones that were initially missed. If not performed on the initial ultrasound, maneuvers such as measuring ureteral jets, RIs, and transvaginal approaches can be used to augment the discriminative capability of ultrasound. This recommendation is based on local expert opinion, as there is a lack of high-quality data on the utility of repeat ultrasound imaging in obstetric patients.

Magnetic resonance imaging (MRI) confers no ionizing radiation and could be performed without contrast to assess for collecting system obstruction (**Figure 2**). A single shot fast spin-echo technique that produces heavily T2-weighted, high-resolution images, e.g., HASTE (HASTE is an imaging sequence trademarked by Siemens (Siemens AG, Munich, Germany) that stands for: Half-Fourier Acquisition Single-shot Turbo-spin Echo) or SS-FSE (Single-shot Fast Spin Echo): the same sequence on GE machines (General Electric Healthcare, Chicago, Illinois), at a higher field strength (1.5 or 3.0 Tesla), can depict collecting system dilatation and perinephric fluid with high specificity. MRI has poor sensitivity for depicting calculi, with only 50% of calculi seen at MRI when compared to CT (24). There is a lack of prospective data validating the utility of MRI. A recent prospective study demonstrated similar positive predictive value (PPV) (calculated using ureteroscopy as gold standard) between MRI and ultrasound (80 vs. 77%), but inferior PPV for MRI vs. CT (80 vs. 95.2%) (23). However, an MRI may not be able to be obtained as quickly as a CT in an emergent scenario (e.g., longer scan time and wait time), making it less useful in urgent situations. There are also theoretical concerns of tissue heating and hearing loss to the fetus when using MRI. Tissue heating can be increased with high specific absorption rate sequences like MRI HASTE/SS-FSE. However, there has been no data to suggest MRI causes significant temperature changes or risks to the fetus, even with the SS-FSE sequences. Tissue heating also decreases as distance increases from the radiofrequency pulses. Nevertheless, the International Commission on Non-Ionizing Radiation Protection (ICNIRP) recommends postponing elective MRI to after the first trimester because of the above theoretical risks (9, 25).

In conclusion, although the effect of ionizing radiation on the fetus from a medical imaging test is uncertain, the radiation dose from a single NC-CT study is very small and the risk to the fetus is considered to be very low. As such, the ACR and the ACOG support the use of abdominopelvic CT for suspected nephrolithiasis if medically necessary, even in the first trimester. In scenarios where the patient is clinically worsening and the diagnosis of renal colic needs to be determined with certainty, NC-CT should be considered as the next diagnostic study.

Discussion Part 2: Intervention

Trial of Spontaneous Passage

It is estimated that 50–80% of stones will pass spontaneously during pregnancy (26, 27). Therefore, conservative management is a reasonable option as long as symptoms are manageable (26, 28, 29). Selective Alpha-1 blockers are category B drugs in pregnancy and thought to be safe (5). Although a small cohort, the safety of alpha1-blocker therapy with tamsulosin was demonstrated in one retrospective study, which showed no significant differences in maternal or fetal outcomes (11). Patients should have established follow up with an urologist to ensure that the stone passes. If conservative management fails, definitive stone treatment "i.e., ureteroscopy" should be offered to prevent long term damage to the obstructed renal unit.

Anesthetic Management

The ACOG Committee Opinion on non-obstetric surgery during pregnancy states "there is no evidence, when given in standard concentrations, that *in utero* exposure to anesthetics is associated with an increased risk of teratogenicity or fetal harm" (30). General and regional (spinal, epidural, and combined spinal-epidural) anesthesia can be safely administered during pregnancy when indicated. However, the physiologic changes to the respiratory and gastrointestinal system during pregnancy increase the risk of difficult airway management and aspiration. Therefore, when feasible, stent placement under regional anesthesia is preferred during pregnancy.

The selection of anesthetic technique for a given surgical procedure should be considered on an individual basis, however, the physiologic changes of pregnancy shift the relative risk and safety of general vs. neuraxial techniques (10). There is an increased risk of difficult airway management in obstetric patients secondary to airway changes including capillary engorgement and tissue friability, increased oxygen consumption, decreased functional residual capacity, rapid desaturation with apnea, and enlarged breasts that can make laryngoscopy challenging (31, 32). Gastrointestinal changes during pregnancy such as decreased lower esophageal sphincter tone and slowing of esophageal peristalsis and intestinal transit increase the risk of gastric aspiration (31, 32). Historically, concerns have been raised regarding neurotoxicity in the developing fetal brain based on animal studies of systemic anesthesia and this may favor regional techniques in the mother to reduce fetal exposure to general anesthetics (10, 33). Despite these concerns, there are circumstances that require general anesthesia for surgery in the obstetric patient and there are no human studies that have demonstrated teratogenicity from anesthetic agents when used in standard concentrations for < 3 h (30). A single center, retrospective, case-control study from 2019 found that patients who received general anesthesia had a small increase in low birth weight in the newborn compared to those who received regional anesthesia, however, this association may simply reflect the patient's underlying condition rather than a direct effect of anesthesia (33). If the clinical condition of the patient and the procedure is amenable to neuraxial techniques, it should be considered to avoid fetal exposure to systemic anesthesia.

More important than the choice of technique is the need to maintain adequate control of hemodynamics and oxygenation throughout the course of the anesthetic. Care should be taken to avoid hypotension, hypoxia, hypercarbia, and hypocarbia (34). Maternal hypoxia results *in uteroplacental* insufficiency and can cause fetal hypoxemia, acidosis, and distress (34). Maternal ventilation should be maintained within the normal $PaCO_2$ of pregnancy, between 30 and 32 mmHg to avoid uterine artery vasoconstriction and resultant fetal acidosis (34). Blood pressure should be maintained by ensuring adequate left uterine displacement "i.e., elevate the right hip 15 or more degrees, if the patient is < 20 weeks gestation or if the uterine fundus is at the level of the umbilicus, and with vasopressors as needed" (12, 18). Phenylephrine is the most commonly used agent to treat maternal hypotension (35).

Volatile anesthetic agents reduce uterine activity, however there is no data to suggest that this is beneficial in preventing preterm labor. Following surgery during pregnancy, the risk of preterm labor is increased and therefore if the fetus is viable, patients should be monitored post-operatively with tocographic and fetal heart rate monitoring per the obstetrician's recommendations (30).

In certain cases, PCN may be a better option. The rationale is: if IR can place the PCN under local anesthesia, ureteral stenting under regional or general anesthesia can be avoided with less systemic and hemodynamic effects. For example, in patients with impending septic shock, regional anesthesia may cause a precipitous decrease in blood pressure. Indeed, septic shock is a contraindication to regional anesthesia. Therefore, for patients with sepsis who are in the first trimester, PCN placement may be preferable if IR can place the nephrostomy tube urgently with local anesthesia and sedation.

However, PCN placement after the first trimester has several problematic issues. First, the patient may be at an increased risk for aspiration and many anesthesiologists will opt for general anesthesia, rather than sedation (34). Second, the prone position may transmit pressure from the gravid uterus onto the great vessels leading to decreased uterine perfusion with subsequent reduced fetal perfusion and maternal hypotension. Third, fetal monitoring is difficult in the prone position. Thus, in most cases ureteral stenting is safer for the obstetric patient and the fetus. However, if IR PCN must be performed, bolsters should be carefully positioned under the obstetric patient to ensure the abdomen is not flat on the operating room table. Furthermore, interventional radiologists can also place PCNs in a semi-prone/oblique position if a complete prone position is not possible.

Collecting System Decompression: Ureteral Stenting vs. Percutaneous Nephrostomy Tube Placement

Both ureteral stent and percutaneous nephrostomy tube placement are highly successful procedures with no high quality evidence in the literature to recommend one modality over the other (36). However, we recommend an attempt at ureteral stent placement as the initial management option. In one retrospective review of a large database of 3,904 obstetric patients with nephrolithiasis, those who underwent PCN placement had a preterm delivery rate of 19.6% from a baseline of 9.1% for women who had stones managed conservatively. Those who underwent ureteroscopy or ureteral stenting had a preterm delivery rate of 11.2% (37). Therefore, there may be a higher preterm delivery rate associated with PCN tube placement.

Other considerations of intervention include quality of life. Ureteral stents are associated with pain, encrustation, infection, and bladder irritability. Similarly, PCN tubes are associated with pain, infection, tube dislodgement, tube obstruction by debris, and bleeding (38). In one case series, half of the women receiving PCN tubes had to undergo tube exchanges/replacements due to occlusion from debris/tube dislodgement (18). One potential advantage of PCN tubes is that it can potentially be placed by IR under ultrasound guidance without use of fluoroscopy. Tips to minimize fluoroscopy use during stent placement are provided in the **Box 1** (39).

Regardless of the tube type, due to gestational hyperfiltration and resulting hyperuricosuria and hypercalciuria, there is a higher rate of tube encrustation during pregnancy and expedited follow up must be scheduled to ensure timely removal/exchange (38). Thus, we recommend exchanging ureteral stents/PCNs every 4 weeks until definitive stone management.

Role of Primary Ureteroscopy

With advancements in endoscopic and laser technology, virtually any aspect of the upper and lower urinary system is accessible to treatment. The ureters are naturally dilated in pregnancy, which facilitates treatment. As discussed previously, drainage tubes are subject to infection and encrustation and require frequent exchanges. Ureteroscopy offers the potential for treating the stone in one session with the theoretical benefit of reduced exposure to anesthetics and avoiding side effects of indwelling tubes as long as the urine is not infected.

Multiple studies have shown that ureteroscopy in pregnancy appears to be safe with complication rates that are comparable to non-obstetric patients (40–43). There were no significant differences in urinary tract infection or ureteral injury. In a retrospective review of 112 women with stones during pregnancy

BOX 1 | Technical considerations for retrograde ureteral stent placement.

- Place a bump underneath the patient's right side so that the uterus is displaced to the left, this relieves pressure on the IVC and helps stabilize blood pressures*
- Minimize use of fluoroscopy
  - Use spot fluoroscopy rather than live imaging
  - Decrease the number of shots per second (pre-set is 15 frames/second, but can go as low as 3 frames/second)
  - Use tactile feel to confirm placement of wire
  - Use ultrasound to confirm proximal stent curl

*Should be performed after 20 weeks gestation or if uterine fundus is at the umbilicus. Achieve at least a 15-degree tilt

over 12 years, there were no obstetric related complications after ureteroscopy and laser lithotripsy (29 women). In comparison, 42.1% of the women who underwent stent placement required early induction of labor at 38 weeks gestation. 10.9% of the patients who had stents experienced preterm labor within 24 h of stent placement (44).

The ACOG suggests that because of the consistent observation of higher incidence of preterm labor in the third trimester, any surgical intervention is recommended to occur during the second trimester if possible (30). This recommendation is extrapolated from general surgery literature (urgent abdominal surgery) (45, 46) with the limitation that these studies did not include endourologic surgery.

Multidisciplinary Operative Intervention

It is paramount that a multi-disciplinary approach is taken with any surgical intervention during pregnancy. At our institution, an emergent ureteral stent for an obstetric patient with a viable fetus (determined after an OB and neonatology consult) is performed at the women and children's hospital, given the proximity to the Neonatal Intensive Care Unit and OB staff in the event an emergent cesarean delivery of a preterm infant care is necessary. Obstetric and neonatal intensive team members are present in the operating room during the pre-induction verification for situational awareness and to ensure necessary medications, surgical and resuscitative equipment are available. The obstetric team will determine if continuous fetal monitoring during the procedure is necessary and will remain readily available to perform a cesarean delivery. Interventional radiology is also notified of a possible pending procedure if the ureteral stent placement fails.

CONCLUSION

The establishment of multi-disciplinary, standardized guidelines for the management of nephrolithiasis during pregnancy has improved and streamlined the care for obstetric patients with nephrolithiasis at our institution. In circumstances where a RBUS demonstrates hydronephrosis but fails to demonstrate an obstructing ureteral stone, urologists may hesitate to order a NC-CT due to concern of fetal radiation. We provide evidence-based guidelines that demonstrate a NC-CT is safe and can be used when diagnostic uncertainty exists. Furthermore, in cases of septic obstructing stones we recommend ureteral stent placement as the preferred first line intervention. Ultimately, a multi-disciplinary approach for the management of obstetric patients with nephrolithiasis, in conjunction with the availability of subspecialty expertise is critical. These guidelines may be modified to fit the needs of the patient and surgical staff in their local environment.

AUTHOR CONTRIBUTIONS

ML, MF, EN, SC, and KG: project development, data collection, manuscript writing, and data analysis. CV, MB, JK, JE, JS, SA, AK, and WR: manuscript writing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.796876/full#supplementary-material

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for Boston Scientific. KG is a consultant for Boston Scientific, Lumenis, Coloplast, Olympus, and Karl Storz.

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Single-Use vs. Reusable Digital Flexible Ureteroscope to Treat Upper Urinary Calculi: A Propensity-Score Matching Analysis

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Objective: The purpose of this research was to compare the treatment outcomes and costs of a single-use and reusable digital flexible ureteroscope for upper urinary calculi.

Methods: Four hundred forty patients with reusable digital flexible ureteroscope and 151 patients with single-use flexible digital ureteroscope were included in this study. Through exclusion and inclusion criteria and 1:1 propensity-score matching analysis based on baseline characteristics, ultimately, 238 patients (119:119) were compared in terms of treatment outcomes. The cost analysis was based on the costs of purchase, repair, and reprocessing divided by the number of all procedures in each group (450 procedures with reusable digital flexible ureteroscope and 160 procedures with single-use digital flexible ureteroscope).

Results: There was no statistical significance in mean operation time ($P = 0.666$). The single-use digital flexible ureteroscope group has a shorter mean length of hospital stay than the reusable digital flexible ureteroscope group ($P = 0.026$). And the two groups have a similar incidence of postoperative complications ($P = 0.678$). No significant difference was observed in the final stone-free rate ($P = 0.599$) and the probability of secondary lithotripsy ($P = 0.811$) between the two groups. After 275 procedures, the total costs of a single-use flexible ureteroscope would exceed the reusable flexible ureteroscope.

Conclusion: Our data demonstrated that the single-use digital flexible ureteroscope is an alternative to reusable digital flexible ureteroscopy in terms of surgical efficacy and safety for upper urinary calculi. In terms of the economics of the two types of equipment, institutions should consider their financial situation, the number of FURS procedures, the volume of the patient's calculus, surgeon experience, and local dealerships' annual maintenance contract when making the choice.

Keywords: upper urinary calculi, single-use, flexible ureteroscope, treatment outcomes, cost analysis

INTRODUCTION

Urolithiasis is a common urological disease and its incidence has been increasing globally in recent years (1). With the progress of modern medicine, flexible ureteroscopic (FURS) lithotripsy has become the main surgical management to treat upper urinary calculi smaller than 2 cm (2), as it can pass through the natural lumen to the renal cavities and stone-free rates (SFR) ranged between 80 and 90% (3). However, there are intractable deficiencies that limit the widespread use of reusable FURS in countries with restricted healthcare expenditures, including high purchase and maintenance costs (4). In addition, reusable FURS disinfection requires specialized equipment and personnel, which increases costs and risks of cross-infection due to disinfection failure (5). Given these deficiencies, single-use FURS have been developed in recent years, which are exempt from disinfection and maintenance. Currently, several single-use devices such as LithoVue^{TM} (Boston Scientific, Natick, MA), Uscope^{TM} (Zhuhai Pusen Medical Technology Co. Ltd., Zhuhai, China), NeoFlex^{TM} (Neoscope; Inc, San Jose, CA), and ZebraScope^{TM} (Happiness Works Medical Technology Co, LTD, Beijing, China) are available. Preliminary studies indicated that single-use FURS can be as effective and safe as reusable FURS (6, 7) and may be cost beneficial by eliminating the expensive reprocessing and repair costs in certain circumstances (8, 9). But we still lack official recommendations and reliable evidence (10).

Therefore, the objective of this study mainly concerns the clinical performance and costs of a single-use digital FURS (ZebraScope^{TM}) compared with a reusable digital FURS (URF-V; Olympus, Tokyo, Japan).

METHODS

Patients and Data Collection

This study protocol was approved by the Ethics Committee of the Xiangya Hospital, Central South University. Four hundred forty patients (10 patients underwent two lithotripsy procedures) were treated with reusable digital FURS (between January 2018 and February 2020) and 151 patients (nine patients underwent two lithotripsy procedures) were treated with single-use digital FURS (between March 2020 and September 2020) for upper urinary calculi and their charts were retrospectively reviewed. All procedures were performed by experienced surgeons at our medical center and the course of the surgery is described in the Surgical Technique (the single-use digital FURS as shown in **Figure 1**). The inclusion criteria were as follows: (1) patients age ≥18 years old; and (2) patients were treated with reusable digital FURS and single-use digital FURS for upper urinary calculi. According to the following exclusion criteria: (1) patients age <18 years old; (2) patients undergoing bilateral procedures or simultaneously combined with other surgery; (3) patients with special situations such as pregnancy, duplicate ureteral deformity and horseshoe kidney, 408 patients and 142 patients were enrolled in single-use FURS and reusable FURS group respectively for treatment outcomes analysis. Subsequently, through 1:1 propensity-score matching analysis based on age, sex, body mass index (BMI), American Society of Anesthesiologists classification (ASA), stone hardness, stone burden, stone location, ureteric stent implanted preoperatively, positive preoperative urine culture, solitary kidney stone, procedural laterality, history of ipsilateral urolithiasis surgery, and degree of hydronephrosis, ultimately, 238 patients (119:119) in the two groups were compared in terms of treatment outcomes. All procedures (450 procedures with reusable FURS and 160 procedures with single-use FURS) were reviewed for costs analysis.

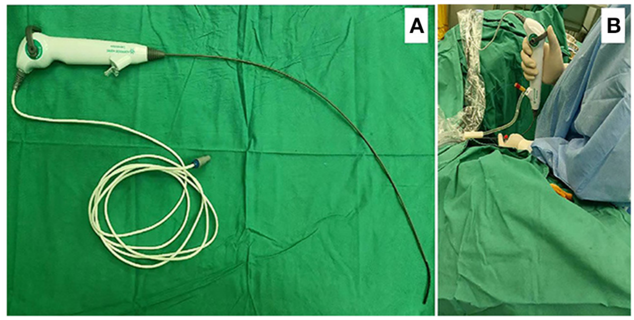

FIGURE 1 | (A) Chinese single-use FURS ZebraScopeTM (Happiness Workshop): The outer diameter of the front end of the lens is F7.4, and the maximum outer diameter of the lens is F8.6. The operating channel is a single channel with an inner diameter of F3.6. The steering angle of the mirror head end is 1:1, and the minimum bending radius is about 8 mm. The head end can bend more than 270 in both no-load. **(B)** Application of the single-use digital FURS ZebraScopeTM during operation.

All patients underwent an abdominal non-contrast computed tomography (CT) scan preoperatively to evaluate the stone size, position, and hardness (measured in Hounsfield units, HU). Plain film of kidney-ureter-bladder (KUB) was performed to evaluate stone-free status at 1 day and 1 month postoperatively, and CT will be performed again only when patients need a secondary lithotrity. The demographic variables, operation time, length of hospital stay, postoperative complications, and other clinical data were collected through our electronic medical record system. The urinary microbial culture was performed in all patients 1 week before surgery. Any patient with a positive culture was given sensitive antimicrobial therapy preoperatively based on antibiotic sensitivity tests and well-controlled urinary tract infections were confirmed by urinary cultures before surgical intervention. Patients with negative urine culture received intravenous antimicrobial (Cefuroxime) prophylaxis 30 min before the anesthetic.

Surgical Technique

Patients were placed in the lithotomy position after general anesthesia. Under the guidance of 4F ureteral catheters, a 9.8-F semirigid ureteroscope (URS) (Karl Storz, Germany) was

Abbreviations: FURS, flexible ureteroscope; SFR, stone-free rates; BMI, body mass index; ASA, American Society of Anesthesiologists classification; CT, Computed tomography; HU, Hounsfield units; KUB, plain film of kidney-ureter-bladder; Hct, hematocrit; Hb, hemoglobin.

placed into the ureter to detect whether there was stenosis or abnormality and to dilate the ureter to facilitate the placement of a ureteral access sheath (UAS). Subsequently, a Zebra guidewire was inserted into the ureter through the URS. Then, the URS was removed and a 12/14-Fr Flexor UAS (Cook Urology, 45 cm for male, 35 cm for female) was advanced into renal pelvis directed by the guidewire (If UAS implantation failed, double J tubes were implanted in the first stage, and the second procedure was performed 2 weeks later). Subsequently, the 8.6-F single-use digital FURS ZebraScope^{TM} (**Figure 1**) or 9.9-F reusable digital FURS (URF-V; Olympus, Tokyo, Japan) was placed into the pelvis through the UAS. Lithotripsy was performed using holmium:yttrium-aluminum-garnet laser (Ho: YAG) with a 200-μm fiber at an output power of 50–60 W and a frequency level of 15–24 Hz. The rubble fragments were recovered using a 2.4F zero-tip Nitinol stone basket (Cook Medical, Bloomington, IN, USA). After repeated examination of the collection system, it was confirmed that the stones were completely broken and removed. The operation ended with the placement of a double J stent in the ureter for drainage for 1 month.

Clinical Outcomes Analysis

The extent of hydronephrosis was assessed according to the Society of Fetal Urology grading system (11, 12). Postoperative complications were evaluated according to the Clavien-Dindo classification system (13). Septic shock was defined according to the third international consensus (14). Stone volume was calculated using the following formula (0.785 $\times$ length$_{max}$ $\times$ width$_{max}$) according to CROES (15), and the burden of multiple stones was calculated as the sum of the volume of all stones. Postoperative stone-free status was defined as the absence of stone fragment > 3 mm on KUB. According to the size and location of residual stones, two experienced professors comprehensively evaluated whether retreatment was needed (CT will be performed only when patients need secondary lithotripsy). In addition, medical images of all patients were independently read by a radiologist and a urologist to measure the calculi burden as determined by CT and to evaluate calculi-free status as determined by KUB after surgery. The clinical outcomes of patients who received their first treatment with FURS lithotripsy during this treatment period were evaluated.

Crude Cost Analysis

As this was a retrospective study, we were unable to balance the preoperative characteristics in the cost analysis. We performed a crude cost analysis for all procedures undergoing FURS lithotripsy during this study period. All costs were presented in dollars ($) (One dollar is ∼6.541yuan). Two reusable FURS were available in our institution which were purchased at market price in 2016 and 2017 respectively. Due to those devices were not new at the time of the study, and we could not count the number of procedures performed before the study. The original purchase costs of the two sets of reusable equipment were modeled as residual value by annual depreciation rate (Approximately $275220; 1800000yuan). Between January 2018 and February 2020, the reusable FURS conducted six repairs at a cost of ∼$183480 (1200000yuan). Extrapolating from the data provided by the Disinfection supply center in our hospital, reprocessing costs were ∼$80 (523yuan) per procedure, which included the costs of inspection, pre-cleaning, decontamination, assembly, and sterilization. Purchasing prices of disinfection equipment have been left out in our study. The personnel cost was about $40 (262yuan) per procedure based on the hourly wage of the central disinfection technician combined with the average approximate time to reprocess FURS. According to the present local market price, the cost of single-use FURS was about $1529 (10000yuan) per procedure. The total costs were estimated based on the following equations which are similar to the provided by Martin et al. (9).

$$\begin{aligned} &\textit{Total costs of single} - \textit{use FURS} \ (\textit{costs of single} \\ &- \textit{use FURS per procedure}) \times X, \\ &\textit{where } X = \textit{number of procedures} \\ &\textit{Total costs of reusable FURS} = (\textit{Original purchasing} \\ &\textit{cost of reusable FURS}) + \\ &\big[(\textit{repair cost per procedure}) + \\ &(\textit{Reprocessing cost per procedure}) \\ &+ (\textit{labor cost per procedure})\big] \times \\ &\textit{where } X = \textit{number of procedures} \end{aligned}$$

The cost per procedure was the total costs divided by the number of procedures. Assuming that the maintenance cost per procedure is roughly constant over a long period (Excluding the possible increase in the number of repairs due to aging of FURS), from the above two equations, we can also get a formula that can help the institution to calculate the number of operations performed when the total costs of the two devices reach the equilibrium point.

$$\begin{aligned} &Y = \textit{Original purchasing costs of reusable FURS} \div \\ &(\textit{cost of single} - \textit{use FURS per procedure} - \textit{ the} \\ &\textit{average maintenace} \\ &\textit{costs of reusable FURS per procedure}) \\ &\textit{where} = Y \textit{ the equilibrim point of procedure volumes} \end{aligned}$$

Statistical Methods

Chi-square test or Fisher's exact test was used to analyze the proportion of categorical variables; Student's t-test was used to analyze numerical variables with normal distribution. A two-sided P-value less than or equal to 0.05 was considered statistically significant. The logistic regression model was used to calculate the propensity score of each research object for 1:1 propensity-score matching analysis. Statistical analysis and 1:1 propensity-score matching analysis were performed using the Statistical Package for the Social Sciences 22.0 (SPSS for Windows, Chicago, IL, USA).

TABLE 1 | Baseline characteristics of the included patients for clinical outcomes analysis.

Parameters	Before propensity-score matching			After propensity-score matching		
	Reusable N (408)	Single-use N (142)	*P*-value	Reusable N (119)	Single use N (119)	*P*-value
Age (years), mean ± SD	52.0 ± 12.3	49.4 ± 12.9	0.030[a]	49.0 ± 12.0	49.4 ± 12.7	0.821[a]
Gender, n (%)						
Male	258 (63.2%)	93 (65.5%)	0.630[b]	77 (64.7%)	79 (66.4%)	0.785[b]
Female	150 (36.8%)	49 (34.5%)		42 (35.3%)	40 (33.6%)	
BMI (kg/m^2), mean ± SD	23.8 ± 3.1	24.1 ± 3.7	0.255[a]	24.2 ± 3.1	24.0 ± 3.4	0.620[a]
Pre-stented, n (%)	60 (14.7%)	19 (13.4%)	0.698[b]	16 (13.4%)	16 (13.4%)	1.000[b]
Positive preoperative urine culture, n (%)	38 (9.3%)	18 (12.7%)	0.254[b]	15 (12.6%)	18 (15.1%)	0.574[b]
Solitary kidney stone, n (%)	50 (12.3%)	14 (9.9%)	0.443[b]	12 (10.1%)	12 (10.1)	1.000[b]
Procedural laterality, n (%)						
Left	215 (52.7%)	71 (50.0%)	0.580[b]	59 (49.6%)	58 (48.7%)	0.897[b]
Right	193 (47.3%)	71 (50.0%)		60 (50.4%)	61 (51.3%)	
History of Ipsilateral urolithiasis surgery, n (%)			0.961[c]			0.973[c]
None	292 (71.6%)	100 (70.4%)		86 (72.3%)	86 (72.3%)	
PCNL	37 (9.1%)	15 (10.6%)		11 (9.2%)	11 (9.2%)	
RIRS or URL	54 (13.2%)	20 (14.1%)		15 (12.6%)	17 (14.3%)	
EWSL	19 (4.7%)	5 (3.5%)		5 (4.2%)	3 (2.5%)	
Open operation	6 (1.5%)	2 (1.4%)		2 (1.7%)	2 (1.7%)	
ASA, n (%)						
Class 1 and 2	304 (74.5%)	111 (78.2%)	0.383[b]	94 (79.0%)	94 (79.0%)	1.000[b]
Class 3 and 4	104 (25.5%)	31 (21.8%)		25 (21.0%)	25 (21.0%)	
Degree of hydronephrosis, n (%)						
None or mild	380 (93.1%)	128 (90.1%)	0.247[b]	107 (89.9%)	110 (92.4)	0.493[b]
Moderate or severe	28 (6.9%)	14 (9.9%)		12 (10.1%)	9 (7.6%)	
Stone characteristics						
Stone hardness (HU), mean ± SD	1000 ± 261	976 ± 260	0.340[a]	964 ± 240	972 ± 257	0.787[a]
Stone burden (cm^2), mean ± SD	59.9 ± 39.5	71.4 ± 38.9	0.003[b]	69.3 ± 37.1	69.5 ± 34.5	0.970[b]
Stone localization, n (%)			0.560[c]			0.958[c]
Upper segment of ureter	158 (38.7%)	57 (40.1%)		46 (38.7%)	49 (41.2%)	
Upper calix	12 (2.9%)	4 (2.8%)		4 (3.4%)	4 (3.4%)	
Middle calix	30 (7.4%)	6 (4.2%)		6 (5.0%)	6 (5.0%)	
Lower calix	37 (9.1%)	17 (12.0%)		13 (10.9%)	16 (13.4%)	
Pelvis	55 (13.5%)	12 (8.5%)		16 (13.4%)	11 (9.2%)	
Upper ureteral segment with pelvis or calices	67 (16.4%)	28 (19.7%)		16 (13.4%)	18 (15.1)	
Pelvis with calices	23 (5.6%)	7 (4.9%)		9 (7.6%)	6 (5.0%)	
Multiple calices	26 (6.4%)	11 (7.7%)		9 (7.6%)	9 (7.6%)	
Comorbidities, n (%)			0.212[b]			0.225[b]
None	264 (64.7%)	97 (68.3%)		72 (60.5%)	83 (69.7%)	
Diabetes mellitus	75 (18.4%)	16 (11.3%)		9 (7.6%)	9 (7.6%)	
Hypertension	16 (3.9%)	9 (6.3%)		24 (20.2%)	12 (10.1%)	
Renal insufficiency	15 (3.7%)	8 (5.6%)		8 (6.7%)	6 (5.0%)	
Multi-comorbidities[d]	38 (9.3%)	12 (8.5%)		6 (5.0%)	9 (7.6%)	

[a]*Continuous variable were assessed by t-test.*
[b]*Chi-square test.*
[c]*Fisher's exact test (two-tailed).*
[d]*Patients with two or more comorbidities.*

RESULTS

Clinical Outcomes Analysis

Preoperative clinical data of the two groups for treatment outcomes analysis (408 vs. 142) are shown in **Table 1**. After 1:1 propensity-score matching analysis, baseline characteristics of those patients were evenly distributed in two groups (**Table 1**).

The treatment outcomes with two surgical devices are shown in **Table 2**. There was no significant difference in the mean

TABLE 2 | Treatment outcomes of the reusable FURS group and the single-use FURS group.

Surgical outcomes	Reusable	Single-use	*P*-value
Decline in Hb level (g/L)	3.74 ± 7.42	2.39 ± 9.46	0.224[b]
Decline in Hct level (%)	1.27 ± 2.48	0.91 ± 3.27	0.345[b]
Operative time (min), mean ± SD	60.43 ± 22.76	61.61 ± 19.36	0.666[b]
Hospital stays (days), mean ± SD	7.42 ± 2.06	6.86 ± 1.82	0.026[b]
Postoperative hospital stays (days), mean ± SD	2.81 ± 1.55	2.64 ± 1.32	0.368[b]
Initial SFR (1 day after surgery), n (%)	90 (75.6%)	93 (78.2%)	0.645[c]
Final SFR (1 month after surgery), n (%)	98 (82.4%)	101 (84.9%)	0.599[c]
Re-operation of the stone, n (%)	10 (8.4%)	9 (7.6%)	0.811[c]
Total complications[a] [Clavien grade classification, n (%)]	12 (10.1%)	14 (11.8%)	0.678[c]
Grade I	6 (5.0%)	9 (7.5%)	0.424[c]
Simple fever[e]	2 (1.7%)	3 (2.5%)	
Flank pain	2 (1.7%)	2 (1.7%)	
Nausea	1 (0.8%)	3 (2.5%)	
Fever and flank pain	1 (0.8%)	1 (0.8%)	
Grade II	3 (2.5%)	4 (3.4%)	1.00[d]
Urosepsis requiring only additional antibiotics	3 (2.5%)	4 (3.4%)	
Grade III	1 (0.8%)	0 (0%)	1.00[d]
Steinstrasse requiring surgical treatment	1 (0.8%)	0 (0%)	
Grade IV	2 (1.7%)	1 (0.8%)	1.00[d]
Septic shock	2 (1.7%)	1 (0.8%)	
Infection-related complications (moderate to severe) [f]	5 (4.2%)	5 (4.2%)	1.00[d]

[a] *Patients with multiple complications are finally classified according to the most severe one.*
[b] *Continuous variables were assessed by t-test.*
[c] *Chi-square test.*
[d] *Fisher's exact test (two-tailed).*
[e] *Fever patients only need antipyretic drugs or physical hypothermia therapy.*
[f] *Patients with Urosepsis or Septic shock.*

operative time between the two groups (60.43 ± 22.76 vs. 61.61 ± 19.36 min, $P = 0.666$). The mean length of hospital stay in the single-use FURS group was significantly shorter than that in the reusable FURS group (6.86 ± 1.82 days vs. 7.42 ± 2.06 days, $P = 0.026$), but there was no significant difference in postoperative length of hospital stay between the two groups (2.64 ± 1.32 vs. 2.81 ± 1.55 days, $P = 0.368$). The average decrease of hemoglobin (Hb) ($P = 0.224$) and hematocrit (Hct) ($P = 0.345$) was also no significant difference between the two groups.

The two groups experienced similar rates of overall postoperative complications (10.1% vs. 11.8 %, $P = 0.678$). The single-use group was associated with a higher incidence of grade I complication (7.5% vs. 5.0%, $P = 0.424$) than the reusable group, but it had no statistical difference. Urosepsis requiring only additional antibiotics was the main grade II complication and occurred no statistically different incidence rates in the two groups (2.5% vs. 3.4%, $P = 1.0$). Only one patient in the reusable FURS group developed steinstrasse after discharge and underwent surgery (Grade III). Septic shock (Grade IV) was observed in 2 (1.7%) and 1 (0.8%) patients in the reusable and single-use groups, respectively ($P = 1.00$). There was also no significant difference in moderate to severe infection-related complications (4.2% vs. 4.2%, $P = 1.00$).

Initial SFR of the reusable FURS group and single-use FURS groups were 75.6% and 78.2% ($P = 0.645$). There was also no significant difference in final SFR between the two groups (82.4% vs. 84.9%, $P = 0.599$). And there were 10 patients (8.4%) in the reusable FURS group and 9 patients (7.6%) in the single-use FURS group who required repeated surgery to remove residual stones ($P = 0.811$).

Crude Cost Analysis

The costs of reusable FURS or single-use FURS per procedure are shown in **Table 3**. Between January 2018 and February 2020, the repair cost per procedure is about $408 (2668yuan) for reusable FURS. After the original purchasing costs, the average cost per reusable FURS was ∼$528 (2453yuan). When taking into account original purchasing costs, we should consider the impact of procedure volume on the final cost per procedure, which will decrease with the increase of procedure volume. The cost per single-use FURS was ∼$1529 (10000yuan). According to our formula, the break-even point between the two alternatives appears to be 275 procedures in our institution. Total costs or cost per procedure of single-use FURS would exceed the reusable FURS after 275 procedures as shown in **Figure 2**.

TABLE 3 | The costs of reusable FURS or single-use FURS per procedure.

Cost items	Reusable FURS per case; dollars (Renminbi)	Single-use FURS per case; dollars (Renminbi)
Original purchasing cost	275220/X	1529 (10000yuan)
Repair cost	408 (2668 yuan)	0
Reprocessing cost	80 (523yuan)	0
Personnel cost	40 (262yuan)	0
Total cost	275220/X +528	1529 (10000yuan)

X, number of procedures.

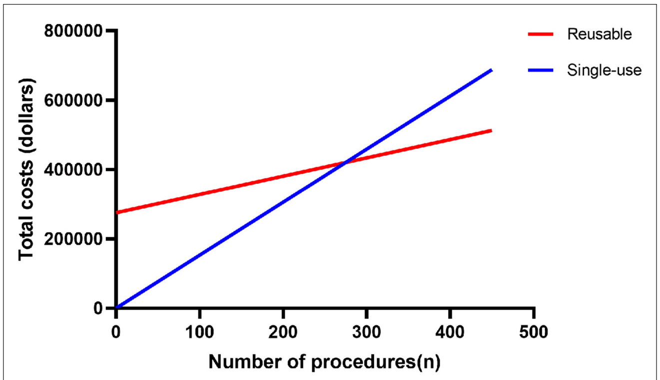

FIGURE 2 | The linear graphs demonstrate the change in total costs of reusable FURS and single-use FURS as the number of procedures increases.

DISCUSSION

With the rapid development of endoscopic surgical equipment, the single-use FURS, which are designed to alleviate the deficiencies of high cost and recurrent damage associated with the use of reusable FURS, gradually come to the attention of our urologists. Some prospective clinical studies have shown that some kind of single-use FURS has comparable performance to reusable FURS (7, 16–19). However, there are many types of single-use FURS on the market at present, and more studies are needed to further confirm their value in clinical application. Additionally, there is a scarcity of retrospective clinical data about the comparison between single-use FURS and reusable FURS.

In this study, through the propensity-score matching analysis, we retrospectively compared the clinical outcomes of 238 patients who experienced single-use FURS or reusable FURS lithotripsy. The results showed that the two devices performed similarly in terms of surgical efficacy and safety, similar to a prospective multicenter randomized controlled trial that compared the clinical outcomes of single-use digital FURS (ZebraScope^{TM}) and reusable digital FURS (URF-V) (17). But a study about single-use digital FURS (LithoVue^{TM}) vs. reusable fiberoptic FURS (URF-P6) showed that the performance of single-use FURS was better than reusable FURS in terms of mean operative time and surgical complications (19). The reason for the different results may be that digital FURS, compared with the fiberoptic FURS, has clearer images and a wider viewing angle (20, 21). There is no consensus in the operative time between single-use FURS and reusable FURS. Although several studies have found that the single-use FURS have the advantage of shorter surgical time (22–24), a series of prospective comparative research between single-use FURS and reusable FURS have found no significant difference in mean operative time between these two surgical devices (7, 17, 18, 25). As such, a prospective study with larger sample size is needed to confirm the performance of single-use and reusable FURS in terms of operative time. In this study, overall postoperative complications of the single-use FURS and reusable FURS group were also similar (10.1% vs. 11.8 %, $P = 0.678$) and are consistent with the incidence of complications (10–15%) have been reported (7, 17, 26, 27).

It has been reported that the positive rate of pre-use ureteroscope cultures was 12.1% after sterilization (28). A single-use FURS can automatically eliminate the possibility of cross-contamination by bypassing the reprocessing and sterility steps. But ever since the revolutionary invention was used in the clinic, no postoperative cross-contamination was recorded in patients after strict compliance with disinfection protocols for ureteroscope (28). Therefore, in this study, it is reasonable to observe that there is no difference in the incidence of moderate to severe infection-related complications between the single-use FURS group and the reusable FURS group (4.2% vs. 4.2%, $P = 1.00$).

Concerning the SFR, the current study found that the performance of single-use FURS is not inferior to reusable FURS (6, 7, 17, 19). Even a pooled analysis of 772 patients who experienced single-use FURS or reusable FURS showed that single-use FURS was associated with a higher SFR (OR: 1.50; 95% CI, 1.06–2.12; $P = 0.02$) than reusable FURS (24). In the present study, to accurately evaluate the performance of the two surgical devices in SFR, we conducted a detailed classification of stone location as shown in **Table 1**. The result showed that the final SFR was 84.9% for the single-use FURS group and 82.4% for the reusable FURS group ($P = 0.599$). Moreover, there was no significant difference in the rate of second-stage surgical treatment of calculi. A multicenter randomized controlled trial evaluated the same single-use FURS(ZebraScope^{TM}) with an SFR of 77% (17), which is lower than the present study. That may be due to the uneven skill of the surgeons involved in the multicenter study. Through the above discussion, in terms of clinical efficacy and safety, single-use digital FURS maybe be an effective and safe alternative to reusable FURS for experienced users. But given the vulnerability of reusable FURS, prioritizing the use of single-use FURS for trainees may significantly reduce the maintenance costs of reusable FURS.

It is difficult to reach a unified conclusion in cost analysis, because the total cost may vary by institution and the local price of commodities. To date, the LithoVue^{TM} is the only single-use FURS with a thorough economic analysis. A micro-costing analysis indicated that the costs per case associated with reusable and single-use ureteroscopes are comparable (29). One study showed that a single-use FURS was considerably less expensive than a reusable FURS when it is priced at 850USD (8). Some studies have shown that using single-use FURS in high-risk breakage cases (such as staghorn stones, stones located in the lower pole) is an economical choice (16, 30). In this research, After the original purchasing costs, the average cost per reusable FURS was ∼$528 (2453yuan), which was lower than $799.60 per case of Martin's study (9). According to our formula, after 275 FURS procedures, the cost-benefit analysis would favor the use of reusable FURS rather than disposable ureteroscope in this hospital, but more start-up capital is needed for the reusable FURS. Thus, at current market prices for single-use FURS, institutions should choose the most suitable device for themselves based on the number of FURS procedures and their financial situation.

There are still several limitations in this study. First, this study was a retrospective single-center study. Although a 1:1 propensity-score matching was used for clinical efficacy analysis, there were still some inevitable biases that could affect the accuracy of results. Second, we have only briefly analyzed the costs of two types of equipment and were unable to balance the preoperative characteristics. Therefore, future prospective randomized studies with large case sizes are needed to confirm the current results.

CONCLUSIONS

Our data demonstrated that the single-use FURS is an alternative to reusable FURS in terms of surgical efficacy and safety for upper urinary calculi. In terms of the economics of the two types of equipment, institutions should consider their financial situation, the number of FURS procedures, the volume of the patient's calculus, surgeon experience, and local dealerships' annual maintenance contract when making the choice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Xiangya Hospital, Central South University (No: 202105087). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article. The authors are accountable for all aspects of the work, including ensuring that questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted following the Helsinki Declaration (as revised in 2013).

AUTHOR CONTRIBUTIONS

FH: conceptualization, visualization, methodology, and writing original draft. XZ and YC: validation, data curation, and investigation. ZZ, YoL, and FZ: investigation and resources. JC: writing review and editing. YaL and ZC: methodology, software, and formal analysis. HC: conceptualization, project administration, and supervision. All authors contributed to the article and approved the submitted version.

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Cystinuria: An Overview of Challenges and Surgical Management

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Keywords: endourology, calculi, ureteroscopy, PCNL, cystinuria, ESWL (Extracorporeal Shock Wave Lithotripsy), ECIRS

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INTRODUCTION

Cystinuria is a genetically inherited condition and a rare cause of kidney stones. It affects approximately 1 in 7,000 of the global population, although wide geographical variances exist (1). It is often quoted that cystine stones make up 1–2% of all urinary stones in adults and 6–8% in pediatric populations (2). Cystinuria is typically thought of as an autosomal recessive disease but can be autosomal dominant with incomplete penetrance (1, 3). It is caused by a defective amino acid transporter in the proximal renal tubules and in the epithelial cell lining of the small intestine affecting transport of cystine and the dibasic amino acids ornithine, lysine, and arginine (COLA). Cystine is relatively insoluble (compared with the other three amino acids), and thus, cystine can precipitate out, causing renal stone formation. The responsible genetic defects are located in genes SLC3A1 (2p21) and SLC7A9 (19q12), which encode the cystine transporter (3). Historically, patients were classified by the levels of urinary cystine excretion, but a more recent genotype classification is now used with Type A (mutations in SLC3A1), Type B (mutations in SLC7A9), or Type AB (1 mutation in each gene) (4).

Most patients present with the stone disease before age 30 years with the peak incidence between 11 and 20 years (1, 5, 6). Patients often suffer from lifelong stone formation, although the phenotype varies from mild (no stones) to severe (highly recurrent). As a consequence of recurrent stone episodes and interventions, chronic kidney disease and hypertension are common, and cystine stone formers have been shown to have worse health-related quality of life compared to noncystine stone formers (3, 7).

Due to the highly recurrent nature of kidney stones, cystinuria can pose significant diagnostic, logistical, and surgical challenges.

CHALLENGES OF CYSTINURIA

Frequent Stone Formation

Typically, cystine stone formers produce stones at a faster rate and from an earlier age than noncystine stone formers (8). Streeper et al. looked at cystinuria patients' overall quality of life and found that stones formed in this cohort, on average, every 12–24 months, with the typical patient having undergone up to seven endourological procedures by middle age (9). In comparison, noncystinuria patients have an overall lifetime risk of urolithiasis of between 10 and 15% and a 10-year risk of recurrence of around 50% (10). In our experience of running a specialist cystinuria clinic, we have found that 83% of patients presented with their first stone before the age of 30 years (5). Moreover, due to the relatively rare nature of cystinuria, up to a quarter had a delayed diagnosis, with an average time from initial presentation to diagnosis of 7.8 years (5). This delay in diagnosis can result in irreversible kidney damage due to repeated renal insult or from continuous or undetected stone disease (5). In total, 8% of our patient cohort had already undergone a nephrectomy, secondary to stone disease, by the time they were seen in our clinic (5). This highlights the importance of prompt recognition and diagnosis of the condition so treatment can be initiated to slow stone formation, with an overall aim to preserve renal function (3, 5, 9, 11).

Dietary Advice for Cystine Stone Formers

The cornerstone of dietary advice for patients with cystinuria is to ensure a high fluid intake aiming for a minimum urine output of 3 L/day (3, 6). This fluid intake should ideally be spread out throughout the day, and in extreme cases, patients are advised to wake at night to drink fluid (3). The aim of this is to reduce the concentration of cystine to <250 mg/L in the urine to prevent crystallization. Diet is important, and patients should be advised to follow a low-salt diet as this has been shown to reduce cystine excretion (8). Restriction of animal protein is also recommended to limit the intake of methionine (a precursor of cystine) (3). Often dietary modifications are not enough on their own, and alkalinization of the urine with potassium citrate is recommended to achieve a urine pH of 7.5 (3, 6). We recommend that patients periodically check their urine pH at different times of the day to assess whether this target is achieved. In patients who continue to form stones despite the above advice and urinary alkalinization, a cystine-binding thiol drug such as tiopronin or D-penicillamine is used (3, 6). Such a drug binds cystine and results in a drug-cysteine complex that is up to 50 times more soluble than cystine. Both these medications can have significant side effects and require regular urinary and serum monitoring for proteinuria and blood counts.

Compliance with Diet and Medications and Engagement with Health Services

Cystinuria typically affects a young cohort of patients (1, 2). Prevention of stone formation is the main objective in cystinuria, aiming to reduce the level of urinary cystine to below the point of solubility that stops crystal formation (13). As discussed, patients are initially trialed with conservative management, which includes dietary modification and fluid intake in excess of 3 L/day, to avoid crystal excretion and aggregation in the urinary tract (14). Medication can be introduced if conservative management alone is not sufficient to control stone formation (15). Adherence to both conservative and medical management can be a hurdle for patients who may require support from urologists, nephrologists, and dieticians to achieve long-term goals (16). Dietary adaptation can be restrictive for patients, as can the requirement to drink in excess of 3 L/day of water for practical reasons. The importance of engagement with medical management and services must be emphasized to patients to ensure they are minimizing their risk of stone formation and surgical intervention while also being monitored and treated for other complications such as chronic kidney disease and hypertension (16, 17).

To maintain satisfactory levels of urinary cystine and reduce the rate of stone formation, a close long-term relationship with the multidisciplinary team managing the condition is key (5). Medical management may need to be closely monitored and adapted to the individual over time, and early stone detection is vital to ensure there is a minimal overall loss of renal function with increasing age (15). This relationship and continuity can be difficult to achieve, particularly through the transition from pediatric and adolescence into adult services, often requiring a change of the nephrologist and surgeon. In addition, geographical location can make this continuity logistically difficult. While finding a regime that is successful and suits the individual, multiple hospital visits are often required to monitor treatment effectiveness. Depending on services and expertise available locally, patients are often referred to tertiary centers to aid with the management of this condition. Depending on geographical location, the added burden of frequent long-distance commutes to centers that specialize in the treatment of cystinuria can take its toll. In our experience, providing a dedicated cystinuria clinic can help with service engagement by providing a one-stop clinic where patients can access all specialties involved in their specialty care during one visit.

Side-Effects/Monitoring and Availability of Medications

For those who are unresponsive to both dietary modifications and increased oral fluid intake alone, pharmacological management may need to be initiated (5, 12, 14). Urinary alkalization with sodium bicarbonate or potassium citrate is the first-line medical treatment for those with unsatisfactory levels of urinary cystine and who still continue to make stones (5). As with conservative measures, strict adherence to medical therapy is required to be effective (5). These medications can be associated with unpleasant side effects including nausea and other gastrointestinal symptoms that can impact patient compliance (18, 19). Urinary pH and plasma potassium or sodium levels need to be closely monitored to ensure they are within satisfactory and safe ranges yet still sufficient to effectively reduce the rate of stone formation (14). Twenty-four-hour urinary cystine concentration can be used to monitor treatment effectiveness, and chelation therapy may be needed aiming for a urinary cystine concentration of <250 μmols/L (5).

Chelation therapy includes thiol-based agents, tiopronin or D-penicillamine (20), that can be added when other interventions have failed to halt stone formation (19, 20). Again, compliance with these medications is important and can remain an issue as they are also associated with a profile of significant side effects (20, 21). They require individual dosing regimes, particularly in the pediatric population that is calculated and adapted relative to body weight (14, 20).

Toxicity and adverse sensitivity reactions can occur in up to 40% of children, which usually present with a rash, fever, or more rarely arthropathy (22). In the wider population, side effects can range from the mild, e.g., gastrointestinal upset, to more severe blood dyscrasias and nephrotic syndrome (15, 22, 23). More rarely, D-penicillamine can induce autoimmune reactions. The incidence of side effects was found to be dose-dependent, therefore making sure correct doses of medications are prescribed and adjusted accordingly through adolescence into adulthood (22).

One challenge with these medications is availability and cost, which varies across the world. In the United Kingdom, tiopronin is unlicensed and thus can only be prescribed in specialist centers and can be difficult to source, while penicillamine is not available in many countries. Both require close and long-term plasma and urinary monitoring (22). In addition, potassium citrate can be very expensive and is often not well tolerated (22).

Prevalence of CKD/Hypertension

The renal insults from recurring stone formation, colic episodes, and interventions can result in damage to the kidneys, reduced overall renal function, and chronic kidney disease (CKD) (5, 17). In a large series from France, Prot-Bertoye et al. reported on 442 cystinuric patients in a retrospective study. In total, 77.5% had an abnormal e-GFR (<90 mLs/min) and 26.7% had e-GFR < 60. Among the patients with CKD, the incidence of hypertension was 28.6% (17). In our series, we reported a similarly high incidence with 75% having CKD, and hypertension was found in 50.8% of our series (16).

SURGICAL MANAGEMENT

Ureteric Stones

The clinical presentation of cystine stone disease is identical, although it can be more frequent than that of other stone compositions (5, 24). Patients may experience episodes of colic due to ureteric stones but can also present with renal pain, urinary infection, haematuria, or stones that can be picked up incidentally through routine imaging (3, 11). Those who have experienced colic pain before will often recognize the symptoms and may try to pass the stone without presenting for imaging or intervention. For these patients, often ultrasound may be enough as a first-line investigation to try and reduce the exposure to ionizing radiation (3, 6). However, if a stone is not passed or if there are persistent symptoms, then a low-dose noncontrast CT will be required.

Anecdotally, cystinuria patients often have more capacious ureters than noncystine stone formers (due to recurrent ureteric stones and multiple endourological interventions) and may be able to pass stones larger than would normally be expected compared to other composition stone formers. As for any stone former, obstruction in a single kidney or the presence of infection should prompt immediate assessment and intervention to relieve the obstruction and preserve overall renal health (2).

Due to the frequent nature of stone formation, cystinuria patients may know the size of stones they are historically able to pass, allowing for surveillance and conservative management of calculi smaller than this. However, if stones do not pass promptly or are unlikely to pass due to size or location, then timely intervention should be offered to prevent the potential loss of renal function from prolonged recurrent episodes of ureteric obstruction (5, 13). For obstructing ureteric stones, either extracorporeal shockwave lithotripsy (ESWL) or ureteroscopy (URS) can be offered depending on the knowledge of previous intervention success rates, availability, and patient preference, helping to guide the decision-making process. However, as cystine stones may not show up on plain imaging and as ureteroscopy offers a very high chance of clearing the stone and relieving the obstruction in one procedure, this is considered the first-line treatment modality with ESWL a second-line alternative in selected patients only (3). Either way, timeliness of access to intervention is important to prevent prolonged obstruction and potential loss of renal function (3).

As well as stone formation, cystinuria patients have the propensity to encrust indwelling stents rapidly (3, 5). If stenting an obstructing stone, swift intervention and stone clearance should be arranged, reducing the overall time a stent is left *in situ* (3). If a stent is placed at the end of the procedure, then consideration should be given to how long this is left indwelling and if the strings/tethers can be left to aid prompt removal. In our clinic, we aim to treat all patients within 2 weeks of stenting and minimize stent time to <2 weeks and use strings/ tethers where practical. Of course, leaving patients' stent-free is preferable if safe. Patients will often know from previous experience how quickly their stents encrust, and so, this inquiry should be made.

Renal Stones

In addition to obstructing ureteric stones, renal pelvis and calyceal stones are common in cystinuria (3). Because of the recurrent nature of these hard stones, complete clearance should be achieved when possible, but this can be challenging (3, 25, 26). The size and location of stones within the kidney will often guide the recommended treatment (5). Hounsfield units are not useful in judging the "hardness" of cystine stones, as is frequently done for calcium-containing stones, and in a large series of cystine stone formers, we found the majority of patients have Hounsfield units in the region of 400–800 (3, 27). Indeed, if Hounsfield units >1,000 are measured in a cystine stone former, then consideration of whether conversion to calcium phosphate formation has occurred as can happen in high pH ranges.

The overarching principles of endourological surgery remain the same for cystine stones as for other compositions (5, 26); however, the surgical planning and decision-making surrounding the management of them may need extra consideration, as cystine stones should not be considered as one-off events but viewed as a succession of intervention that is likely to be needed throughout the patient's lifetime (7). In addition, the rate of stone growth may alter the surgical approach to achieve stone clearance, and certainly, the timing of the initial surgery and any follow-up procedures required should be carefully planned (28).

SURGICAL MODALITIES

Extracorporeal Shockwave Lithotripsy

Patients should be asked whether they have had ESWL previously and whether it had been successful. While cystine stones are often considered to be harder and resistant to ESWL, this is not always the case, and ESWL can be an effective treatment option with the right case selection (28). The literature supports that a single session of ESWL is overall less effective at achieving SFR than either URS or PCNL (29), but it is considered to be the least invasive treatment option (30). While 2 cm is usually considered the upper limit for ESWL in guidelines for general stone types (2), consensus guidelines would suggest that for lower pole cystine stones, 10 mm would be the upper limit for ESWL, and for stones 10–20 mm in other renal locations, ESWL would be a third-line option after URS and PCNL (2, 3).

Cystine stones can be further classified by the shape of their external surface into two subgroups; cystine-S, with a smooth outer layer and cystine-R, with a rough outer layer. The composition and surface shape can be detected by CT imaging. The surface type can be considered when assessing a patient for cystine stone management as those with cystine-R stones may be more amenable to successful ESWL therapy (31, 32). We previously analyzed a small cohort of our patient series and found that 47% (15/32) had stones that had responded to ESWL, and thus, for these patients, this treatment might be considered, particularly for smaller stones <1 cm (5).

Flexible Ureteroscopy (Retrograde Intrarenal Surgery)

Globally, the rates of URS have been steadily increasing in the last 20 years, which is likely to be the result of the technological advances and improvements in scope and laser technology in this time period (33). As scopes have become smaller and more operator friendly, the ability to tackle larger, harder, and more complex renal stones using this method has increased (34). URS is often the first-line surgical approach for standard renal stones <20 mm in diameter and is an effective way of surgically managing cystine stones up to 20 mm (3, 34).

URS offers many advantages over other surgical interventions in that it is less invasive than PCNL and associated less overall complications (5). URS is associated with more favorable outcomes in terms of stone clearance and resolution than SWL. It has lower complication rates compared to PCNL for stones <2 cm (34), making it ideal for cystinuria patients who will likely require multiple lifetime procedures (3). In addition, as URS is usualy performed as a day case, this is an important consideration for patients who may require multiple procedures in their lifetime as this limits the overall impact on the disruption to their life (10, 34, 35). Recovery times are generally good, and high levels of stone clearance can be achieved in one procedure, with a relatively low retreatment rate (33). The Holmium laser fiber is effective at fragmenting all types of stones, including cystine stones (36), and leads to the characteristic sulfur smell from breakage of the disulfide bond, which is indicative that the stone contains cystine. Recently, the introduction of thulium fiber has been proposed as an effective alternative to the Holmium laser (37). This appears effective on all stone types, although larger clinical series are needed to understand the effectiveness in cystine stones.

Although considered effective, a recognized limitation of URS, and all surgical techniques to varying degrees, is the presence of retained stone fragments postsurgery and the impact this can have in cystinuria, particularly with larger stones (38). The consequence of retained stones with noncystine stones is less problematic as small fragments usually pass in the weeks or months postsurgery. In the cystinuria population, however, some literature works support that the retained stone fragment size directly correlates to further stone development and further intervention (38). Thus, whatever procedure is chosen, it should be with the aim of complete stone clearance. Thus, in larger stone burdens, it may be necessary to perform a staged "relook" procedure to completely treat large stones (3, 38).

The main disadvantage of URS can be the size of calculi urologists are able to take on, particularly those that are in difficult-to-reach locations (32). Lower pole stones, stones in angled calyces, or calyces with narrow infundibulum can sometimes be difficult to reach and fragment (32, 33). The use of ureteric access sheaths may allow larger fragments to be removed during surgery; however, they are associated with their own risk profile (39).

In the context of cystinuria, and in close discussion with the individual patient, urologists may choose to take on larger stone burdens using this approach to avoid the insult from PCNL, given the likelihood of needing multiple lifetime procedures. Consensus guidelines advocate that URS is a first-line treatment for all stones up to 10 mm in the kidney (3). For stones 10–20 mm in the lower pole, URS or PCNL may be chosen depending on lower pole anatomy and patient/surgeon preference. For stones 10–20 mm in other locations in the kidney, URS would be considered the first option with PCNL as the second line (2, 34).

Percutaneous Nephrolithotomy

International and European guidelines recommend the use of PCNL as a first-line surgical management option for stones greater than 20 mm (2), and this is the same for cystinuria (3). PCNL traditionally requires overnight in-patient stay; however, it may also be offered as a day-case procedure for selected patients (40). In addition to large singular stones, PCNL combined with URS (ECIRS) provides excellent access to complex calculi that involve multiple areas of the collecting system and calyces (39). The improved degree of access and vision within the renal pelvis allows for larger fragments of stone to be removed and gives the greatest chance of complete stone clearance compared to other treatment modalities (40, 41). Puncturing and dilation of a tract cause trauma to the parenchyma, and complications can include bleeding, infection, and damage to nearby structures and vessels that can rarely require embolization or even nephrectomy (42).

Repeated PCNL procedures at the same location or site may compound the amount of surgical trauma to the affected kidney and result in localized scar tissue, loss of nephrons, and ultimately impact renal function over time (43). As a result, the threshold to treat stones percutaneously may be higher for cystine stone formers than it would be for other stone types, taking into consideration lifetime procedure rates and unavoidable trauma sustained to the kidney with this surgical method (3). However, due to the rate of stone formation seen in cystinuria patients, PCNL may be necessary to surgically treat large stone burdens safely and effectively. Care must be given to those with established CKD or a single kidney, both commonly seen in this cohort, to avoid further renal insult in this cohort (5).

Recently, the miniaturization of PCNL has been popularized and offers an alternative to the "standard" 24–30 Fr sheath used in conventional PCNL (40, 44). Mini-PCNL is also a good alternative to flexible ureteroscopy for larger renal stone burdens, especially when the surgeon does not feel able to clear the stone completely in one sitting. Overall, mini-PCNL is associated with less overall renal trauma than standard PCNL, with a quicker recovery time, and can result in reduced hospital stay (45). In addition, it is associated with less overall blood loss, lower transfusion rates, and fewer complications overall with the exception of infective complications (44, 45). For cystinuria patients, mini-PCNL offers a good alternative to a standard PCNL as it is associated with equivocal stone clearance results, albeit at the expense of longer operating times (45). The exact optimum or maximum stone size is unknown and will depend on surgeon preference. We have found it particularly useful in cystinuria patients, either where multiple tracts are required or with combined URS to try and ensure complete stone clearance.

Endoscopic combined intrarenal surgery (ECIRS) aims to resolve some of the limitations associated with both PCNL and URS individually by combining the two procedures (46). Both PCNL and URS are each performed simultaneously on the ipsilateral collecting system (46). ECIRS is particularly beneficial when there are stones in multiple calyces that might not be accessible through a single percutaneous tract (47). We prefer to use a single-use or "disposable" flexible ureteroscope for our ECIRS procedures due to the risk of damage to a reusable scope (48). For cystine stones, it may be advantageous to use single-use in certain cases, particularly those with high stone volume and significant stone burdens in lower poles, to avoid scope damage (49). In addition to the reduced cost of scope damage, using a single-use scope also avoids the need for a second bulky stack system to display images (48, 49).

CONCLUSION

Cystinuria, and the associated formation of calculi, can be a challenging condition to manage due to recurrent pain and stone formation in a predominantly young group of patients. Compliance with both diet and fluid advice can be difficult, coupled with side effects, monitoring requirements, and availability of preventative medications to remain stone free. We have recognized these challenges and set up a dedicated cystinuria clinic that involves a multidisciplinary approach, utilizing urologists, nephrologists, radiologists, and dieticians in order to provide a one-stop clinic wherein patients are able to access these vital services, improving both compliance and the effectiveness of cystinuria management. Our cystinuria patients are routinely followed-up every 3–12 months depending on historical stone formation rates, which allows prompt detection and treatment of stone disease. The dedicated cystinuria clinic has allowed for a pragmatic and proactive approach to cystine stone management to improve patients' quality of life and overall kidney function.

From a surgical perspective, ureteroscopy offers a first-line treatment for most patients with either renal or ureteric stones, with PCNL and mini- PCNL being reserved for particularly challenging stone burdens. ECIRS offers an opportunity to render patients with complex stone burdens stone-free in a single procedure.

AUTHOR CONTRIBUTIONS

CC: first author; SG: second author; KT: third author; and MB: final author and supervisor. All authors contributed to the article and approved the submitted version.

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Mini-Percutaneous Nephrolithotomy With an Endoscopic Surgical Monitoring System for the Management of Renal Stones: A Retrospective Evaluation

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Purpose: To compare the outcomes and postoperative quality of life of patients with renal calculi who underwent standard percutaneous nephrolithotomy (sPNL), mini-invasive percutaneous nephrolithotomy (mPNL) or mPNL with an endoscopic surgical monitoring system (ESMS) using a retrospective clinical trial.

Methods: Eighty-six adult patients with renal stones who were treated with sPNL were retrospectively compared to ninety-two patients who were treated with mPNL between July 2014 and December 2017. Next, further studies were retrospectively conducted using a matched paired method. The ninety-two patients treated with mPNL were divided into two groups based on whether the endoscopic surgical monitoring system (ESMS) was used (ESMS-mPNL vs. non-ESMS-mPNL). The ESMS used strain gauge transducers to measure the inflow and outflow of irrigation solution. Bleeding and fluid absorption during endoscopic surgery could be accurately calculated by computer program in ESMS.

Results: The fluoroscopy time, complication rate, stone-free status and clinically insignificant residual fragment (CIRF) rate were not significantly different between the two groups (sPNL vs. mPNL). The mPNL group had a significantly longer operation time than the sPNL group, and the mPNL group exhibited a markedly reduced 12-h postoperative visual analogue pain scale (VAS) score, mean hospitalization time, and return to work time, had slightly reduced haemoglobin loss, and underwent more tubeless operations. Moreover, among the 92 patients who underwent mPNL, the operation time ($P = 0.090$), complication rate ($P = 0.996$), stone-free status ($P = 0.731$), CIRF rates ($P = 0.125$) and number of tubeless operations ($P = 0.760$) were not significantly different between the two subgroups (non-ESMS-mPNL vs. ESMS-mPNL); however, the patients in the ESMS-mPNL group had significantly longer irrigation times than those in the non-ESMS-mPNL subgroup, along with marked reductions in irrigation fluid, blood loss, haemoglobin loss, 12 h postoperative VAS score, mean hospitalization time, and return to work time.

Conclusions: mPNL is less painful than sPNL in patients undergoing treatment for 20–40 mm renal stones. Similar stone-free rates were achieved by the two procedures, but mPNL was superior to sPNL in terms of blood loss, discomfort, hospitalization time and return to work time. We think that ESMS-mPNL is less painful for patients and more efficacious than non-ESMS-mPNL, and ESMS-mPNL achieves a stone-free rate that is similar to non-ESMS-mPNL in patients receiving treatment for 20–40 mm kidney stones.

Keywords: standard percutaneous nephrolithotomy, mini-percutaneous nephrolithotomy, endoscopic surgical monitoring system, renal calculus, retrospective study

INTRODUCTION

Percutaneous nephrolithotomy (PNL) should be the most commonly used first-line treatment for patients with large or complex renal stones (1); however, PNL can cause serious complications and morbidities, including bleeding, organ injury, pain, infection, vascular embolism and accidental death (2, 3). Therefore, there is a need for alternative treatments that minimize the risks associated with PNL (4). Mini-PNL (mPNL) was originally used for paediatric patients, and later, it was widely applied to the general population because it can reduce complications and morbidities (5).

In the last 20 years (with the development of minimally invasive nephroscopy, nephrostomy sheath and computer imaging technology), sPNL has been partially replaced by mPNL (6). However, whether mPNL is more effective and safer than sPNL is still inconclusive, and the debate is ongoing. Ruhayel et al. (1) confirmed that mPNL can achieve a considerable stone-free rate (SFR), but the operation time is longer. However, mPNL has the obvious advantages of reduced bleeding and a shorter hospital stay. Jiao et al. (7) demonstrated that the overall evidence was not sufficient to prove a significant difference between mPNL and sPNL in terms of complications and morbidities.

Some studies have reported that operation with a continuous open flow system using X-ray or endoscopic guidance can also be used to prevent electrolytic imbalance. When the difference between the inflow and outflow fluid exceeds 500 ml, further procedures should be terminated, a nephrostomy tube must be used, and the electrolyte levels need to be measured (8, 9). Endoscopic monitoring is also helpful to evaluate changes in irrigating fluid absorption, hemodynamics and electrolyte levels (10). We measured irrigation fluid absorption and bleeding with a new strategy called the endoscopic surgical monitoring system (ESMS). The use of the ESMS to guide percutaneous renal access during mPNL has never been reported; hence, we performed a retrospective study to assess the safety and efficacy of ESMS-guided renal access in PNL.

It is still uncertain whether mPNL with the use of an endoscopic surgical monitoring system is superior to mPNL or sPNL; hence, we performed a retrospective study comparing the outcomes of the three major surgical techniques currently used in patients with kidney stones.

METHODS

Patients and Grouping

This retrospective study was approved by the Ethical Committee of the Lanzhou University Second Hospital (No. 2016A-059; Date: July 20th, 2016), and patients signed an informed consent form before the operation. Between June 2014 and November 2017, 354 patients underwent surgery for renal calculi.

Demographic data, patient history, symptoms and signs, image analyses, ultrasound data, and surgical procedures were collected through chart review. In addition, postoperative clinical data were collected through chart review and outpatient records.

The study design and workflow are summarized in **Figure 1**. We selected the appropriate patient for each procedure according to the patient's preference. A total of 178 patients were divided into two groups based on surgical procedure. Group 1 included 86 patients who underwent sPNL, while Group II included 92 patients who underwent mPNL. The ninety-two patients with renal stones who underwent mPNL were further divided into two subgroups based on whether the endoscopic surgical monitoring system was used during mPNL (ESMS-mPNL): Group III (ESMS-mPNL, 46) and Group IV (non-ESMS-mPNL, 46).

The exclusion criteria were age < 18 years or > 65 years and congenital renal abnormalities, solitary kidney or hydronephrosis, impaired renal function or coagulation disorder. In the preoperative period, all the patients were evaluated by urinalysis, urine culture, coagulation tests and radiologic studies, including ultrasonography, radiography of the kidney, ureter, and bladder (KUB) and computerized tomography (CT), and the haemoglobin (Hgb), serum urea and creatinine levels of the patients were measured. The stone sizes were determined by measuring the longest axis of the stones on radiology.

Surgical Techniques

All the patients were assessed by noncontrast CT (NCCT) before the operation. The size of each stone was determined by measuring the maximum size of each stone. For multiple stones, the sum of the maximum size of each stone was calculated. All patients with preoperative urinary infections

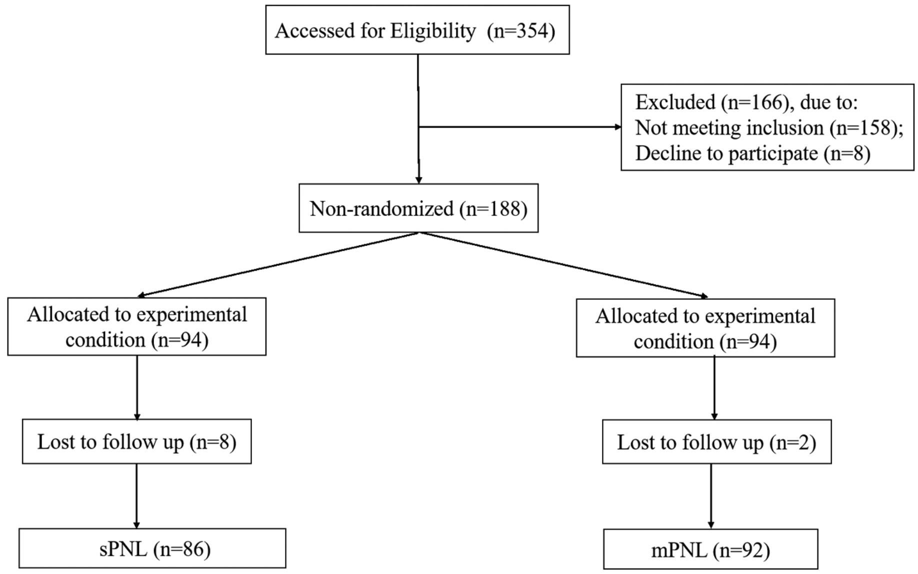

FIGURE 1 | Specific procedures for case screening and patient grouping.

were treated with antibiotics based on the bacterial culture and sensitivity tests. When the urine cultures became sterile, the patients were scheduled for PNL. For antibiotic prophylaxis, second-generation cephalosporins were administered before surgery, and the antibiotics were continued until the nephrostomy catheter was removed. Percutaneous renal puncture under fluoroscopic guidance was performed with patients in the prone position.

For patients undergoing sPNL, the nephrostomy tract was dilated up to 22–30 F using an Alken metal expander (Karl Storz, Tuttlingen, Germany), followed by the placement of the Amplatz sheath. A 24-F nephroscope (R. Wolf, Knightlingen, Germany) was applied. Finally, the stones were fragmented by pneumatic lithotriptor (Swiss lithotriptor EMS, Switzerland), and the fragments were removed using a grasper. When the operation was almost complete, a ureteral catheter was sometimes placed based on the intraoperative findings and the decision of the surgeon.

For the mPNL procedure, the bundle was expanded to 18–20 F using a single-step expander under spinal anaesthesia. A 12-F rigid nephroscope was used. A pneumatic ballistic lithotripsy was used to break the stones. During the removal of the nephroscope, the stone fragments were removed through the ureteral catheter. When the operation was nearly complete, the ureteral stent was placed and the sheath was directly led out by visual inspection. The nephrostomy tube (no tube) was not inserted if there were no complications (e.g., bleeding, perforation of the renal calyceal system) or presence of obvious residual stones, and the patient was not scheduled for a second examination. The kidneys were continuously rinsed with NaCl solution (0.9%), and the absorbed fluid volume was worked out according to previously described criteria (11). Briefly, the volumes of total irrigation fluid used and total drainage fluid, including the fluid found on the floor and in the curtain, were measured, and the difference between them was considered as the volume of absorbed liquid.

The endoscopic surgical monitoring system (ESMS) was patented and approved by the Chinese Food and Drug Administration, and this system is starting to be produced (approved no: 20162210011) (**Figure 2**). The working principle of the ESMS is illustrated in **Figure 3**. The ESMS was confirmed to be accurate and valid during urological endoscopic surgery (10). For the mPNL procedure, an 18 G percutaneous needle was used to enter the renal collection system under ultrasound guidance. The renal collection system was dilated to 20 F with a fascia expander, and a stripping sheath was placed. The fragmentation and removal of stones were performed by a rigid nephroscope passing through the sheath. Continuous irrigation of the kidney was performed with normal saline at room temperature (22°C), and an automatic pumping irrigation system was used to maintain a fixed pressure. All the patients were administered intravenous fluids with lactated Ringer's solution. The hemoglobin, haematocrit, electrolyte, urea and creatinine levels were measured 10 min before the operation for postoperative comparison. The irrigation time, volume of irrigation fluid used, blood loss and irrigation fluid absorption were monitored by the ESMS. The process of liquid absorption measurement for patients who underwent surgery with the ESMS is shown in **Figure 4**.

Follow-up

The visual analogue scale (VAS) was used to assess the patient's pain after the operation (11). In our clinic, we routinely perform VAS measurements in the postoperative period. The VAS was used to classify pain severity of ten 1-cm horizontal segments, with 0 cm indicating no pain and 10 cm indicating the worst

FIGURE 2 | The prototype of endoscopic surgical monitoring system.

pain. The VAS scores were assessed at 12 h postoperatively (12). The fluoroscopy time (FT), operation time (OT), JJ stent insertion rate, hospitalization time (HT) and return to work time (RWT) were also noted. Complications were classified based on the Clavien classification system (13).

On the first postoperative day, the general condition and pain status of the patients were evaluated, and the KUB was evaluated to verify JJ stent insertion and to verify that the patient had a stone-free status. During the first postoperative month, low-dose computed tomography was performed. A stone-free status was defined as no residual debris on CT evaluation during the first month after the operation. Residual stones ≤4 mm in size were defined as clinically insignificant residual fragments (CIRFs). After obtaining approval from the local ethics committee, we retrospectively assessed the patient files and documents in our clinics. An informed consent form including the ethical information and the detailed surgical procedures was given to all the patients before the surgery.

Statistical Analysis

All statistical analyses in this retrospective study were conducted using SPSS 26.0. The complication rate, stone-free rate, CIRF rate, and number of tubeless procedures, as well as other perioperative variables, were compared between the two groups (sPNL vs. mPNL) using Student's t test. A logistic regression analysis was performed to compare the fluoroscopy time, operative time, haemoglobin loss, mean hospitalization time, and return to work time between the groups. The analysed factors also included the mean age, sex, stone size, BMI, history of previous open renal surgery (ORS), stone characteristics (number, size, localization), hydronephrosis grade, and whether sPNL or mPNL was performed. Baseline characteristics and perioperative parameters in both subgroups (ESMS-mPNL vs. non-ESMS-mPNL) were compared by means of paired, Tukey's, and independent t tests. *P* values <0.05 were considered statistically significant.

RESULTS

Patient Recruitment and Clinical Features

In the present study, a total of 178 patients (86 underwent sPNL and 92 underwent mPNL) were enrolled. The mean age of the patients was 40.42 ± 11.68 and 41.93 ± 11.9 years in the sPNL group and the mPNL group, respectively. **Table 1** summarizes the preoperative data analysis of all the enrolled patients. Clinical parameters did not differ significantly between the groups (mPNL vs sPNL), including mean age, sex, BMI, stone size, number of stones, side of surgery, stone localization, and preoperative haemoglobin. However, the previous ORS of the patients were significantly higher in the mPNL group.

We retrospectively compared 92 mPNL patients, including 46 in the ESMS-mPNL group and 46 patients in the non-ESMS-mPNL subgroup. The operative data are presented in **Table 2**. No difference was detected between the groups (ESMS-mPNL vs non-ESMS-mPNL) regarding mean age, sex, BMI, previous ORS, preoperative haemoglobin, number of stones, side of surgery, stone location, or hydronephrosis grade.

sPNL vs. mPNL for Renal Stones

The complications and postoperative outcomes of the patients in the sPNL group vs. the mPNL group are presented in **Table 3**. A shorter fluoroscopy time was reported in the mPNL group (118 ± 13.0 vs. 122 ± 14.1 s), which was not statistically significant ($P = 0.051$). The CIRF rate and SFR at 1 month were both similar between the two groups. Clavien grade 1 complications were comparable between the groups, 3 patients in the sPNL group vs 2 patients in the mPNL group. In both the sPNL and mPNL groups, 1 patient had a Clavien grade 2 complication and received transfusions. In terms of postoperative complications, no difference was observed between the groups ($P = 0.182$).

A longer operative time was reported with the mPNL group (67.4 ± 8.1 vs. 57.3 ± 7.5 min, respectively; $P < 0.001$). The amount of haemoglobin loss was significantly reduced in the mPNL group (1.46 ± 0.93 vs. 1.14 ± 0.74, respectively;

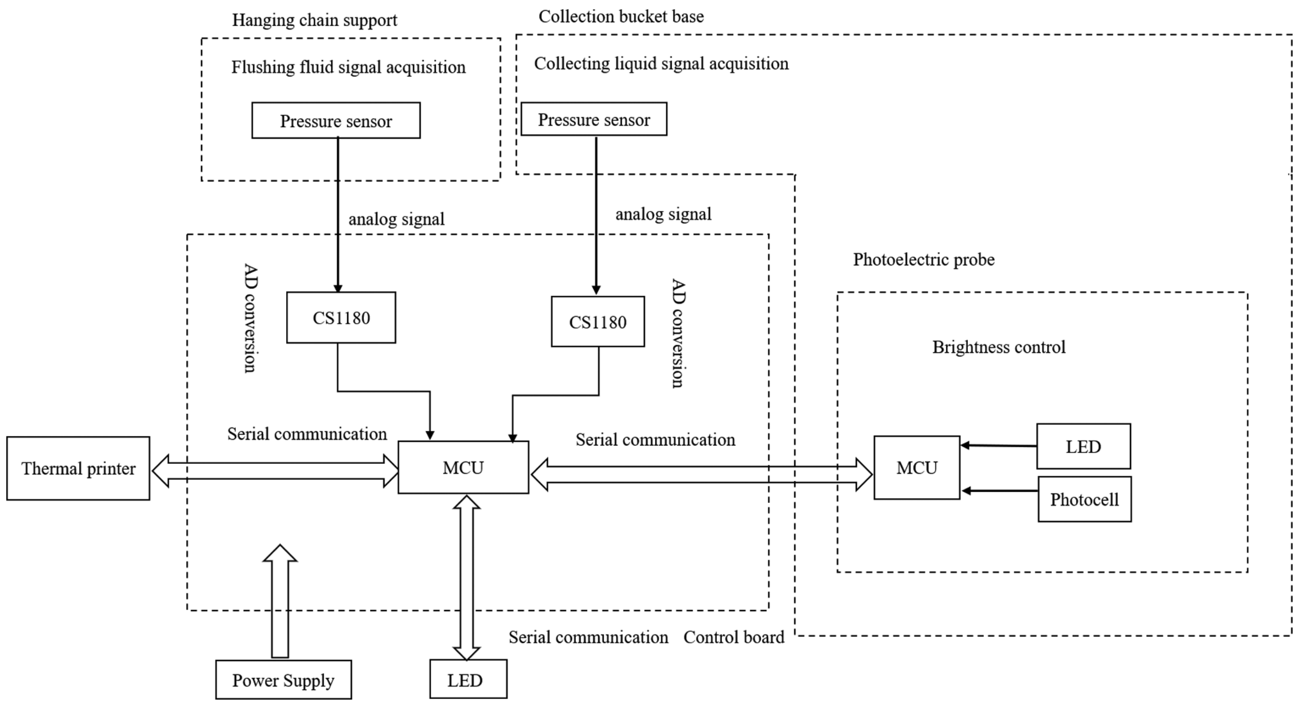

FIGURE 3 | The working principle of ESMS is used in PNL. CS1180: high precision conversion chip; LED: light emitting diode; MCU: micro control unit.

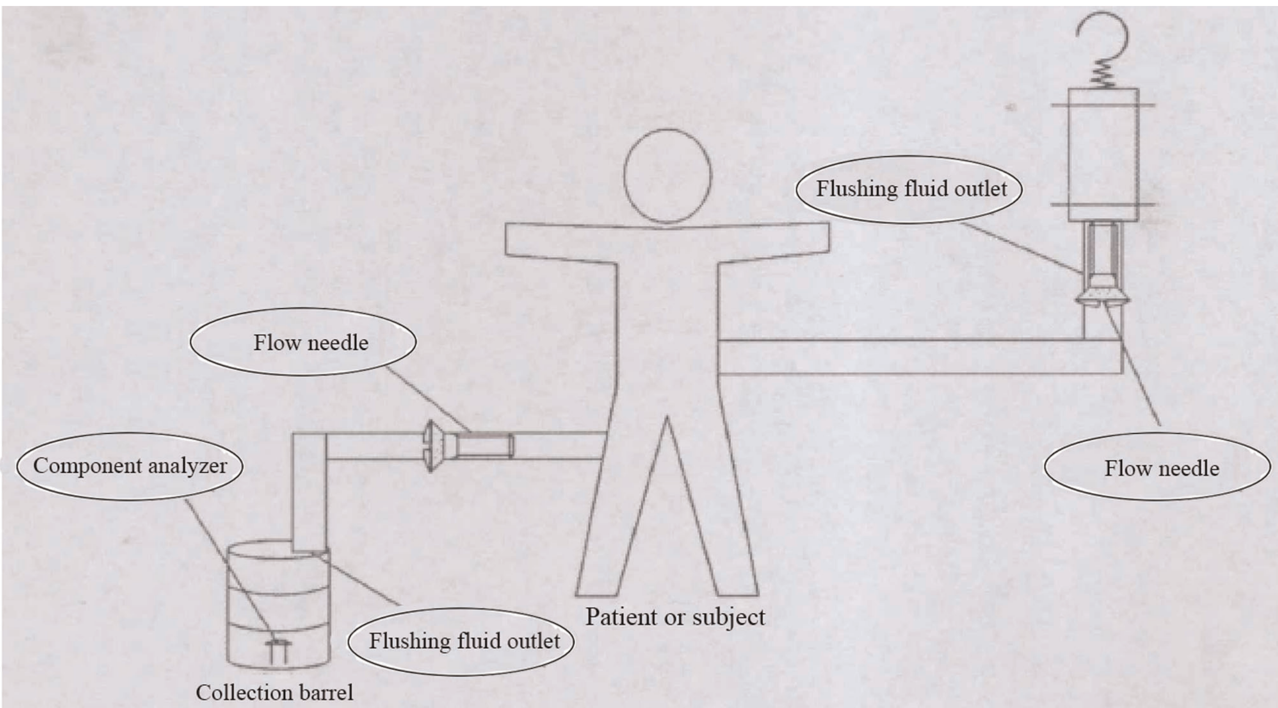

FIGURE 4 | Measurement of fluid absorption in ESMS-mPNL patients.

TABLE 1 | Preoperative data of all patients.

Demographic data	sPNL (*n* = 86)	mPNL (*n* = 92)	*P* value
The mean age, mean ± SD	40.42 ± 11.68	41.93 ± 11.9	0.395
Gender (male/female)	56/30	62/30	0.750
The mean stone size (mm), mean ± SD	29.0 ± 5.32	28.74 ± 4.93	0.735
BMI (kg/m^2)	24.7 ± 3.54	24.4 ± 4.02	0.599
Previous ORS	9/86	22/92	0.020
Number of stones			
1	71	72	0.473
≥2	15	20	
Side of surgery			
Left	45	46	0.758
Right	41	46	
Location of stone (%)			
Upper pole	35	32	0.991
Middle pole	25	36	
Lower pole	26	24	
Hydronephrosis grade, *n* (%)			
G0	15	17	0.998
Mild (G1 or G2)	30	28	
Moderate (G3)	20	22	
Severe (G4)	21	25	

BMI, body mass index; G0, grade 0; G1, grade 1; G2, grade 2; G3, grade 3; G4, grade 4; mPNL, mini-PNL; ORS, open renal surgery; PNL, percutaneous nephrolithotomy; SD, standard deviation; sPNL, standard PNL.

TABLE 2 | Preoperative data of 92 mPNL patients.

Demographic Data	Non-ESMS-mPNL (*n* = 46)	ESMS-mPNL (*n* = 46)	*P* value
The mean age ± SD, mean ± SD	41.36 ± 12.32	42.08 ± 12.66	0.781
Gender (male/female)	34/12	28/18	0.182
The mean stone size (mm), mean ± SD	29.22 ± 5.36	28.26 ± 4.38	0.349
BMI (kg/m^2)	25.3 ± 3.67	24.5 ± 4.05	0.319
Previous ORS	10/46	12/46	0.631
Preoperative hemoglobin (gm/dL)	12.39 ± 1.21	12.94 ± 1.62	0.070
Number of stones			
1	35	37	0.613
≥2	11	9	
Side of surgery			
Left	22	24	0.677
Right	24	22	
Location of stone (%)			
Upper pole	16	16	0.287
Middle pole	15	21	
Lower pole	15	9	
Hydronephrosis grade, *n* (%)			
G0	9	8	0.896
Mild (G1 or G2)	14	14	
Moderate (G3)	12	10	
Severe (G4)	11	12	

BMI, body mass index; ESMS, endoscopic surgical monitoring system; G0, grade 0; G1, grade 1; G2, grade 2; G3, grade 3; G4, grade 4; mPNL, mini-PNL; ORS, open renal surgery; PNL, percutaneous nephrolithotomy; SD, standard deviation; VAS, visual analogue scale.

$P = 0.012$), and the 12 h postoperative VAS score was lower in the mPNL group (2.05 ± 0.48 vs. 1.82 ± 0.54, respectively; $P = 0.003$). We found that the patients in the mPNL group had significant reductions in the return-to-work time ($P = 0.002$) and the hospitalization time ($P = 0.024$). Thirty-four (37.0%) patients in the mPNL group and 4 (4.7%) patients in the sPNL group were treated by tubeless surgery ($P < 0.001$).

ESMS-mPNL vs. non-ESMS-mPNL for Renal Stones

The complications and postoperative outcomes of ESMS-mPNL vs. non-ESMS-mPNL are presented in **Table 4**. A longer operation time was reported with ESMS-mPNL (66.1 ± 6.2 vs. 68.2 ± 5.6 min), which was not statistically significant ($P = 0.090$). The CIRF rate and stone-free rate at 1 month were both similar between the two subgroups ($P = 0.125$). Eighteen (39.1%) patients in the non-ESMS-mPNL group and 16 (34.8%) in the ESMS-mPNL group underwent tubeless surgeries ($P = 0.670$). Two patients had Clavien grade 1 complications, and both patients received transfusions. In terms of the postoperative complications, no difference was found between the groups ($P = 0.996$).

The comparison of the laboratory values in the patients in the ESMS-mPNL and non-ESMS-mPNL subgroups showed a significant decrease in irrigation fluid absorption ($P = 0.001$), blood loss ($P < 0.001$), and haemoglobin loss ($P = 0.044$) (**Table 4**). A longer irrigation time (52.0 ± 18.3 vs. 42.2 ± 14.1 min) and a smaller volume of absorbed fluid (502 ± 102 vs. 712 ± 95 ml) were observed in the patients in the ESMS-mPNL group compared with those in the non-ESMS-mPNL group ($P = 0.005$ and $P < 0.001$, respectively).

The mean hospitalization time in the non-ESMS-mPNL subgroup was 53.82 ± 13.48, compared to 47.31 ± 12.04 in the ESMS-mPNL subgroup; these values were significantly different ($P = 0.017$). The mean return to work time was 12.06 ± 3.21 in the non-ESMS-mPNL subgroup and 9.87 ± 2.76 in the ESMS-mPNL subgroup, which was a significant difference ($P = 0.001$).

DISCUSSION

Numerous studies debate the merits of minimally invasive PNL (14, 15), and there are considerable debates regarding the merits of mPNL and sPNL (16–18). Irrigating fluid absorption, bleeding and haemodynamic abnormalities are common. PNL-related complications are common, and patient recovery from

TABLE 3 | Operative, postoperative and outcomes of sPNL and mPNL.

Data	sPNL (*n* = 86)	mPNL (*n* = 92)	*P* value
Fluoroscopy time (sec.), mean ± SD	122 ± 14.1	118 ± 13.0	0.051
Operation time (min.), mean ± SD	57.3 ± 7.5	67.4 ± 8.1	<0.001
Hemoglobin loss (mg/dl)	1.46 ± 0.93	1.14 ± 0.74	0.012
VAS score postop 12 h, mean ± SD	2.05 ± 0.48	1.82 ± 0.54	0.003
Complications rate			
Clavien 1	3 (5.2)	2 (4.1)	0.182
Clavien 2	1 (1.9)	1 (1.6)	
Clavien 3	–	–	
Clavien 4	–	–	
Mean hospitalization time (hour), mean ± SD	53.47 ± 13.21	49.27 ± 11.34	0.024
Stone-free rate (1. month)	75 (89.1)	80 (90.3)	0.961
CIRF rate (%)	2 (2.3)	3 (3.3)	0.71
Return to work time (day), mean ± SD	12.16 ± 2.41	10.98 ± 2.48	0.002
Tubeless procedure (%)	4 (4.7)	34 (37.0)	<0.001

CIRF, clinically insignificant residual fragment; mPNL, mini-PNL; PNL, percutaneous nephrolithotomy; SD, standard deviation; VAS, visual analogue scale.

TABLE 4 | Comparison of operative data and complications for Non-ESMS-mPNL vs ESMS-mPNL groups.

Data	Non-ESMS-mPNL (*n* = 46)	ESMS-mPNL (*n* = 46)	*P* value
Operation time (min.), mean ± SD	66.1 ± 6.2	68.2 ± 5.6	0.090
Irrigation time (min)	42.2 ± 14.1	52.0 ± 18.3	0.005
Volume of irrigation fluid (ml)	1651.9 ± 631.4	1245.6 ± 548.2	0.001
Volume of fluid absorbed (ml)	712 ± 95	502 ± 102	<0.001
Blood loss (ml)	142.1 ± 93.54	82.2 ± 41.2	<0.001
Hemoglobin loss (mg/dl)	1.21 ± 0.78	1.02 ± 0.63	0.044
VAS score postop 12 h	1.95 ± 0.56	1.66 ± 0.42	0.005
Complications rate			
Clavien 1	2 (4.8)	2 (3.2)	0.996
Clavien 2	–	–	
Clavien 3	–	–	
Clavien 4	–	–	
Mean hospitalization time (hour), mean ± SD	53.82 ± 13.48	47.31 ± 12.04	0.017
Stone-free rate (1. month)	41 (89.1)	42 (90.3)	0.731
CIRF rate (%)	2 (4.3)	1 (2.2)	0.125
Return to work time (day), mean ± SD	12.06 ± 3.21	9.87 ± 2.76	0.001
Tubeless procedure (%)	18 (39.1)	16 (34.8)	0.670

CIRF, clinically insignificant residual fragment; ESMS, endoscopic surgical monitoring system; mPNL, mini-PNL; PNL, percutaneous nephrolithotomy; SD, standard deviation; VAS = visual analogue scale.

anaesthesia is challenging, especially in high-risk groups (19, 20). There are few studies on PNL-related blood loss, haemodynamic changes and electrolyte levels. Similarly, there are only a few studies that compare the differences in blood loss and haemodynamic changes between sPNL and mPNL; thus, it was decided that the effect and the flushing fluid absorption level associated with the two different surgical methods should be analysed. In addition, there are few studies on the haemodynamic and metabolic changes that occur due to mPNL, and there is a lack of studies that compare the haemodynamic and metabolic changes between ESMS-mPNL and non-ESMS-mPNL; thus, we aimed to explore the effects and the fluid absorption levels associated with the two surgical procedures.

In the present retrospective study, our data indicated the following. (a) Compared with that of sPNL, the operation time of mPNL was significantly longer, and the degree of pain, hospitalization time, and return to work time were significantly reduced. Additionally, in the mPNL group, more tubeless procedures were performed, and the amount of haemoglobin loss was slightly reduced. (b) The results confirmed that there was no difference in fluoroscopy time, complication rate, stone-free rate, or CIRF rate between the mPNL and sPNL groups. (c) The ESMS-mPNL group had a significantly longer irrigation time and a smaller volume of fluid absorbed than the non-ESMS-mPNL group (but these values were clinically comparable), with markedly reduced volume of irrigation fluid, blood loss, haemoglobin loss, degree of pain, hospitalization time, and return to work time. (d) There was no difference in the operation time, complication rate, stone-free rate, CIRF rate or number of tubeless procedures between the non-ESMS-mPNL and ESMS-mPNL subgroups. Our study provides insights that mPNL is more effective and safer than sPNL for managing renal calculi with a diameter of 20–40 mm. However, sPNL is associated with a longer operative time. In addition, ESMS-mPNL is a better method for managing renal calculi than non-ESMS-mPNL.

From a technical perspective, mPNL has more advantages and greater safety for the treatment of kidney stones. First, mPNL uses a smaller percutaneous catheter than sPNL, so the renal parenchyma is less damaged. On the other hand, although smaller renal tubules may hinder the fragmentation and removal of stones, research has shown that mPNL has an obvious advantage in managing renal calculi with diameters of 20–40 mm (21, 22).

Although different definitions of operation time were used in the trials, our summary analysis showed that the operation time of mPNL was obviously longer than that of sPNL. This difference may be due to the narrower field of view of the micro endoscope and the need to break the stones into smaller pieces to remove the pieces through a smaller channel. Moreover, the larger treatment range provides more options for lithotripsy.

The hospitalization and return-to-work times associated with mPNL were shorter than those associated with sPNL. The possible reason is that patients who undergo mPNL have less postoperative discomfort and are more likely to undergo a tubeless surgery (23, 24). The placement of the postoperative nephrostomy tube usually depends on the size of the renal tubules (25); therefore, mPNL is more likely to be completed without a nephrostomy. Previous studies compared the postoperative discomfort between patients treated with mPNL and patients treated with sPNL (17). One tool for analysing surgical discomfort is the VAS for pain analysis (26). In our retrospective study, the VAS was used after 12 h. Although mPNL patients showed significant improvement in their VAS after 12 h, it was uncertain whether this advantage was due to the use of smaller catheters or the omission of nephrostomy tubes.

The volume of irrigation fluid during the operation was significantly lower in the ESMS-mPNL subgroup than in the non-ESMS-mPNL subgroup ($P < 0.0001$). The volume of fluid absorbed during ESMS-mPNL decreased significantly compared to the non-ESMS-mPNL group, and the endoscopic surgical monitoring system might promote better fluid absorption during ESMS-mPNL than during non-ESMS-mPNL. Liquid absorption mainly depends on the flushing pressure and the length of the equipment. Although the non-ESMS-mPNL group absorbed more fluid, it may not be enough to improve the haemodynamic imbalance during surgery.

The advantages of ESMS-mPNL over non-ESMS-mPNL include reduced bleeding, fewer complications, less postoperative pain, a shorter hospitalization time and shorter return to work time, and the main disadvantage is that the operation time and irrigation time are longer. A possible explanation for this is that ESMS provides early real-time monitoring and a timelier warning of irrigation fluid absorption and blood loss to make endoscopic surgical procedures safer for patients.

This study is not without limitations and shortcomings. First, this is a retrospective analysis within a single research institution. Second, mPNL was performed using two different procedures. Third, a two-dimensional calculation of stone size was not obtained. In addition, multicentre, large-scale randomization studies should be performed to further verify the above conclusions, and these studies would increase the statistical significance.

CONCLUSION

mPNL and ESMS-mPNL are excellent methods for the treatment of renal stones. ESMS-mPNL is a newer mPNL technique with good efficacy and reduced morbidity and hospitalization times, which benefit patients and improve national health costs. The safety profile of ESMS-mPNL suggests the utilization of ESMS-mPNL for the treatment of renal calculi may be beneficial. Prospective studies are needed to further understand this.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Suplementary Material.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Research idea, study design, and data analyses: HG and ZW. Data acquisition: HW, DK, and RR. Interpretation and first draft: HG with input from ZW. All authors contributed to the article and approved the submitted version.

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FOOTNOTE

The charging standard for this device has been established, RMB 130 per hour. The suggested retail price of the machine is RMB 200000. The average cost-benefit ratio was 1.20 ± 0.24. Available at http://www.gsakyx.cn/index.html.

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Developments in ureteroscopic stone treatment: Key themes and remaining challenges

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Editorial on the Research Topic
Developments in ureteroscopic stone treatment: Key themes and remaining challenges

By Becker REN, Roberts WW, Lipkin ME, Ghani KR. (2022) Front. Surg. 9: 1050285. doi: 10.3389/fsurg.2022.1050285

The 2022 edition of the Developments in Ureteroscopic Stone Treatment (DUST) symposium brought together an international group of content experts and thought leaders in Miami, Florida for a spirited discussion of recent advances and challenges in the field. The content spanned important themes from preventative management to technological advances in ureteroscopes and working instruments, choices around intraoperative parameters such as laser type, energy settings, irrigation methods, lithotripsy strategies (dusting, fragmenting), stenting practices, and post-operative management. Safety and efficacy outcomes remain paramount, but considerations of cost and the patient experience have also gained considerable recognition and interest. **Figure 1** provides a conceptual overview of some of the current themes that are expected to shape discussion over the next decade in the field, several of which are featured in this *Frontiers in Surgery* collection.

One topic of intense interest at the DUST symposium was the proliferation of single-use digital ureteroscopes. As highlighted in work by {Huang et al.} and summarized by {Meng et al.}, these ureteroscopes aim to alleviate some of the challenges of reusable platforms, such as financial cost and complex sterilization. Many new designs also seek to incorporate ergonomic advances such as lighter weight and different grip positions. Single-use platforms have overall become far more affordable, even as their quality has improved to closely rival that of reusable ureteroscopes. Studies comparing safety and efficacy outcomes between single-use and reusable ureteroscopes find they perform similarly overall, and even on parameters such as overall program cost, environmental footprint, and image quality, single-use ureteroscopes are increasingly competitive with reusable platforms.

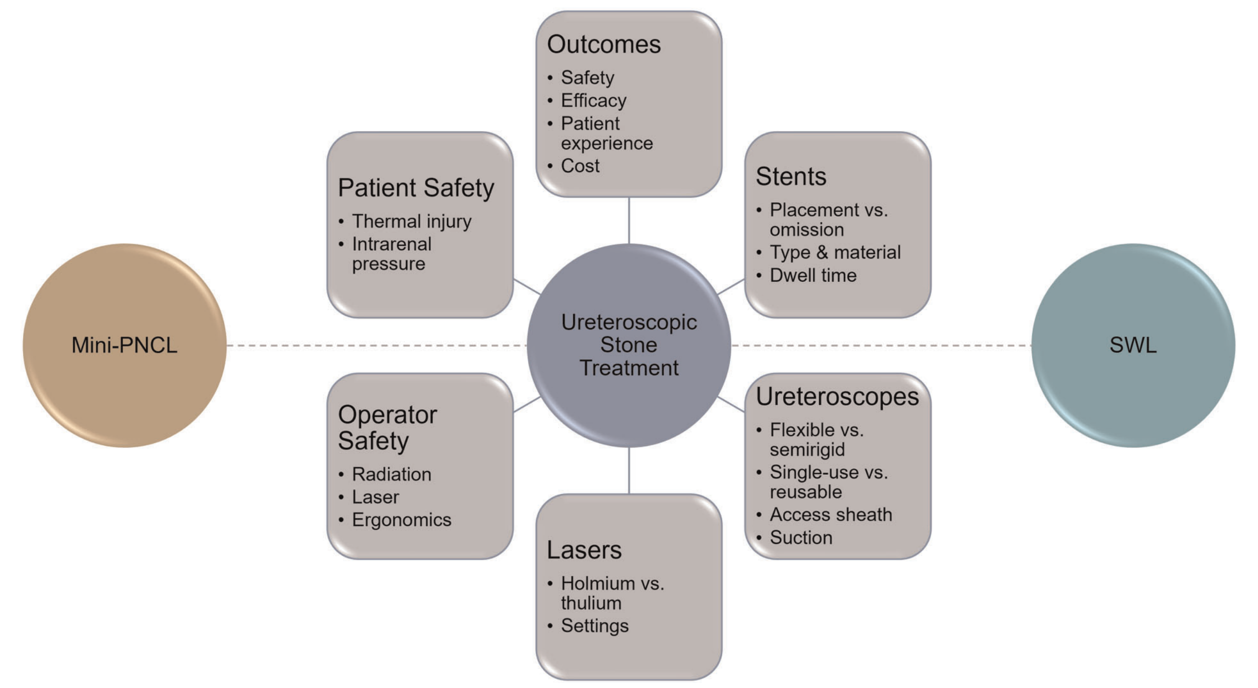

FIGURE 1
Key themes and remaining challenges in ureteroscopic stone treatment. (Mini-PCNL: mini-percutaneous nephrolithotomy; SWL: shockwave lithotripsy).

Similarly, ureteral stent technology continues to improve with the goals of improving patient comfort while maintaining functional performance. {J. Lee et al.} describe several promising new designs in various stages of development. These incorporate a range of innovations from novel stent compositions and coatings to radical reconceptualization of the stent as we know it, such as suture-based stents or dissolvable material.

Other groups continue to push the field forward with novel technologies for active stone fragment evacuation. Removal of fragments and debris from the collecting system during or after laser lithotripsy may theoretically reduce the risk of steinstrasse, stone recurrence, and/or other complications. At the DUST symposium we heard that fluoroscopic-guided steerable aspiration catheters are currently being tested in US clinical trials, while the in-line system described by {Lai et al.}, which maintains synchronous visualization by adapting a rigid ureteral access sheath into a controlled closed-suction fluid system, has been described in China.

A similar controlled fluid system for mini-percutaneous nephrolithotomy (PCNL) has also been developed in China (Endoscopic Surgical Monitoring System, ESMS), which employs inflow and outflow monitoring gauges to facilitate intraoperative calculations of irrigant fluid absorption and blood loss. {Gui et al.} found in a retrospective comparison that patients undergoing mini-PCNL with the ESMS system had significantly reduced irrigant fluid absorption and blood loss, as well as improved postoperative pain scores and return-to-work time, compared to patients undergoing mini-PCNL without ESMS.

A secondary benefit of such regulated fluid systems is the ability to monitor and modulate intrarenal pressures and thermal dissipation. These previously underappreciated intraoperative parameters were heavily emphasized at the DUST symposium, as emerging data continue to elucidate their critical roles in determining key outcomes such as tissue injury, patient pain, and post-procedural infections. As described by {Khusid et al.}, vigilance of intrarenal pressures and the potential for pyelovenous backflow represents an emerging key strategy for preventing infectious complications. Others, which have been the focus of professional society guidelines include preoperative urine testing, evaluation of patient risk factors, and evidence-based antimicrobial prophylaxis.

Recent years have also seen an improved awareness of operator and staff safety, with increased emphasis on provider wellness and career longevity. Alongside our colleagues throughout the health sciences, urologists are increasingly recognizing that we cannot take the best care of our patients, unless we also take care of ourselves. In their review, {Miller & Semins} summarize many of the key considerations for those performing and assisting with ureteroscopy, including radiation safety, laser safety, and surgical ergonomics. The authors provide numerous simple, practical, and easily implemented strategies to help optimize safety for urologists and operating room staff.

As the field continues to work toward optimizing every aspect of the "index" ureteroscopic stone procedure, we have also accumulated better evidence to guide management of special circumstances and subpopulations. The particular challenges of cystinuria are reviewed in detail by {Clark et al.}, including both medical and surgical management. A systematic review and meta-analysis by {Yi et al.} compares surgical options of flexible ureteroscopy and shockwave lithotripsy (SWL) for stone disease in patients with horseshoe kidney, finding that while both are safe with low complication rates, ureteroscopic treatment offers better stone-free rates. Rounding out the collection, {M. Lee et al.} provide an excellent review and practical guideline for workup and management of nephrolithiasis in pregnancy. This is a prime example of how technological and methodological advances in ureteroscopy have led to its adoption as a safe and successful first line treatment option in these complex patients. The evidence-based multidisciplinary consensus statements fill several important gaps in existing society guidelines, and will undoubtedly prove to be an invaluable resource for the on-call general urologist.

DUST 2022 was an expository glimpse into the future of ureteroscopic stone treatment, touching on many exciting new developments, as well as remaining controversies and challenges. For many attendees, the highlight of the meeting once again was the infamous Balloon Debate, which pitted renowned experts against one another on which is the optimal management strategy for an asymptomatic 9 mm lower pole renal stone. Perhaps by DUST 2023 we will be closer to an answer.

Author contributions

RENB and KRG wrote editorial. MEL and WWR edited and contributed. All authors contributed to the article and approved the submitted version.

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