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Shockwave Lithotripsy of Upper Urinary Tract Calculi - Outcomes of a Multicentre International Prospective Observational Study

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Surgery
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ABSTRACT

Introduction

Shockwave lithotripsy (SWL) is a surgical procedure used in urolithiasis treatment. Several factors can influence its results. This study aims to evaluate “real-world” success rates and identify predictors of treatment success in patients undergoing SWL.

Methods

Adult patients undergoing SWL for urolithiasis at three institutions in Canada and Oman were prospectively enrolled. Treatment success after a maximum of two SWL sessions was assessed by post-operative imaging. Logistic regression assessed for predictors of treatment success.

Results

Between May 2021 and February 2022, 271 patients were prospectively enrolled. Overall success rate was 46.1% after one SWL session, and 58.3% after two sessions. In the univariable and multivariable analyses, smaller stone size and stone surface, and lower stone attenuation on Computerized Tomography were predictors of treatment success.

Conclusion

After two SWL sessions, overall success was 58.3%. Factors related to the stone appear to be the most important in predicting treatment success after SWL.

KEYWORDS

Shockwave Lithotripsy

Urolithiasis

SUMMARY FOR LAY AUDIENCE

Shockwave lithotripsy is a procedure first described in the 1980s for the treatment of stones located in the kidney or in the portion of the urinary tract that connects the kidneys to the bladder (ureters). It is performed with the use of a machine called a lithotripter that applies shockwaves to break the stones. Although it is a minimally invasive and safe procedure, there are factors related to the patient, stone characteristics, and to the procedure itself that influence the success of the treatment. In this study the goal was to include patients who were scheduled to undergo shockwave lithotripsy in three different centers in the world using the same lithotripter and analyze the results and the factors influencing the procedure success. Analyzing the patients' imaging performed after the procedure, 58.3% of the patients were considered as having had a successful shockwave lithotripsy, after a maximum of two procedures. The factors related to the stone, such as a stone size, were found to influence whether or not the procedure would be successful. Although the rates of success in this study were lower than previously described, it was performed by analyzing real-world patients receiving shockwave lithotripsy with the same lithotripter in different centers around the world, and the results should encourage other centers to analyze and understand their own results.

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DECLARATION OF CONFLICT OF INTERESTS

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FUNDING

All participant institutions received funding from Storz Medical, the lithotripter manufacturer.

DEDICATION

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LIST OF ABBREVIATIONS

AUA	American Urological Association
BMI	Body Mass Index
CI	Confidence Interval
CT	Computerized Tomography
CUA	Canadian Urological Association
EAU	European Association of Urology
HU	Hounsfield units
HRQoL	Health-related quality of life
IQR	Interquartile range
KUB	Kidneys, ureters, and bladder plain film X-ray
MET	Medical Expulsive Therapy
MRI	Magnetic Resonance Imaging
PCNL	Percutaneous Nephrolithotomy
OR	Odds ratio
RD	Risk difference
RR	Relative risk

r_s Rho Spearman Correlation Coefficient

SFR Stone free rates

SMLI Storz Medical Lithotripsy Index

SSD Skin to stone distance

SWL Shockwave Lithotripsy

TISU Therapeutic Interventions for Stones of the Ureter

TOWER Team of Worldwide Endourologists Research

UPJ Ureteropelvic junction

URS Ureteroscopy

UVJ Ureterovesical junction

US Ultrasound

UTI Urinary Tract Infection

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 BACKGROUND

Urolithiasis is a prevalent condition in both adult and pediatric populations worldwide. Scales *et al*. reported an 8.8% prevalence in the adult population in the United States in 2012[1]; in China, the prevalence was 6.4% in 2014[2], and in the United Kingdom, the prevalence was 13% in 2016[3]. The incidence of urolithiasis has been increasing in the last few decades[4] due to a number of potential risk factors including dietary patterns, the aging population, climate changes, populational growth, genetics, presence of comorbidities, as well as the increase in the availability of intrabdominal imaging[5,6]. Furthermore, urolithiasis is a recurrent condition, and Eisner *et al*. reported a recurrence rate of 20% at 5 years, and 31% at 10 years[7]. The peak incidence of urinary calculi is the fourth to sixth decades of life[8]. Its recurrent nature significantly impacts health care system costs[9,10] and contributes to increases in indirect costs, such as missed days of work[8,10,11].

Although urinary calculi comprise stones located in the upper tract (kidneys and ureters) and in the bladder, the latter have a different stone formation mechanism (mainly related to bladder outlet obstruction) and requires different management strategies. Therefore, in this context, and for the purposes of this research, urolithiasis refers only to upper tract calculi.

Upper tract stones can have varying presentations, but flank and/or lower abdominal pain radiating to the groin is most common. The intense pain might be accompanied by nausea and vomiting. Other frequent presentations are hematuria (macroscopic or microscopic) and recurrent urinary tract infections (UTI). Some patients though, are asymptomatic and are diagnosed by an incidental finding on imaging performed for other medical reasons.

1.2 UROLITHIASIS MANAGEMENT

Once urolithiasis is diagnosed, there are essentially three different management strategies: observation, medical expulsive therapy (MET), and surgical treatment. The management choice will depend on several factors, such as the patient's symptoms, the stone size, the stone location, the presence of comorbidities and other complicating factors such as anatomic variants and urinary tract infections (UTI), and at times social factors, such as occupation.

Clinical guidelines created by several national urological associations provide guidance to assist urologists in the decision-making process of urolithiasis treatment, with the recommendations being based primarily on the size and location of the stone within the urinary tract. The American Urological Association (AUA) released the latest version of their guideline on surgical treatment of urolithiasis in 2016[12,13] while the most recent version of the European Association of Urology (EAU) guideline was released in 2020 with a limited update on medical management in 2021[14]. The Canadian Urological Association (CUA) also has released a guideline on management of ureteric stones, with its latest version been released in August 2021[15]. Although all of them are largely adopted by urologists worldwide, their recommendations differ slightly. Table 1 synthetizes the guidelines' recommendations.

Within the last 30 years, the surgical treatment of urolithiasis has evolved significantly, and the trends in the surgical treatment have also changed. For smaller stones, widely defined as less than 2 cm in size, an increase in ureteroscopy (URS) rates and a corresponding significant decline in the number of shockwave lithotripsy (SWL) procedures has been reported worldwide[9,16]. This is thought to be driven in part by the development of newer, more efficient laser technologies, smaller endoscopes with better imaging and navigability, as well as a larger number of urologists trained in endourological procedures[17]. However, the debate about the best treatment option for ureteric and renal calculi has continued.

The exact location of the stone within the urinary tract can significantly impact treatment decisions and recommendations. Calculi can be categorized as renal calculi (residing within the kidney) or ureteric calculi (present within the ureter). Historically, ureteric calculi have been classified according to their location within the ureter. Some authors have divided the ureter in three portions: the upper ureter, between the ureteropelvic junction (UPJ) and the upper border of the sacrum; the middle ureter, the portion between the upper border and the lower border of the sacrum; and the lower or distal ureter, located below the lower border of the sacrum until the ureterovesical junction (UVJ). Other authors have simply divided the ureter in two portions: proximal ureter, defined as extending between the UPJ and the crossing of the iliac vessels; and distal ureter, the portion distal to the crossing of the iliac vessels until the UVJ[18].

As mentioned previously, observation may be an appropriate management strategy for certain stones. For renal stones that are asymptomatic or non-obstructing, surveillance may be the best approach. For small stones located in the ureter, they may pass spontaneously and may not require surgical intervention. For stones 5 mm or less, the chances of spontaneous passage within 4 to 6 weeks from the initial presentation is estimated to be 68%, while for stones between 5 and 10 mm in size, this rate drops to 47%[19,20].

The AUA guideline recommends observation with or without medical expulsive therapy (MET) with alpha-blockers for distal ureteric stones (below the iliac vessels) of 10 mm or less. If spontaneous passage does not occur after 4 – 6 weeks or if symptoms worsen, the guideline recommends offering URS as first line treatment for distal and mid ureteric stones and either URS or SWL for proximal ureteric stones[12,13]. The EAU guideline recommends MET for stones larger than 5 mm, and for those who fail this strategy, surgical treatment should be considered with either URS or SWL if the ureteric stones are 10 mm or less. For stones greater than 10 mm, the EAU guideline recommends URS as a first line option and SWL as a second alternative[14].

MET aims to promote the spontaneous passage of ureteric stones in order to avoid more invasive procedures, or to facilitate the stone clearance following SWL[21]. The most commonly used drugs are the alpha-blockers, although others such as calcium channel blockers have also been historically used. Alpha-blockers act on the alpha-adrenergic receptors located within the distal ureter to decrease basal smooth muscle tone and the frequency and amplitude of the peristaltic waves, resulting in a reduction of the intra-ureteric pressure and an increase in urinary flow[22]. In the last few years, multiple studies and meta-analyses have shown conflicting results regarding the efficacy of MET; consequently, the controversy regarding the use of MET has grown[22,23]. A randomized controlled trial comparing placebo, nifedipine (calcium channel blocker), and tamsulosin (alpha-blocker) did not demonstrate any difference in the need for further intervention within 4 weeks between patients who received active treatment or placebo (p = 0.78) nor between patients who received tamsulosin or nifedipine (p = 0.77)[24]. Meanwhile, a systematic review and meta-analysis that included 55 studies showed a shorter time to stone passage (pooled mean difference -3.79 days, 95% CI, -4.45 – -3.14)[25], and a Cochrane systematic review and meta-analysis also suggested that patients using alpha-blockers had shorter stone expulsion times (mean difference -3.40 days, 95% CI, -4.17 – -2.63) and experience fewer hospitalizations (RR 0.51, 95% CI 0.34 – 0.77). In this study, the effect appears to be greater for stones larger than 5 mm (RR 1.45, 95% CI, 1.22 – 1.72, p < 0.0001); however, an increase in major adverse events was noted (RR 2.09, 95% CI, 1.13 – 3.86)[26]. Despite the differences in the various studies, the guidelines[12–15] continue to support MET for ureteric stones given the low risk of side effects from the medication, but they encourage urologists to discuss the advantages and disadvantages with their patients in a shared decision making model[22,23].

Given the differences in guideline[12–14] recommendations regarding the use of URS or SWL for the treatment of ureteric stones, several studies have attempted to clarify the optimal treatment of these stones. A meta-analysis published in 2012 that included seven randomized controlled trials and 1205 patients compared URS and SWL for the treatment of ureteric calculi. Patients who underwent SWL had lower stone free rates (SFR) (RR 0.84, 95% CI, 0.73 – 0.96, $p = 0.11$) and higher re-treatment rates (RR 6.18, 95% CI, 3.68 – 10.38, $p < 0.00001$); however, this group also had fewer complications (RR 0.54, 95% CI, 0.33 – 0.88, $p = 0.01$) and shorter length of hospital stay (mean difference -2.55 days, 95% CI -3.24 – -1.86, $p < 0.00001$)[27].

The Therapeutic Interventions for Stones of the Ureter (TISU), a non-inferiority trial comparing SWL to URS for ureteric stones, assessed the need for further treatment within 6 months of the initial procedure. Patients who underwent SWL had an absolute risk difference of 11.7% (95% CI, 5.6% – 17.8%) compared to patients submitted to URS, which was below the threshold for non-inferiority of 20% defined for the trial. However, subanalysis in the per protocol group, excluding patients who passed their stones spontaneously prior to the allocated treatment, failed to show SWL non-inferiority when compared to URS (absolute risk difference 18%, 95% CI, 10% – 26%, $p = 0.31$)[28].

Analysing proximal ureteric stones, Lam *et al*. compared 67 patients who underwent either URS or SWL using the Doli 50 lithotripter (Dornier)[29]. In patients with stones larger than 1 cm, the SFR in the SWL was 50% compared to 93% in the URS group while in patients with stones smaller than 1 cm, the difference was less dramatic (100% in the URS group vs 80% in the SWL group). In this series, the authors calculated the efficiency quotient, a measure of treatment effectiveness to compare lithotripters described by Denstedt *et al*.[30] and, for larger stones, the difference between treatment groups was statistically significant (0.76 for URS vs 0.43 for SWL, $p = 0.04$)[29].

Similarly, in another cohort treated with either URS or SWL for proximal ureteric stones, after one SWL session, the overall SFR was 63.9% compared to 83.2% in patients who underwent URS ($p = 0.001$). Subgroup analysis according to the stone burden showed a more pronounced difference in the group with stones larger than 1 cm (35.2% in the SWL group vs 76.8% in the URS group, $p < 0.001$). In addition, when considering both the stone size and operative time, the URS group presented higher SFR than the SWL group ($p < 0.001$)[31].

Conversely, a prospective comparison between URS and SWL in patients with proximal ureteric calculi between 5 and 10 mm showed that at 3 weeks the SFR was different, although not statistically significant (78% in the URS group vs 58% SWL group, $p = 0.061$) and at 3 months the SFR were very similar (88% for SWL vs 89% for URS, $p = 1.00$). Comparisons of quality of life showed that both groups were equally satisfied with the treatments they received ($p = 0.315$). However, patients who underwent SWL reported fewer occasions where the treatment interfered with their lives (2.5, range 1 – 10, in the SWL group vs 6.8, range 1 – 14, in the URS group) and were more likely to choose the same treatment if a second procedure were needed ($p = 0.006$)[32].

In summary, several studies show a higher SFR for proximal ureteric calculi treated with URS in comparison to those treated with SWL. This difference is more pronounced for larger stones[29,31]. In addition, patients treated with URS usually achieve a stone-free status earlier than patients treated with SWL, but the long-term SFR are similar, and patients treated with SWL appeared to have a better post-operative quality of life in comparison with patients who underwent URS.

Regarding stones in the distal ureter, the discussion is even more poignant, especially after most recent update of the AUA guideline[12,13] which removed SWL as one of the primary treatment options for distal ureteric stones. The first reports that compared patients with distal ureteric calculi treated by either URS or SWL showed a higher SFR in the URS group compared to the SWL group (95 % vs 73%). However, patients undergoing URS also demonstrated higher complication rates (5.2%) compared to patients treated with SWL, where no complications were reported[33]. Another randomized study showed significantly shorter fluoroscopy time, operating time, and shorter time to achieve stone-free status in the URS group compared to the SWL group regardless the stone size. The SWL group also demonstrated a 10% re-treatment rate, while one URS session provided 100% success[34]. In a different series of 168 patients, the group undergoing SWL took up to 4 months to achieve stone-free status while in the URS group the time was two days[35]. The majority of series demonstrate a shorter operative time for URS compared with SWL[34]; however, the findings of Pearle and colleagues differed from other authors with significantly shorter mean procedure times in the SWL group than in the URS group (34.1 ± 8.2 minutes vs 64.7 ± 37.1 minutes, respectively, $p < 0.001$), and this difference was maintained when subgroup analysis was performed according to stone size[36]. This finding may be explained by differences in individual surgeon technique.

In 2006, Ghalayini *et al*. demonstrated similar findings to the initial studies when prospectively comparing 92 patients who were treated for a distal ureteric calculus. The SFR at 3 months favoured URS (81.5% vs 97.5%, $p < 0.0001$), and although the URS group had higher complication rates (8.3% vs 3.3%), this difference was not statistically significant. Regarding patient satisfaction, both procedures achieved high scores with the earlier stone-free status in the URS group likely contributing for the difference observed between them (94% for URS and 80% for SWL, $p = 0.002$)[37].

A more recent larger prospective randomized trial with 273 patients showed similar overall SFR (92.7% for SWL vs 94.85% for URS); additionally, a subgroup analysis according to stone size did not show differences in the overall SFR, operative times, and complication rates. The re-retreatment rates though, were higher in the SWL group (44.88% vs 7.75%, $p < 0.05$), whereas URS for larger stones presented a mean longer operative time ($p < 0.005$). Patients in the SWL group with stones larger than 1 cm required more auxiliary procedures, had higher re-treatment rates, and higher complication rates than patients with stones smaller than 1 cm ($p < 0.05$), suggesting that stone size should be carefully observed when recommending SWL for distal ureteric stones[38].

Theoretical concerns have been raised regarding fertility issues in females and males treated with SWL for distal ureteric calculi. Although pregnancy is a contraindication for SWL, studies have not demonstrated alterations in the fertility for men[39,40] and women[41] who undergo SWL[42].Therefore, SWL is considered a safe procedure for ureteric calculi even within the distal ureter.

For the treatment of renal calculi, the EAU guideline categorizes stones according to their size and location within the kidney. For stones located in lower pole between 10 and 20 mm, the guideline recommends that other predictive factors should be taken into consideration when deciding between URS and SWL. For stones located in other calyces or the renal pelvis, the recommendation is either SWL or URS if they are smaller than 20 mm, and percutaneous nephrolithotomy (PCNL) if stone size is more than 20 mm[14]. The AUA guideline does not discriminate between stones located in the lower pole or other kidney locations and recommends either URS or SWL for stones with less than 20 mm and PCNL for stones with 20 mm or more[12,13].

Although a multicentered prospective randomized study conducted by Pearle *et al*.[43] did not show differences in the SFR for lower pole stones between SWL and URS (35% vs 50%, respectively, $p = 0.92$), other studies have demonstrated significantly lower stone free rates following SWL for lower pole stones which was not observed when analyzing other locations within the kidney.

A retrospective review compared 326 patients who underwent either SWL or URS for the treatment of renal calculi and subgroup analysis showed higher SFR for patients with lower pole stones treated using URS (OR 6.7, 95% CI, 3.1 – 14.6), whilst complication rates between groups were similar[44]. Meanwhile, another randomized trial showed comparable SFR for lower pole caliceal stones of 10 mm or less treated with either SWL or URS (84.9% vs. 87.7%, $p = 0.32$). However, for stones between 10 and 20 mm, URS was more efficacious and presented lower re-treatment rates (11.1% vs 61.1%, $p < 0.001$). The complication rates were not significantly different (11.1% for URS and 6.6% for SWL, $p = 0.21$)[45]. Corroborating these data, a systematic review and meta-analysis evaluated seven randomized controlled trials comparing PCNL, URS and SWL for the treatment lower pole stones. URS had higher SFR when compared to SWL at 3 months (89.5% vs 70.5%, respectively, RR 1.71, 95% CI, 1.24 – 2.35, $p = 0.00$) and subgroup analysis demonstrated that this difference was less marked if stones were 10 mm or less (RR 1.11, 95% CI, 1.03 – 1.19, $p = 0.004$)[46].

SWL as a treatment method for urinary calculi was described in 1982 by Chaussy *et al*. with a high success rate[47]. Since then, lithotripters have changed significantly with more precise focus, more efficient energy sources, and elimination of the water bath which was present in the first-generation lithotripters. In addition, with the modern lithotripters, the procedure can be performed in an outpatient setting and without general anesthesia. The overall stone free rates for SWL vary between lithotripter generations and location of the stone. Neisius *et al*.[48] evaluated 183 patients with ureteric and renal calculi who underwent SWL using a third-generation lithotripter, the Lithoskop® (Siemens Medical Systems) and reported an overall SFR of 91% at 3 months. In another study with 1913 patients using a Storz Modulith® SL-20, the overall SFR was 77.6%[49]. Using the same lithotripter, Tan *et al.* reported an overall success rate of 81% for renal calculi and 85% for ureteric calculi[50].

Despite recent changes in the published guidelines[12,13] and a reduction in its overall use, SWL continues to play an important role in the treatment of renal and ureteric calculi, combining a minimally invasive approach with reasonably good efficacy, a short recovery time, low complication rates, and high patient acceptance[32]. However, it is important to note that several factors related to the patient and the stone are known to impact the results of SWL such as stone size[38,48,51], stone location[51], stone composition, stone attenuation on computerized tomography (CT)[52], and anatomic parameters[53] such as skin to stone distance (SSD)[54,55], body mass index (BMI)[51,56], and degree of hydronephrosis[57,58]. In addition to these, technical parameters during the procedure such as energy output[59], positioning[60,61], and frequency of shocks[62] also influence the treatment success (Table 2). Understanding the mechanisms of stone disintegration, the technology involved in lithotripter design, and the impact of each of these factors in treatment efficacy helps urologists guide their patients through the decision-making process to improve the chances of satisfactory results.

1.3 MECHANISMS FOR STONE DISINTEGRATION

There are various theories addressing how lithotripters promote stone disintegration and, although none of them completely explain the phenomenon, it is important to understand the differences in the machines and the changes that have occurred over time. The most accepted mechanisms to describe stone comminution with SWL are tensile and shear stress, cavitation, spallation, quasistatic squeezing, dynamic squeezing, and dynamic fatigue[63,64].

The pressure wave generated by the lithotripter is composed of two parts: positive and negative gradients. Both impact the tensile strength of the stone, resulting in stone fragmentation. The negative part of the wave generates almost a homogenous tensile stress by acting directly on the stone. The tensile stress resulting from the positive part of the pressure wave is only significant if the length of the wave is shorter than the stone dimension, and it is responsible for creating pressure gradients that lead to shear stress, tensile stress, and strain. When the focus diameter of the lithotripter is smaller compared to the stone diameter, this mechanism results in crater-like fragmentation erosion. However, if the focus diameter is less sharp, the wave is reflected at the posterior aspect of the stone-water interface with pressure inversion, which fragments the stone by the tensile stress in the reflection wave (Hopkinson effect). The tensile stress causes fractures particularly in the third distal part of the stone. This phenomenon is also called spallation[64,65].

Cavitation is also a result of the negative part of the pressure wave, occurring in the water surrounding the stone, as well as in the water contained in microcracks within the stone. This mechanism appears to be the most important factor contributing to tissue injury[65,66]. Xi and Zhong have demonstrated *in vitro*, an increase in fragmentation when a second shockwave is applied during the collapse of cavitation bubbles generated by a first shock[67]. According to the quasistatic squeezing theory, the positive part of the pressure wave acts by creating a circumferential squeezing of the stone, leading to fragmentation parallel or perpendicular to the wave propagation. This phenomenon occurs when the focal diameter is larger than the stone and needs a relatively lower pressure range[63]. Dynamic squeezing is created by the shear waves inside the stone, initiated by squeezing waves alongside the stone[64,68]. Dynamic fatigue is the result of the cumulative effect of the shockwaves on the stone, leading to the destruction of its structure during the course of the treatment[66].

1.4 THE EVOLUTION OF SHOCKWAVE LITHOTRIPTERS

Lithotripters have a shockwave generator and the shockwaves produced exit through an aperture. The size of the aperture defines the size of the F2 focal point, the converging point of the shockwaves in which the patient’s stone should be positioned during the procedure. To decrease the energy loss between the source and the stone, and improve results, a coupling mechanism which helps to transmit the shockwaves is utilized.

The first article describing lithotripsy as a treatment for renal stone disease in patients reported a success rate of 91.5%, with seventy-two patients treated under general or epidural anesthesia and positioned in a water bath[47]. At each lithotripsy session, the patients were given 500 to 1000 shockwaves with a duration of 0.5 microseconds. The Dornier HM3 (Dornier Medical Systems), depicted in Figure 1, was the first commercially available lithotripter and had the highest reported SFR in comparison with several other lithotripters[69]. It had an F2 focal point dimension of 15 x 90 mm, a small aperture of 14 cm, and a spark-gap shock generator of 80 nF[70]. The modified version of the Dornier HM3 had a reduced 40 nF generator, and an aperture of 17 cm, resulting in a smaller focus. The locating system was maintained with the use of 2 under-couch X-ray tubes[63].

The Dornier MFL 5000 (Dornier Medical Systems) was launched after the Dornier HM3, and the water bath was replaced by a water cushion containing the shockwave ellipsoid. It had a 60 nF generator, a F2 focal point dimension of 7.5 x 38 mm, a multifunctional table, and a higher single dose kV setting. The efficacy of both lithotripters was similar for renal pelvic and ureteric calculi, but for lower pole stones, the Dornier HM3 presented higher SFR (80% vs 56%, respectively, $p = 0.005$). Also, the treatment time was longer using the MFL 5000 ($p < 0.001$)[70,71].

One of the challenges with the first-generation lithotripters was to position the stone in the focal point. As an example, the Siemens Lithostar® (Siemens Medical Systems) initially had a focal length of 9.5 cm and upper ureteric stones were usually localized 2 to 3 cm beyond the focal point. To overcome this issue, new shock heads with a focal length of 11.5 cm were implemented[72] and the focal lengths in the subsequent lithotripters tended to be longer, a feature specially important when treating obese patients[73]. With the second-generation lithotripters, a piezoelectric energy source and ultrasound (US) guided focus were implemented. US targeting allowed for the treatment of radiolucent stones, though for stones in the mid and proximal ureter, localization was challenging. An important advantage of the second-generation lithotripters compared to the first-generation was the significantly lower pain levels experienced by the patients due to a large aperture with smaller focal sizes[74]. However, the same parameters also led to higher re-treatment rates and lower overall success rates. A multicentric trial comparing 5 different second-generation lithotripters showed an overall SFR of 45%[75], which was significantly lower than the 96% success rate with the Dornier HM3[76].

One example of a second-generation lithotripter is the Wolf Piezolith 2300 (Richard Wolf) in which 3000 piezoelectric elements were arranged in a 50 cm concave spherical dish that moved in three planes. A chamber between the dish and the patient was filled with heated, degassed water, and the shockwaves converged to the same point with an area of 1.4 x 10.8 mm. Focus was achieved using two real-time B-mode ultrasonic scanners which could be rotated 90˚ and pressure ranged from 400 to 1200 bar[77]. Using this lithotripter, Cope *et al*. reported a SFR of 75% at 3 months, and an additional 20% of the patients had fragments smaller than 3 mm without any major complications reported[77].

In most third-generation lithotripters, both ultrasonic and fluoroscopic stone localization were incorporated, and the large aperture with smaller focus were maintained to reduce patient discomfort and allow for outpatient procedures. In order to increase the efficacy, a wider range output of shockwave source was implemented. The Wolf Piezolith 3000 (Richard Wolf), an example of a third-generation lithotripter, had a double layer of piezoelectric elements, a high peak pressure of approximately 1000 bar, a maximum depth of penetration of 165 mm, an isocentric fluoroscopic C-arm and coaxial ultrasonography as targeting system, and three focal zones (F1: 2 mm; F2: 4 mm; F3: 8 mm)[51,63,78]. A cohort from a North American centre using the Wolf Piezolith 3000 showed a SFR of 45% at one month, and 64% of the patients had fragments smaller than 4 mm[79].

Another example of a third-generation lithotripter was the Storz Modulith® SL-20 (Storz Medical) with a 12 to 20 kV variable-potency cylindrical electromagnetic generator, 189 – 1056 bar of pressure, and a F2 area of 28 x 6 mm. Stone targeting was performed using an in-line US and fluoroscopy with a mobile C-arm with isocentric motion[49,50]. In a series with 1441 cases treated using the Storz Modulith® SL-20, the overall SFR was 87.4% for all patients, and 70.8% for patients who only underwent a single SWL session[49].

For fourth-generation lithotripters some manufacturers opted to pursue the high SFR observed with the first-generation lithotripters by broadening the shock wave aperture resulting in a smaller focal zone and higher peak pressures, like in the Storz Modulith® SLX[64,80]. Meanwhile, other manufacturers opted for maintaining the larger focal zone and lower peak pressures but developed other strategies to increase the SFR[81]. The Sonolith Vision (Technomed Medical Systems) is a fourth-generation lithotripter with an electroconductive shock-wave generator containing an elliptical reflector filled with a conductive fluid capable of transmitting almost the entire impulse generated to the F2 focal point. It uses an isocentric C-arm X-ray and lateral US for focusing, and the coupling mechanism is a water cushion. The focal diameter is 12.8 to 25 mm, and pulse duration is 138 – 279 ns, with a peak pressure of less than 9 MPa. In a study with 355 patients who underwent SWL using the Sonolith Vision, the high success rate (75%) was attributed to the relatively lower peak pressure and larger focal diameter[81]. The Storz Modulith® SLX-F2 lithotripter (Figure 2), another fourth-generation lithotripter, has an electromagnetic cylindric energy source and a dual focus. The larger focus (50 x 9 mm) is recommended for renal stones, and the smaller (28 x 6 mm) recommended for ureteral stones. The localization system is a combination of in-line X-ray and US[64,82]. In a study of 233 patients with renal and ureteric calculi who underwent SWL using the Storz Modulith® SLX-F2 lithotripter, the SFR at 3 months was 77%, and the re-treatment rate was 11.7%[82].

The differences in specification between the various lithotripter generations are shown in further detail in Table 3. Several studies proposed a comparison of effectiveness between different types and generations of lithotripters. A centre in Scotland compared three lithotripters with different energy sources, the Wolf Piezolith 2300 (Richard Wolf), a piezoelectric lithotripter, the Dornier MPL9000 (Dornier MedTech), an electrohydraulic lithotripter, and the Dornier Compact Delta (Dornier MedTech), an electromagnetic lithotripter. The adjusted comparison between the three machines for SFR at 3 months showed that the Dornier MPL9000 had a higher SFR compared to the Dornier Compact Delta (OR 1.72, 95% CI, 1.39 – 2.11, $p < 0.0005$), and the Wolf Piezolith 2300 (OR 1.38, 95% CI, 1.15 – 1.65, $p < 0.0005$). Pair-wise comparison was also statistically significant ($p < 0.0005$)[83]. Another series of 173 patients compared an electrohydraulic lithotripter, the Dornier MFL 5000 (Dornier Medical Systems), to an electromagnetic lithotripter, the Storz Modulith® SLX, with similar results. The Dornier MFL 5000 group had a higher SFR at 1 month (77% vs 67%, $p = 0.01$) despite a higher median stone burden (103 mm^2 vs 71 mm^2, $p = 0.015$)[84].

Gerber *et al*. compared patients who were prospectively randomized for SWL using two lithotripters (the Dornier HM3 and the Lithostar® Plus) with consecutive patients undergoing SWL with the Storz Modulith® SLX. The groups were matched for stone burden and stone location. On postoperative day one, the Storz Modulith® SLX had a lower SFR compared to the Lithostar® Plus and the Dornier HM3 (48% vs 65% and 91%, respectively) and pairwise comparison was statistically significant (Dornier HM3 vs Lithostar® Plus: $p < 0.001$; Dornier HM3 vs Storz Modulith® SLX: $p < 0.001$; Lithostar® Plus vs Storz Modulith® SLX: $p = 0.015$). Interestingly, at 3 months, the SFR were not significantly different among the three groups[80]. Using a similar approach with a shorter time from treatment to follow up imaging, a comparison between the Storz Modulith® SLX-F2 and the Dornier HM3 showed a trend for higher SFR for the Dornier HM3 at postoperative day one (31% vs 20%, $p = 0.06$). At 3 months, however, there was no difference in SFR between both groups (74% for the Dornier HM3 vs 67% for the Storz Modulith® SLX-F2, $p = 0.36$), though the Dornier HM3 was more efficacious specifically for ureteral stones (90% vs 81%, $p = 0.05$)[85].

As previously mentioned, several factors may influence lithotripsy outcomes, including treatment settings during the SWL session, specifications of the various lithotripters, differences within patient populations and stone characteristics. Hence, studies comparing different types of lithotripters are challenging to interpret and usually fail to identify a single cause for the differences seen in the SFR.

1.5 FACTORS IMPACTING STONE FRAGMENTATION

1.5.1 FACTORS RELATED TO THE PATIENT

1.5.1.1 AGE

The use of SWL for urolithiasis treatment in elderly patients, especially those with multiple comorbidities, would be greatly favoured due to its safety profile and ability to be performed under sedation instead of general anaesthesia. Kramolowsky *et al*. demonstrated similar length-stay and success rates in 96 patients over 70 years when compared with all patients who had undergone lithotripsy in the same institution, corroborating SWL efficacy and safety in this population[86]. However, some reports have demonstrated a decrease in SWL efficacy in older age groups. For example, a study with 2954 patients showed that older age impacted the SFR for renal stones ($p < 0.001$)[87]. Ng and colleagues hypothesized that age-related changes in kidney impedance could impact SWL results. Patients older than 60 years had lower SFR in comparison to younger patients (OR 0.643, 95% CI, 0.506

– 0.818, $p < 0.001$) and fragmentation rates in older patients were decreased for renal stones in comparison with ureteric calculi[88]. Other authors, however, did not demonstrate difference in SFR in this population according to stone site[89].

The real impact of age in SWL remains unclear, and older patients appear to have lower SFR compared to younger patients. Nevertheless, SWL is a safe procedure in this population with overall good efficacy reported.

1.5.1.2 BODY MASS INDEX AND SKIN-TO-STONE DISTANCE

Considering all the factors impacting SWL results, the skin-to-stone distance (SSD) and the body mass index (BMI) are certainly among the most important patient-related factors. Different ways to measure the SSD have been proposed, and the method described by Pareek *et al*. was used by several studies. The authors calculated the SSD from axial CT imaging using the average of the distances from the center of the stone to the skin at 0°, at 45°, and at 90° and in the series, patients who were stone-free had lower mean SSD and lower mean BMI than patients who had residual stones (8.12 ± 1.74 cm vs 11.53 ± 1.89, $p < 0.01$ and 26.13 ± 3.85 Kg/m^2 vs 28.53 ± 4.45 Kg/m^2, $p < 0.05$, respectively). However, in the multivariable analysis, SSD was the only predictor of SFR (OR 0.32, 95% CI, 0.29 – 0.35, $p < 0.01$), and a SSD of 10 cm was proposed as threshold value to predict treatment success with a good sensitivity and specificity[55]. A retrospective series with 83 patients also demonstrated significantly different mean SSD between patients who were stone free and patients with residual stones (83.3 ± 21.9 mm vs 107.7 ± 28.9 mm, respectively, $p \leq 0.005$) and again, SSD was the only predictor of stone-free status (OR 0.96, 95% CI, 0.95 – 0.98, $p = 0.001$)[90]. Some series have failed to identify any effect of SSD in SWL success[91], while others demonstrated that SSD was one of multiple parameters affecting SWL outcomes[92,93]. Furthermore, the literature has proposed different cut off values of SSD to predict treatment success such as 90 mm[54] and 110 mm[94].

A prospective cohort study with 120 patients showed a higher a BMI in patients who failed SWL than in patients who underwent a successful treatment (32.5 ± 5.2 Kg/m^2 vs 28.1 ± 5.1 Kg/m^2, p = 0.002). They also demonstrated that BMI together with stone attenuation greater than 1000 Hounsfield Units (HU) were the only predictors of treatment failure in their multivariable analysis (RR 1.12, 95% CI, 1.006 – 1.25, p = 0.039 and RR 8.1, 95% CI, 1.433 – 45.82, p = 0.018)[95]. These results are similar to the findings of Pareek and colleagues, who also demonstrated lower SFR rates in patients with a higher BMI and greater stone attenuation on pre-operative CT imaging[56].

Although BMI and SSD are related and some authors use BMI as a surrogate for SSD, the effect of BMI on SWL success is less clear than the SSD effect[94] and some series have failed to show any influence of BMI on treatment outcomes[96]. Despite this, the BMI is an easy parameter to collect while calculating the SSD is time consuming and requires a pre-operative CT, elevating both treatment costs and patient radiation exposure.

1.5.2 FACTORS RELATED TO THE STONE

1.5.2.1 STONE SIZE

Stone size is a decisive factor when considering an optimal surgical treatment strategy for urolithiasis as per the treatment guidelines of several national urological associations[12–15]. However, even for stones within the recommended size range, individual stone size can still greatly impact the efficacy of SWL. Some studies have shown stone size as the only predictor of treatment success[48,79,82,97,98], while others demonstrated its importance even when other factors were taken into consideration[51,99,100].

Sorensen *et al*. proposed to evaluate the impact of the lower pole anatomy and stone size in the stone clearance following SWL. Although the anatomical features were not predictive of treatment success in this cohort, the SFR was inversely related to the stone size. Stones smaller than 10 mm resulted in a SFR of 74% while for stones between 11 and 20 mm, the SFR dropped to 41%, $p < 0.001$[97].

Aiming to evaluate the efficacy of a new fourth generation lithotripter, the Storz Modulith® SLX-F2, a cohort study of 233 patients identified stone size smaller than 10 mm as the only predictor of treatment success on the multivariable analysis ($p < 0.05$)[82]. Similarly, a series using a different lithotripter, the Wolf Piezolith 3000, also showed significantly higher success rates for stones smaller than 10 mm when compared to stones larger than 10 mm (73.9% vs 41.4%, respectively, $p = 0.004$)[79]. Reinforcing the importance of the 10 mm threshold, Neisius *et al*. showed that renal calculi larger than 10 mm required a higher number of SWL sessions for complete stone disintegration ($p = 0.019$) and had a lower SFR than stones smaller than 10 mm (85% vs 92%, respectively, $p = 0.036$). The same pattern was observed for ureteral stones with a higher number of sessions being required for larger stones ($p = 0.001$) and a higher SFR in the group with stones smaller than 10 mm (95% vs 93%, $p = 0.026$)[48].

Although most authors use only maximum stone dimension to analyze for predictors of SWL success, others have used stone surface area and were also able to demonstrate its impact on SFR[98,101]. For lower pole stones, a study with 246 patients demonstrated higher SFR for stones with a surface area of 26 to 100 mm^2 compared to stones with areas between 101 and 400 mm^2 (69% vs 33%, respectively, $p < 0.001$)[97]. Another series analyzing distal ureteral stones showed that stones requiring secondary or tertiary procedures for complete stone clearance had a higher mean total axial surface area compared to stones that required only one procedure (32.94 ± 17.58 mm^2 vs 23.63 ± 12.20 mm^2, respectively, $p < 0.05$)[98].

Even though stone size has been demonstrated to be an important factor for treatment success, it is certainly not the only one. Bajaj *et al*. evaluated several parameters under “real-world conditions” in a study of 421 patients with upper tract calculi. In the multivariable analysis, stone size greater than 10 mm (OR 3.4, 95% CI, 1.98 – 5.84, $p < 0.001$) and SSD of less than 15 cm (OR 0.133, 95% CI, 0.027 – 0.65, $p = 0.013$) were predictors of treatment success[99]. In another study involving SWL in patients with ureteral stones, stone size of 1 cm or greater was highly associated with an unsuccessful outcome (OR

10.5, 95% CI, 3.0 – 36.2, $p = 0.001$) and other factors such as BMI higher than 25 Kg/m^2 (OR 3.5, 95% CI, 1.1 – 11.0, $p = 0.027$), stone location in the mid-ureter (OR 8.49, 95 % CI, 1.5 – 45.7, $p = 0.013$), and severe hydronephrosis (OR 12.3, 95 % CI, 1.9 – 79.5, $p = 0.008$) were also identified as predictors of treatment failure[51]. Similarly, a prospective cohort demonstrated that a larger stone size (OR 1.253, 95% CI, 0.988 – 1.053, $p < 0.001$), an increased SSD (OR 1.39, 95% CI, 1.134 – 1.713, $p = 0.002$), and the stone attenuation on CT (OR 1.005, 95% CI, 1.003 – 1.006, $p < 0.001$) were predictors of SWL failure on the multivariable analysis[100].

1.5.2.2 STONE COMPOSITION AND ATTENUATION ON IMAGING

Aside from stone size, other radiologic stone characteristics have been reported to have an impact on the SFR after SWL. Bon *et al*. proposed that the radiographic appearance of the stone was related to the stone composition[102] and therefore, affected the SWL success. Uric acid and calcium oxalate dihydrate stones are known to break up more easily with SWL than calcium oxalate monohydrate, brushite or cystine stones. However, the fragility of a stone is not always uniform across stones with the same composition[103]. Stone attenuation measured on CT can also be used to predict stone composition[104,105], with uric acid stones having significantly lower attenuation values than calcium oxalate and calcium phosphate stones[52]. Therefore, measured attenuation of a stone on CT directly affects the SFR[52,54,56,93,94].

A preliminary study involving 30 patients showed significantly lower stone clearance following SWL for patients with stone attenuation on CT greater than 1000 Hounsfield Units (HU) ($p < 0.001$)[106]. This finding was supported by a prospective study with 220 patients in which stone attenuation greater than 1000 HU and larger stone size were predictors of treatment failure ($p < 0.001$ and $p < 0.001$, respectively)[100]. El-Nahas *et al*. also demonstrated that stone attenuation greater than 1000 HU ($p = 0.018$) and higher BMI ($p = 0.039$) correlated with SWL failure on the multivariable analysis[95].

Historically, the 1000 HU threshold has been used by most urologists to predict chance of treatment success with SWL, but several studies have proposed different values[52,54,94,107]. A new threshold of 970 HU was suggested as a predictor of SWL failure in prospective cohort with 50 patients. In this series, those who failed treatment had higher stone attenuation on CT than patients who underwent a successful SWL (1196 vs 715 HU, respectively, $p < 0.001$)[107]. A retrospective cohort study identified stone attenuation on CT and SSD as predictors of SWL failure. Patients with a stone attenuation lower than 900 HU were 6.2 times more likely to undergo a successful SWL than patients with higher stone attenuation values ($p < 0.001$), as did the patients with SSD of less than 9 cm (OR 2.8, 95% CI, 1.1 – 7.2, $p = 0.02$). Patients with both favourable characteristics (SSD less than 9 cm and stone attenuation lower than 900 HU) had the highest success rates compared with other groups ($p < 0.001$)[54]. In a similar study of 422 patients, SSD and stone attenuation were found to be predictors of SWL success, and although the cut-off value for stone attenuation was also 900 HU (OR 0.49, 95% CI, 0.32 – 0.75, $p < 0.01$), the SSD threshold was 110 mm (OR 0.49, 95% CI, 0.31 – 0.78, $p < 0.01$)[94]. An even lower cut off to predict SWL success based on the stone attenuation on CT was proposed by Nakasato *et al*. who retrospectively analyzed the impact of several parameters on SWL success rates and demonstrated lower treatment success in patients with stone attenuation greater than 815 HU on CT ($p = 0.0265$)[52].

Although the literature reports different cut-off values, the guidelines[14,15] cite a threshold of 1000 HU as the stone attenuation value where poorer outcomes are observed. Hence, the stone attenuation should be analyzed on the perioperative CT if available, and this factor should be considered in conjunction with other parameters when recommending SWL as a primary treatment for upper tract calculi. In addition, a patient’s history of prior stone composition if known should also be taken into consideration and used to counsel patients on the efficacy of SWL.

1.5.2.3 STONE LOCATION

Ureteric stones

The literature reports overall high success rates for the treatment of ureteric stones with SWL. For instance, Holden *et al*. reported an overall SFR of 88.1% for ureteral stones following SWL[72]. In addition, Halachmi and colleagues reported an overall SFR of 86.5%, and a SFR of 80.2% in patients with ureteric stones larger than 10 mm who were treated with a single session[108].

However, some authors have reported different SFR for ureteric stones based on specific ureteric location. A multicentric study using the Dornier MFL-5000 compared 658 patients with kidney and upper ureteric calculi to 323 patients with mid and lower ureteric calculi. The latter group had a higher re-treatment rate (18% vs 13%) despite a higher SFR at 90 days (83% vs 67%, $p < 0.001$)[71]. Conversely, a retrospective cohort study of 2836 patients with ureteric calculi between 5 and 15mm noted an overall SFR of 87%, and no differences in the SFR were demonstrated based on stone location (85.1% in the proximal ureter, 83.9% for mid ureteric stones and 88.4% for distal ureteric stones, $p = 0.257$)[109].

Regarding quality of life, patients undergoing SWL for the treatment of ureteral stones were more likely to choose the same modality when compared to patients subjected to URS ($p = 0.006$)[32]. In another cohort, patients with distal ureteric stones who underwent URS required more oral pain medication than patients who underwent SWL (92% vs 63%, $p = 0.04$), although overall patient satisfaction was not significantly different between both groups (96% in the SWL group vs 89% in the URS group)[36]. In an evaluation of patients with renal stones, a prospective randomized trial comparing health-related quality of life (HRQoL) scores on postoperative day one following URS and SWL showed significantly lower HRQoL scores in the URS group than the SWL group in all six out of the eight scores analyzed including physical, emotion, and social functioning, energy, fatigue, and pain[110].

Renal stones

Lower pole stones

The stone location within the kidney collecting system has been repeatedly shown to impact SWL success. In particular, lower pole stone location is associated with a lower SFR compared to other locations. Coz *et al*. evaluated 1441 urinary stones 90 days after treatment using a Modulith® SL-20™ (Storz Medical). The overall SFR was 87.7%, although for stones in the lower pole the SFR dropped to 84.8%. In contrast, the SFR for stones located in the mid pole was 90.5%, 89.2% in the upper pole, and 86% and in the renal pelvis[49].

Sampaio and Aragao hypothesized that gravity plays a role in the lower SFR for stones located in the lower pole, and certain anatomical characteristics of the lower pole could impact the stone clearance following SWL[111]. To investigate this, they used polyester resin endocasts of the pyelocaliceal system from fresh adult cadavers to study lower pole drainage[112]. In 1994, the authors proposed that characteristics such as an infundibulopelvic angle (measured as angle between the lower border of the pelvis and the medial border of the lower-pole infundibulum) of less than 90° (acute), a lower pole infundibula diameter of less than 4 mm, and the spatial distribution of the lower pole calyces could decrease SWL success rates[53]. A prospective study evaluated patients with lower pole calculus between 7 and 25 mm who underwent SWL with the Lithostar® Plus (Siemens Medical Systems). The patients were divided in two groups according to their infundibulopelvic angle, which was measured between lines I and II (line I being the line linking the central axis of the superior ureter and the central axis of ureteropelvic junction and line II being the central axis of the more inferior infundibulum). After 3 months, 75% of the patients who had an infundibulopelvic angle of more than 90° were stone-free compared to 23% of the patients with an acute infundibulopelvic angle, and the difference was statistically significant ($p < 0.01$)[113]. In another retrospective analysis, the infundibulopelvic angle was measured as the angle between a line in the direction of the infundibulum of the lower calyx and the pelvis. This study included 133 patients who under SWL for lower pole stones and examined SFR 6 months post-procedure. All patients with an infundibulopelvic angle greater than 90°, an infundibular diameter larger than 4 mm, and a simple calyceal pattern were found to be stone free[114]. Keeley and colleagues retrospectively reviewed patients with lower pole stones treated with SWL using the Dornier MFL 9000 lithotripter (Dornier Medical Systems) and showed an overall SFR of 52%. The infundibulopelvic angle, measured as described by Sampaio *et al*.[112], was the only predictor associated with stone-free status (p = 0.012), and patients with an infundibulopelvic angle of less than 100° demonstrated lower SFR than patients with an infundibulopelvic angle greater than 100° (34% vs 66%, respectively, p = 0.012)[115].

Elbahnasy *et al*. proposed another method to measure the infundibulopelvic angle, at the intersection of the ureteropelvic axis and the central axis of the lower pole infundibulum. Comparing patients who underwent either URS or SWL to treat a lower pole calculus, the overall SFR at 1 month was 62% in the URS group and 52% in the SWL group (p = 0.7). In the SWL group, patients who were stone-free had larger infundibulopelvic angles (75° vs 51˚, p = 0.009), shorter infundibular lengths (38 mm vs 32 mm, p = 0.01), and greater infundibular width (9.1 mm vs 6.0 mm, p = 0.03)[116]. Another series compared patients who had either a SWL with a Dornier HM3 lithotripter, a PCNL, or a URS to treat a lower pole stone. In the SWL group, patients who presented with the three unfavourable characteristics (infundibulopelvic angle of 70° or less, infundibular length of more than 3 mm and infundibular width of less than 5 mm) had lower SFR compared to patients with two or three favourable anatomic characteristics (44% vs 91%, respectively)[117]. However, different results were demonstrated in a large series with 246 patients evaluated one month after undergoing SWL. Using the same method of infundibulopelvic angle measurement described by Elbahnasy and colleagues[116], the presence of favourable anatomy (infundibulopelvic angle of more than 70°, lower pole infundibular width greater than 5 mm, and infundibular length of less than 30 mm) was not a significant predictor of stone clearance[97].

Given the variability in methods used to measure the infundibulopelvic angle, Tuckey *et al*. proposed the concept of caliceal pelvic height, measured as the distance between a horizontal line from the lowest point of the calyx to the highest point of the lower lip of the renal pelvis. Patients with caliceal pelvic height less than 15 mm had a stone clearance rate of 92% compared with 52% in patients with caliceal pelvic height of 15 mm or greater ($p < 0.05$). Also, an infundibular width of 5 mm or greater was associated with higher rates of stone clearance than an infundibular width of less than 5 mm (74% vs 41%, $p < 0.05$)[118]. Similarly, in a study by Arzoz-Fabregas *et al*. only infundibular height was a predictor of stone clearance at 3 months and the mean infundibular height in patients who were stone free was 21.7 mm compared to 26.6 mm in patients with residual fragments ($p = 0.001$). The authors calculated that an infundibular height cut off point of 22.5 mm would be able to predict the response to SWL with a specificity and sensitivity of approximately 70%[119]. Symed and colleagues corroborated these findings regarding the impact of the pelvicalyceal height in stone clearance for lower pole stones[118,119]. Patients with an incomplete stone clearance had a mean pelvicalyceal height of 22.9 mm compared to 15.1 mm in patients who were stone free ($p < 0.0001$). Interestingly, in patients with a pelvicalyceal height below 15 mm, the SFR was very high (97%)[120].

Fong *et al*. also proposed a different anatomic parameter, termed the lower pole ratio, to estimate SWL success. The lower pole ratio was defined as the lower pole length divided by the lower pole width, both measured in millimetres. Patients with a lower pole ratio of 3.5 or less ($p < 0.001$), an infundibular length of 30 mm or less ($p = 0.049$) or an infundibular width greater than 5 mm ($p = 0.01$) were all shown to have improved stone clearance rates. Interestingly, the infundibulopelvic angle was not a predictor of SFR in the univariable or multivariable analysis of this study[121].

Although different ways of measuring the anatomical parameters of the lower pole have been proposed over the last several decades, there is a consensus that its anatomy influences the stone clearance following SWL. This should be taken into consideration when discussing treatment recommendations with patients with lower pole calculi, especially for those with a larger stone burden.

Upper pole stones

Considering the anatomic influence on stone clearance for lower pole stones, Küpeli *et al*. investigated whether or not these parameters would also influence SFR for upper pole stones. They defined the upper pole infundibulopelvic angle as the angle between the ureteropelvic axis and the upper pole central axis. Patients who were stone free had a mean upper pole infundibulopelvic angle of 172.3° compared to 174.6° in patients with residual fragments ($p = 0.85$). Similarly, the upper pole infundibular width and upper pole infundibular length were compared between the two groups and were not statistically significant ($p = 0.37$ and $p = 0.89$, respectively). Further analysis was performed by stratifying the patients according to their stone burden, and once again the anatomic parameters were not predictors of stone clearance for upper pole stones[122]. Contrary to the lower pole, upper pole anatomy does not appear to impact SWL success. Consequently, SWL is a good option for the treatment of patients with stones in this location and is supported by the guidelines[12–14]. Although it is important to note that other parameters may also influence treatment decisions for stones in the upper pole.

1.5.3 FACTORS RELATED TO THE PROCEDURE

1.5.3.1 PATIENT POSITION

Patient positioning during SWL may impact treatment outcomes especially for stones located in the distal ureter, where the sacrum and the pelvic bones could function as a barrier between the stone and the energy source. In 1988, the prone position was described by Jenkins and Gillenwater who treated 10 patients with distal ureteric calculi using a Dornier HM3 (Dornier) with excellent results[123]. Using a Direx Tripter X1, a second-generation device, authors of a series of 28 patients described a SFR of 82% after 12 weeks with a re-treatment rate of 21% for patients treated in the prone position[124]. One patient developed hematospermia which resolved spontaneously after 15 days. Since then, the prone position has been used by many urologists to treat stones located in the distal ureter. However, reports of complications such as bowel injury[125,126], and other concerns such as an increase in the SSD[60,127], possible attenuation of the shockwaves due to bowel gas[128] and poorer patient tolerance[128] have led to new proposals for patient positioning[129–131].

One of the proposed changes in position was from Kose *et al*. who described the "modified-prone" position for stones located near the UVJ and in the distal ureter up to 1 cm from the UVJ. Compared to the prone position, SWL in the "modified-prone" was more likely to be successful (OR 4.56, 95% CI, 1.18 – 17.66, $p = 0.02$) and was associated with higher SFR (97.5% vs 89.9%, respectively, $p = 0.015$)[130].

The transgluteal approach has also been proposed, as it would allow the treatment of distal ureteric stones in the supine position given that the shockwaves would travel through the greater sciatic foramen and reach the distal ureter without the interference of the bony structures. Phipps *et al*. compared 110 patients who underwent SWL for distal ureteral calculi using prone and supine positioning with the transgluteal approach. Two weeks after the first SWL session, 40% of the patients in the prone position group were stone free compared to 78% in the supine group ($p < 0.001$), and overall success rates were also favourable to the supine position group (92% vs 63%, $p < 0.001$)[127]. A randomized trial demonstrated similar results with 76.7% of patients demonstrating treatment success after one SWL session in the transgluteal group compared with only 58.7% in the prone group ($p = 0.019$). Although, in this series the pain score was higher for patients in the transgluteal approach group (2.56 ± 1.33 vs 2.13 ± 1.01, respectively, $p = 0.030$), these patients also had a higher overall satisfaction score (4.21 ± 0.81 vs 4.03 ± 0.88, $p = 0.762$)[128]. Even more marked differences were found in another randomized trial comparing prone to supine position with shockwaves applied via the gluteus maximus. After one SWL session, the SFR was 75.5% in the supine position and 44.9% in the prone position group

($p < 0.001$), with the overall success rate also being higher in the supine group (91.8% vs 65.3%, $p < 0.001$)[132].

A systematic review and meta-analysis of four studies compared SWL in the prone and supine positions for distal ureteric calculi in 647 patients. After a single treatment, the SFR in the supine group was significantly higher than in the prone group (OR 4.17, 95% CI 2.53 – 6.87, $p < 0.00001$), and the same results were observed when analysing patients after all SWL sessions (OR 3.02, 95% CI 1.96 – 4.67, $p < 0.00001$)[60]. A second systematic review and meta-analysis published in 2020 reviewed four studies with 516 patients and demonstrated that the transgluteal approach improved the overall SFR when compared to SWL in the prone position (OR 4.03, 95% CI, 2.43 – 6.69, $p < 0.00001$)[61]. Today many urologists prefer the supine position to treat distal ureteric calculi as this position provides high SFR without the drawbacks observed with the use of prone positioning, and this practice is supported by the majority of studies in the literature.

1.5.3.2 FREQUENCY OF SHOCKS

Considering the cavitation mechanism for stone disintegration and the fact that cavitation bubbles decrease in number with time, a longer interval between shockwaves is thought to result in a smaller decrease in the energy delivered to the stone due to the presence of fewer bubbles[64]. Having this mechanism in mind, lower frequency settings would allow for a better stone fragmentation as the bubbles would expand and collapse with a higher energy[133]. Pace *et al*. conducted the first randomized trial with 220 patients comparing 60 shocks per minute (1 Hz) to 120 shocks per minute (2 Hz). Patients in the lower frequency group demonstrated higher success rates compared to patients in the 2 Hz group (75% vs 61%, $p = 0.027$) and the difference was also significant for patients with stones larger than 100 mm^2 (79.1% for lower frequency vs 67% for the higher frequency group, $p = 0.043$). However, treatment time was longer in the 60 shocks per minute group (40.6 vs 24.2 minutes, $p < 0.001$)[62]. These findings were confirmed in another trial with 206 patients in which the authors described an overall success rate of 50.5% in the lower frequency group compared to 35.9% in the 120 shocks per minute group ($p = 0.035$). In addition, the lower frequency group also had higher success rates for stones larger than 10 mm (43.3% vs 10.8%, $p = 0.002$), and there was no difference in analgesia requirements between groups[134].

Observing the results of these previous studies, Altok and colleagues proposed to evaluate even lower frequencies. A comparison of 60 shocks per minute with 30 shocks per minute did not demonstrate differences in the overall success rates (71.6% vs 68.9%, respectively, $p = 0.719$). On the other hand, the lower frequency group presented higher pain scores ($p = 0.003$)[133].

A systematic review and meta-analysis that included nine randomized controlled trials and 1572 cases compared 120, 90 and 60 shocks per minute. For stones smaller than 10 mm, there was no difference in the success rates or complication rate; however, for stones larger than 10 mm, lower frequencies were associated with higher success rates using 60 shocks per minute compared to 120 shocks per minute (RD -0.27, 95% CI, -0.27 – -0.39, $p < 0.001$) and also using 90 shocks per minute compared to 120 shocks per minute (RD -0.31, 95% CI, -0.57 – -0.06, $p = 0.02$). No difference was observed when 90 and 60 shocks per minute were compared ($p = 0.28$). Of note, the treatment duration was significantly different among all the frequencies analyzed (120 vs 60 shocks per minute: $p < 0.001$; 120 vs 90 shocks per minute: $p < 0.001$; 90 vs 60 shocks per minute: $p < 0.001$)[135]. The frequency of shockwave administration does not appear to have a substantial influence on the success rates of SWL for stones smaller than 10 mm, but for larger stones, lower frequencies have demonstrated better outcomes, albeit at the expense of longer treatment times. Urologists should seek a balance between these variables during SWL treatments.

1.5.3.3 ENERGY

The total energy applied during a SWL session is one of the modifiable factors that could impact treatment outcomes and may also be related to complications[136,137]. Although there is no consensus in the literature regarding the best energy levels and strategy, several authors have investigated this matter and reported conflicting findings. Some techniques such as a pre-treatment with a lower voltage, to induce renal vasoconstriction and decrease complications[138], and a stepwise voltage increase during the first hundred shocks to decrease the risk of complications and improve the SFR[139–141], have been proposed.

A prospective study of 50 patients compared fixed voltage to an escalating voltage and demonstrated higher success rates in the escalating voltage group compared to the fixed voltage group (96% vs 72%, respectively, $p < 0.005$)[142]. Lambert *et al*. used a similar strategy and also described higher SFR in the escalating voltage group (81% vs 48%, $p < 0.03$). In this series, microalbumin and β2-microglobulin levels were evaluated at 1 week to assess for renal damage and were significantly higher in the fixed voltage group ($p = 0.046$ and $p = 0.045$, respectively)[141].

Ng and colleagues prospectively compared escalating voltage to fixed voltage protocols and did not find any difference in treatment success between groups (67.8% vs 73.6%, respectively, $p = 0.267$). However, the fixed voltage group received higher total energy levels ($p < 0.001$) and had significantly higher rates of incidentally detected perinephric hematomas on postoperative day 2 imaging (43.8% vs 23.8%, $p < 0.001$)[143], emphasizing the importance of the escalating voltage protocol. Conversely, a prospective randomized trial with 120 patients comparing constant voltage to escalating voltage per 1000 shocks failed to demonstrate a difference in the SFR after 1 week ($p = 0.447$)[59], which was similar to the findings of You and colleagues[144]. Another prospective randomized controlled trial compared immediate voltage escalation to delayed voltage escalation and failed to show any difference in the adjusted SFR between both strategies at 3 months (53.8% in the immediate group vs 41.6% in the delayed group, $p = 0.151$)[145]. Despite the contradicting findings in various studies regarding the impact of voltage escalation on treatment success, clinical practice guidelines support a stepwise increase in voltage during SWL[14,15] or pre-treatment with lower voltages[15] aiming to decrease complications, most specifically renal bleeding and hematoma.

1.6 THE ROLE OF ALPHA-BLOCKERS FOLLOWING SHOCKWAVE LITHOTRIPSY

Considering the results of MET for ureteric calculi[24–26], the use of alpha-blockers to facilitate stone clearance after SWL has also been proposed. A prospective study with 249 patients did not demonstrate a difference in the SFR when comparing patients who received tamsulosin to patients in the control group following SWL treatment (78% vs 69%, respectively, $p = 0.108$)[146]. Another placebo-controlled studied also failed to show differences in the SFR between patients who received alpha-blockers, tamsulosin (58%) and silodosin (47%), and the control group (55%) in the 3-week follow up after SWL ($p = 0.399$)[147]. Conversely, Bhagat *et al*. showed higher SFR in patients who received tamsulosin in comparison with the control group (96.6% vs 79.3%, respectively, $p = 0.004$). This difference was maintained in the group of patients with stones 11 to 24mm in size (93.3% in the group who received the alpha-blocker vs 58.3% in the control group, $p = 0.03$)[21].

The combination of tamsulosin and SWL has also been evaluated in a systematic review and meta-analysis. A benefit in stone expulsion (RR 1.2, 95% CI, 1.15 – 1.26) was demonstrated and subgroup analysis showed an improvement in stone clearance for stones with sizes between 11 and 24 mm (RR 1.49, 95% CI, 1.28 – 1.75)[148]. Another systematic review and meta-analysis with four trials compared the use of alpha-blockers versus placebo post SWL and favoured the use of alpha-blockers (RD 0.17, 95% CI, 0.09 – 0.24). Again, a more pronounced effect was seen in larger stones[149].

Although some studies did not demonstrate a clear improvement in stone clearance with alpha-blockers, other benefits of its usage were described. Falahatkar showed that patients who received tamsulosin needed less time to pass the stone ($p = 0.002$)[150] and a series of 130 patients showed that these patients used less diclofenac doses ($p = 0.004$)[151]. In addition, Moursy *et al*. demonstrated that tamsulosin was beneficial to treat steinstrasse, a complication of SWL, with higher expulsion rates in the alpha-blocker group when compared to the control group (72.7% vs 56.8%, respectively, p = 0.017)[152].

Especially for patients with larger stones, the effect of alpha-blockers as an adjuvant therapy following SWL should be considered as it appears to facilitate stone clearance and might be beneficial to prevent steinstrasse.

1.7 COMPLICATIONS OF SHOCKWAVE LITHOTRIPSY

SWL has overall low complication rates[38]. A study reviewing 1838 patients who underwent SWL reported a complication rate of 6.3% within 14 days of the procedure and a 4% hospital admission rate[153]. The most common complications of SWL are pain and urinary tract infection, with incidences ranging from 7.7% to 23.5% of the cases in the literature. More serious complications, such as bacteraemia and sepsis, occur less frequently[154].

Steinstrasse occurs when the fragments resulting from SWL fail to pass through the ureter, align in a column, and may possibly cause obstruction. Madbouly *et al*. reported a 3.97% steinstrasse rate in a cohort of 4634 patients and the occurrence was associated with stones larger than 2 cm ($p < 0.001$), stones located in the kidney, and total energy used during the treatment[155]. This complication, however, may require further intervention including stent or nephrostomy tube insertion or ureteroscopy, especially if associated with infection or obstruction.

A smaller proportion of patients develop subcapsular or perirenal hematomas, although the reported rates vary according to the imaging modality used postoperatively[156]. A series that included 3620 patients reported an incidence of perinephric hematoma of 0.66% and was associated with pre-existing hypertension[157]. Similarly, another study showed an even lower incidence of 0.34% and identified intraoperative hypertension as a risk factor (HR 3.302, 95% CI, 1.066 – 10.230, p = 0.038) for this complication[158]. Dhar *et al*. reported a higher incidence of 4.1% using CT as the postoperative imaging modality, and in this series older patients had a higher risk of developing subcapsular or perinephric hematomas[156]. It should be noted that SWL is contraindicated in patients with an active coagulopathy or on anti-coagulants as the risk of perirenal hematomas is much higher in these populations.

Shockwave lithotripsy is a safe procedure with low complication rates, and even lower rates of serious complications that require further intervention and hospital readmission. Due to its intrinsic safety, SWL is a reasonable option for most patients with multiple comorbidities.

1.8 THESIS RATIONALE

Considering the multiple parameters described above that might influence the success of SWL, a multicenter trial under "real-world conditions" was proposed. Prospective data collection of real-world data can allow evidence generation based on pragmatic clinical trials that support randomized study designs without the disadvantages such as difficulties with recruitment, the time required and the expense. Realizing that many factors must be considered when recommending treatment, it is evident that certain optimal characteristics when conducting clinical trials are not always reflective of the typical clinical practice, and the stone free rates found in the "real-world" scenario are expected to be inferior to those reported in randomized trials utilizing strict entry criteria. Using the same manufacturer and lithotripter, representing the latest technology at each of the participating sites, a wide array of patient populations and approaches used by each center will allow for a more meaningful understanding of the contemporary outcomes of SWL.

CHAPTER 2

MATERIALS AND METHODS

2.1 STUDY DESIGN

The purpose of this study was to perform a multicentric prospective observational study to evaluate the outcomes of SWL in three reference centres for the treatment of renal calculi, in order to better evaluate the clinical outcomes of SWL in "real-world" scenarios. We hypothesize that our study will show clinically acceptable stone free and complication rates following SWL treatment, but that the stone free rate will be lower than what has previously been reported in published randomized controlled trials which utilize strict entry criteria. Our data may provide more realistic treatment outcomes given the "real-world" conditions and may help both practitioners and patients in selecting treatment modalities for urolithiasis. Three institutions which are regional referral sites and part of TOWER (Team of Worldwide Endourological Researchers) from the Endourological Society, obtained approval from their respective institutional ethics review boards. Participant sites included London (Canada), Vancouver (Canada), and Muscat Governorate (Oman). All three institutions have an extensive experience with shockwave lithotripsy and use the same lithotripter, the Storz Modulith® SLX-F2 (Storz Medical). Vancouver has been using the Storz Modulith® SLX-F2 since 2008 and four urologists are responsible for their shockwave lithotripsy procedures; in London, this lithotripter has being used for the past 10 years and six urologists trained in shockwave lithotripsy perform all the procedures with supervised trainees involved in some of the cases; in Oman, one urologist and four trained and certified technical nurses have been using the Storz Modulith® SLX-F2 since 2010, and similar to London, supervised trainees may be present during the procedures.

All data was collected locally and the enrolled patients were given a unique Study ID. The Master List linking personal identifiers to the unique Study ID was kept in a secure environment at each site.

The de-identified data using the unique Study ID was entered by each institution in a REDCap database[159,160] hosted at a secure server of the University of British Columbia where it was combined and analyzed.

2.2 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria consisted of male and female patients older than 18 years who were scheduled to undergo SWL as a primary treatment for upper urinary calculi in the participant centers.

Exclusion criteria comprised pregnant patients, patients who were unable to give consent, and patients in whom an adjunctive procedure was initially planned for the urolithiasis treatment, such as patients undergoing SWL as a bridge treatment before a ureteroscopy or percutaneous nephrolithotripsy. Patients unable to return for follow up or whose post-operative imaging was not available to the investigators were excluded.

2.3 STUDY OUTCOMES

The primary outcome was treatment success after a maximum of two SWL sessions. Overall success was defined as either complete clearance of the treated stone on postoperative imaging with no residual fragments, or the presence of residuals fragments within the kidney with a cumulative size of less than 4 mm without need for further treatment. This criteria for treatment success has been extensively used in multiple previous studies examining SWL outcomes[145,161–164]. The type and timing of the postoperative imaging modality was defined by each center and not standardized during the study period across the sites.

Secondary outcomes included identifying predictors of treatment failure and differences between patients who had treatment failure or success. The factors were categorized as related to the patient, the stone, or treatment parameters.

2.4 DATA COLLECTION POINTS

Common collection points were used at each site and consisted of four sections: related to the patient, related to the stone, related to the procedure, and follow up information. The data collection points are shown in the Data Collection Sheet in the Appendices section.

2.4.1 RELATED TO THE PATIENT

Data related to the patient included demographics such as sex, age, and BMI. Comorbidities including hypertension, ischemic heart disease, diabetes mellitus, hypercholesterolemia, hyperparathyroidism, gout, history of bowel resection, obesity surgery or inflammatory bowel disease, presence of neurological conditions, and previous surgical history. In addition, the presence of anatomic variants, such as ureteropelvic obstruction, horseshoe kidney, and duplex collecting system; renal function and previous stone composition were recorded when available although due to the nature of the data, no further information about anatomic variants or their previous treatments was collected. Medication and supplement use including alpha-blockers, steroids, diuretics, chemotherapy, indigestion tablets, and vitamin C were documented.

2.4.2 RELATED TO THE STONE

Data related to the stone episode including presentation date, initial imaging modality, and presence and degree of hydronephrosis were recorded.

The characteristics of the stone such as size, location, side, surface area, skin to stone distance, and attenuation on computerized tomography (CT) were recorded. Stone size was defined as the maximum diameter of the stone in any view on imaging. Surface area was measured in axial imaging. Skin to stone distance (SSD) and stone attenuation were recorded only when CT was the pre-operative imaging of choice. SSD was measured perpendicularly from the stone to the skin edge. Stone attenuation on CT was measured in Hounsfield Units (HU) and defined as the highest HU measured within an area of the stone on pre-operative imaging.

2.4.3 RELATED TO THE PROCEDURE

Data related to the treatment characteristics including date of procedure, type of anesthesia or analgesia, number of shocks, maximum energy used, radiation dose, fluoroscopy time, ureteric stent insertion, patient positioning (prone/supine), and the Storz Medical Lithotripsy Index (SMLI) were collected. The SMLI is an integrated measurement of the total energy used during an individual patient treatment and is automatically calculated by the lithotripters used at the three treatment sites. One centre (Oman) uses a bolster when the renal calculus targeting is impaired by the ribs, this position was also recorded as supine. The prescription of alpha-blockers and antibiotics following the SWL by the treating physician was also recorded. The local responsible treating physician and the presence of trainees during the SWL session were not recorded.

2.4.4 FOLLOW UP INFORMATION

Follow up data included the date and modality of follow up imaging, presence and size of residual fragments, presence of complications according to the Clavien-Dindo classification[165], and further management defined by the patient's referring urologist. Further management included the following categories: discharge with complete stone clearance, discharge with fragments not requiring further treatment, and re-treatment.

2.5 METHODOLOGY

Patients who met the study inclusion criteria in the three institutions were approached about study participation prior to their scheduled SWL session. The study was explained to them, and they were given a Letter of Information to review. Patients were given sufficient time to read the Letter of Information and ask questions. Those who agreed to participate signed a Consent Form, were enrolled in the study, and were assigned a unique Study ID number. Clinical information relating to the patient and the stone were collected prior to the procedure, and information related to the procedure were collected during and after each SWL session.

Patients were followed according to each site's standard of care for up to three months after the procedure with a post-operative imaging. The imaging modality choice and timing was not standardized in order to reflect the variation between institutions, and options included CT, ultrasound (US) or kidneys ureter and bladder plain film x-ray (KUB). The follow up imaging was analyzed at each site and further management was assessed locally by the patient's treating urologist. If a patient required additional treatment for the target stone, the treatment modality was noted, and if a second SWL session was performed, the data collection points for the second session and subsequent follow up were also recorded.

2.6 STATISTICAL ANALYSIS

Descriptive statistics was used to describe patients' demographics. Binomial logistic regression was utilized to assess for predictors of treatment failure in the univariable and in the multivariable analyses. The predictors were subdivided in the following categories: related to the patient (sex, age, BMI, and SSD), related to the stone (size, surface area on axial imaging, attenuation on CT, stone location within the collecting system, and laterality), and related to the treatment (number of shocks, patient position, frequency of shocks, maximum energy, and total energy or SMLI). Sex, stone location within the collecting system, laterality, patient position, and frequency of shocks were considered as categorical variables and the remaining predictors as continuous variables. Hosmer and Lemeshow goodness of fit test was used to assess the significance of the model.

To compare patients who had a successful treatment to those who failed SWL, chi-square was utilized for categorical variables; for normally distributed continuous variables, Student's t-test was used to assess differences in means, and the Mann Whitney U test was used when the variables were non-parametric.

Results are reported as counts and percentages for categorical variables, means (± standard deviation, minimum – maximum values) for continuous, normally-distributed variables or medians (interquartile range (IQR)) for continuous variables that were non-normally distributed. All analyses were reported using a 2-tailed test and were considered statistically significant when $p < 0.05$ with a 95% Confidence Interval (CI) and using odds ratio (OR). The statistical analysis was performed using IBM SPSS® Statistics Version 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY: IBM Corp). Deidentified patient data was supplied from each respective site via RedCap database, all data summarization and analysis were undertaken by FGB in London, Ontario.

CHAPTER 3

RESULTS

3.1 COHORT

Between May 2021 and February 2022, three hundred and twenty-three patients undergoing SWL as the primary treatment for renal or ureteric calculi were enrolled at three institutions located in London, Canada, Vancouver, Canada, and Muscat Governorate, Oman. Fifty-one patients did not have follow up imaging available to the investigators and were excluded from the study as per the exclusion criteria, and one patient with missing demographic information was also excluded; therefore, two hundred and seventy-one patients were included in the final analysis (Figure 3).

3.2 DEMOGRAPHICS

The mean patient age was 48.5 years (± 14.9, 18 – 89), and median BMI was 27.09 Kg/m^2 (IQR 24.23 – 30.27). One hundred and eighty-five (68.3%) patients were male, and 86 were female (31.7%). Ninety-nine (36.3%) patients presented with comorbidities, and ischemic heart disease was the most prevalent in 15.9%. Eight patients presented with anatomic abnormalities (2.9%). Demographics are summarized in Table 4.

Primary preoperative imaging modality was CT in 202 patients (74.5%) followed by US in 188 patients (69.3%). One hundred and five patients (38.7%) underwent multiple imaging modalities. Stones were located primarily in the kidney (59%) with 111 patients (41%) having ureteric stones. The majority of the treatments were performed on the left side (56.8%). Mean stone size was 9.88 mm (± 3.38, 3 – 31), and median stone surface area was 42 mm^2 (IQR 27.48 – 61.12). Median stone attenuation on CT was 1018 HU (IQR 719 – 1239.5). Stone characteristics are summarized in Table 5.

Previous stone composition was confirmed in 29.5% of the cases. Seventy patients had calcium oxalate stones, 10 patients had a calcium phosphate stones, and 3 patients had stones of uric acid composition (Figure 4).

Patients were treated mainly in the supine position (86.7%), while prone position was used in 35 cases (12.9%) and only for stones located in the mid and distal ureter. Median number of shocks was 3000 (IQR 3000 – 4000), and the most used frequency was 1.5 Hz in 61.6% of the treatments followed by 2 Hz (34.3%). Median maximum energy level was 5 (IQR 4.5 – 6.0), and the median SMLI was 188 (IQR 172.62 – 255.62). Median radiation dose was 733.12 $cGycm^2$ (IQR 452.46 – 1164.2), although radiation dose data from one site (Oman) was not included due to the intrinsic characteristics of their system, which does not include this measurement. Median fluoroscopy time was 135 seconds (IQR 86.25 – 217.75). Thirty-five patients (12.9%) had a ureteric stent inserted either prior to or at the time of their SWL. Time elapsed between stent insertion and SWL session were not recorded. Treatment details are summarized in Table 6.

The vast majority of the cases were performed under intravenous sedation (98.2%) while one patient was treated under general anesthesia (0.4%), and three patients received only oral analgesics (1.1%). Alpha-blockers were prescribed after the procedure for 132 patients (48.7%), and postoperative antibiotics were used in 44.6% of the cohort.

The first postoperative imaging was performed a median of 17 days (IQR 12.75 – 27) after the procedure and was primarily KUB in 244 patients (90%) followed by US in 136 patients (50.1%). Multiple imaging modalities were performed in 47.2% of the cohort. Preoperative and postoperative imaging modalities are depicted in Figure 5.

Complications were reported in 62 patients (22.8%). Pain (14.7%) and hematuria (14.3%) were classified as Clavien-Dindo I and were the most common complications, which did not require further intervention. Five patients (1.8%) presented with *steinstrasse,* and two of them underwent further treatment with URS, while the three remaining patients passed the fragments without surgical intervention. The three patients who passed their stones spontaneously were all treated with medical expulsive therapy. Unfortunately, data was not available on whether the patients who required subsequent URS for their *steinstrasse* were also treated with medical expulsive therapy. There was no correlation between stone size or stone attenuation and the development of *steinstrasse*; however, the sample size is too small to provide meaningful analysis. There were no perinephric or subcapsular hematomas in the cohort. Table 7 describes the complications recorded and their management.

3.3 SUCCESS RATES

Patients who were considered stone free after one or two SWL sessions and patients who, after a maximum of two SWL sessions, had remaining fragments within the kidney with a cumulative size smaller than 4 mm and did not need additional treatment were considered to be SWL successes (overall success). The overall success rate was 46.1% after one session and 58.3% after two SWL sessions in the cohort. There was no statistical difference in the overall success rate among the treatment centers after one or two SWL sessions ($p = 0.108$ and $p = 0.256$, respectively). Overall success rates after one and two sessions according to the treatment centre are depicted in Table 8.

Patients who required further treatment after one SWL session were primarily retreated using SWL (28.4%), while 40 patients underwent URS (14.7%). Patients who required additional treatment after two SWL sessions were considered as having failed this treatment modality.

3.4 PREDICTORS OF TREATMENT SUCCESS

Predictors of treatment success were assessed according to the following categories: related to the patient, stone, or treatment characteristics. Regarding the factors related to the patient characteristics, younger age was the only significant predictor of treatment success in the univariable analysis (OR 0.982, 95% CI, 0.966 – 0.998, $p = 0.031$). Table 9 shows the results of the univariable analysis for all analyzed variables. Student's t-test was performed to compare the difference in mean ages of patients who had a successful treatment to patients who failed SWL. Mean age in the treatment success group was 46.83 years compared to 50.82 years in the treatment failure group, $p = 0.030$ (Figure 6). Comparison between patients who were older or younger than 60 years of age was not associated with treatment success ($p = 0.238$).

BMI can often be used as an inference of SSD, but in this cohort, the variables did not demonstrate multicollinearity in the multivariable analysis (VIF 1.41, tolerance 0.710 and VIF 1.37, tolerance 0.729, respectively), and both were considered separately in the analysis as potential predictors of treatment success related to the patient. In the multivariable analysis, all patient related variables including age, BMI, sex, and SSD were not found to be predictors of treatment success (Table 10). Using the Mann Whitney U test, there was no difference in the median BMI or in the median SSD between patients who had a successful treatment and patients who failed treatment ($p = 0.493$ and $p = 0.933$, respectively). Presence of comorbidities or anatomic variants was not a predictor of treatment success and due to the small numbers of some comorbidities evaluated, they were not analyzed separately.

In the univariable analysis, smaller stone size was a significant predictor of treatment success (OR 0.876, 95% CI, 0.810 – 0.948, $p < 0.001$), as was smaller stone surface area (OR 0.982, 95% CI, 0.973 – 0.991, $p < 0.001$), and lower stone attenuation on CT (OR 0.998, 95% CI, 0.997 – 1.000, $p < 0.001$). Laterality of the stone and stone location (kidney or ureter) were not predictors of treatment success in the univariable ($p = 0.092$ and $p = 0.748$, respectively) analysis. As stone size and stone surface were highly positively correlated ($r_s = 0.829$, $p < 0.001$), they were analyzed separately in the multivariable analysis. Smaller stone size (OR 0.832, 95% CI, 0.735 – 0.940, $p = 0.003$), smaller stone surface (OR 0.983, 95% CI, 0.971 – 0.995, $p = 0.007$), and lower stone attenuation on CT (OR 0.998, 95% CI, 0.997 – 1.000, $p = 0.006$) were redemonstrated as predictors of SWL success in the multivariable analysis. While location of the stone (renal or ureteric) and stone laterality were once again not significant. Results of the multivariable analysis for factors related to the stone are summarized in Table 11. The specific location of the stone within the collecting system (upper calyx, mid calyx, lower calyx, and renal pelvis for renal calculi; upper, mid, and lower for ureteric stones) was not associated with treatment success (p = 0.912).

Patients who underwent a successful treatment had a mean stone size of 9.29 mm and in patients who failed SWL, mean stone size was 10.71 mm, p < 0.001 (Figure 7). Patients who failed treatment also had a higher median stone surface area than patients who were classified as a successful SWL (median 49.20 mm^2, IQR 46.67 vs 36.29 mm^2, IQR 31.15, respectively, p < 0.001). Comparison between both groups regarding stone attenuation on CT, demonstrated mean lower stone attenuations in patients who had a successful SWL than in patients who failed treatment (906.58 HU vs 1106.68 HU, respectively, p < 0.001). The boxplot comparing both groups is demonstrated in Figure 8. Analyzing stone size and stone location, smaller stone size was a significant predictor of treatment success for ureteric stones (OR 0.736, 95% CI, 0.616 – 0.880, p < 0.001) but not for renal stones (p = 0.052).

Factors related to the treatment, such as number and frequency of shocks, energy level, total energy (SMLI), and fluoroscopy time were not predictors of treatment success in both the univariable and in the multivariable analyses. As energy level and total energy were highly correlated (r_s = 0.873, p < 0.001), they were analyzed separately (Table 12). Ureteric stones were treated using higher median energy levels than renal stones (median 6.0, IQR 2.0 vs median 5.0, IQR 1.0, respectively, p < 0.001). Patient position was analyzed as a predictor of treatment success for stones located in the mid and lower ureter and it was not statistically significant. The use of alpha-blockers postoperatively was not associated with treatment success regardless of stone location.

CHAPTER 4

DISCUSSION

This multicenter study evaluated two hundred and seventy-one patients from three institutions in two countries with different backgrounds and population characteristics. To minimize possible confounders, all the institutions used the same fourth-generation lithotripter, the Storz Modulith® SLX-F2. Previous studies evaluating SWL success rates and factors influencing its results were mostly conducted in a controlled setting, using different lithotripters, or in a single centre where the technique used during the procedure had little to no variation. In this study, each centre used its own standard of care before, during and after the procedure while using the same lithotripter. The variety of the population included, and this particular approach aimed to allow for the results of this cohort to be generalizable to other shockwave treatment centers and provide an analysis of "real world conditions".

4.1 SUCCESS RATES

Stone free status is the most commonly used definition to quantify SWL success, although some authors include patients with "clinically insignificant fragments" as successful cases. There is still controversy regarding the terminology "clinically insignificant fragments" and its appropriateness in the reporting of SWL outcomes. The most used values range from 2 to 5 mm[166] and the long-term implications of these fragments vary from high stone passage rates within 12 months[167] to recurrence rates up to 50%, which are typically associated with larger fragments[168]. In this study, as all patients included in the analysis underwent post-operative imaging, and "clinically insignificant fragments" were defined as those located within the kidney, with a cumulative size of less than 4 mm, in patients who did not require further intervention to treat the target stone, after a maximum of two SWL sessions. The overall success rate also included patients who were completely stone free on postoperative imaging. Patients with ureteric calculi were considered as having a successful SWL only if they were stone free on follow up imaging.

The main national urological association guidelines[12–14] currently do not recommend invasive treatment for asymptomatic patients with renal stones smaller than 5 mm. While classifying patients with small residual fragments following SWL as successful cases could increase the success rates, this choice would allow for a more accurate portrayal of "real-life" outcomes as pursuing the stone free status might just put these patients in a higher risk of complications with additional interventions without a clear benefit. Nonetheless, establishing 4 mm as the maximum cumulative size for the residual fragments excluded patients with just slightly larger fragments who did not require further treatment from the successful treatment group, potentially decreasing the success rates in the study.

In our cohort, the success rate after one SWL session was 48.1% and after two SWL sessions, 58.3%. The SWL success rates are known to increase with the number of sessions[48,77,98,130,169,170] and some centers, such as the centre from Oman included in this study, may perform multiple SWL sessions to treat the same stone. A higher number of sessions might increase the risk of complications, especially for stones located in the kidneys[137]. URS has a higher chance to be successful in a single-procedure than SWL[12,13] and is often selected as the second line option should 1 or 2 SWL treatment attempts fail. Considering there is conflicting opinion in the literature on the benefits and cost-effectiveness of repeated SWL sessions if a patient has failed prior SWL,[171] the cut off of a maximum of two SWL sessions to evaluate treatment success was defined for analytic purposes in this study.

Although the newer generations of lithotripters had lower success rates when compared to the first generation[80,85], previous series using the Storz Modulith® SLX-F2 lithotripter showed success rates ranging from 67%[85] to 83%[82]. In this cohort, the final overall success rate (after a maximum of two SWL sessions) was lower (58.3%) and contrasted with the other studies due to not being performed in controlled setting. Patients who would not meet the criteria to be enrolled in the series conducted by

De Sio and colleagues[82], such as patients with stone diameter over 20 mm and patients with unfavourable anatomic lower pole characteristics, were included in this study as it aimed to reflect the "real-world" patients that are being treated in a urolithiasis reference centre. In addition, a higher stone attenuation on CT, especially above 1000 HU[95,100,106], has been associated with lower shockwave lithotripsy success rates. In this cohort, the median stone attenuation on CT was 1018 HU (IQR 719 – 1239.5), which is above the 1000 HU threshold, and this specific characteristic could have also influenced the overall success rate. Patients with less-than-ideal characteristics for SWL (large stone size, higher attenuation, higher SSD) but with significant co-morbidities precluding other more invasive treatments might undergo SWL as an example.

In this cohort, the follow up was performed according to each centre's standard of care and the median time until the first imaging was significantly shorter (17 days) than other series evaluating SWL outcomes[49,77,85]. A commonly used follow up time interval has been 1 to 3 months. Longer follow up times are shown to increase stone passage rates and thus success rates after SWL[32] . It is conceivable that had patients in this study been followed longer, the stone clearance rate might have increased also.

4.2 FACTORS IMPACTING SHOCKWAVE LITHOTRIPSY RESULTS

4.2.1 FACTORS RELATED TO THE PATIENT

SWL is a safe procedure for elderly patients and it is often used for urolithiasis treatment in this population as it does not require general anesthesia and has low complication rates. Studies showed that older age is associated with lower stone free results following SWL[83,87], especially in patients older than 60 years, although the exact mechanism in which aging affects the SWL outcomes is not completely elucidated. The extent of the impact of patients' age on SWL results is also still unclear. In our cohort, age was a predictor of treatment success in the univariable analysis but not in the multivariable. The mean age of patients who underwent a successful treatment was 46.83 years while patients who failed SWL had a mean age of 50.82 years and, although the difference in means was statistically significant (p = 0.030), the clinical significance of this finding is questionable as these patients would be in the same age group, the fifth decade of life, in most classifications. Furthermore, in this cohort, treatment success was not associated with age when patients older than 60 years were compared to younger patients (p = 0.238).

Regarding the characteristics related to the patient that influence SWL results, BMI and SSD are the most commonly reported in the literature. BMI and SSD are often correlated and, due to BMI being an easier parameter to obtain, it is frequently used as a surrogate for SSD, which requires a patient to undergo a CT preoperatively. Most studies associate higher BMI and higher SSD with lower SFR[55,100] although Jacobs *et al*. did not find a relationship between these parameters and SWL success[91]. In fact, authors have proposed cut off values to SSD that would predict SWL failure ranging from 90 mm[54] to 110 mm[94] with the most commonly used being 100 mm. The challenge with higher values of SSD if that the focal distance of the lithotripter might not be sufficient to reach the stone. Modern lithotripters have longer maximum focal depths than the earlier generations and the Storz Modulith® SLX-F2, the lithotripter used in all the treatment centres involved in this study, has a maximum focal depth of 180 mm. The median BMI in the cohort was 27.09 Kg/m^2 (IQR 24.23 – 30.27) and the mean SSD was 108.4 mm (± 23.22), and no difference was found between either BMI or SSD and SWL success rates. The long maximum focal depth of the lithotripter used in this study, could have influenced results by minimizing the difference in success rates in patients with higher BMI and SSD values when compared to patients with lower BMI and SSD. The Storz Modulith® SLX-F2 table supports 225 Kg, and its long maximum focal depth, along with the results of this cohort reinforce that it is suitable for the urolithiasis treatment of obese patients.

4.2.2 FACTORS RELATED TO THE STONE

Although Demirbas *et al*.[109] did not demonstrate difference in SWL success rates according to the stone size when analyzing patients with ureteric calculi, larger stone size[87,99,100,172] and larger stone surface[97,98,101] are associated with lower SWL success rates in multiple studies. When SWL was introduced as a urolithiasis treatment modality, it was used to treat a variety of stones, including staghorn stones. Following the findings of lower success rates for larger stones, the main national urological association guidelines[12–14] changed their recommendations and SWL is currently no longer recommended for renal stones larger than 20 mm or ureteric stones larger than 10 mm. Regardless of the stone location within the collecting system, a threshold of 10 mm was defined by studies comparing SWL to URS[38,45,46] and studies analyzing SWL success rates alone[48,51,77,99]. Stones beyond this size would have a significantly lower success rates after SWL than smaller stones.

In this cohort, both smaller stone size and smaller stone surface area were predictors of treatment success in the univariable ($p < 0.001$ and $p < 0.001$, respectively) and in the multivariable analyses ($p = 0.003$ and $p = 0.007$, respectively). When comparing patients who failed SWL to patients who underwent a successful treatment, the mean stone size was 10.71 mm in the first group and 9.29 mm in the second, $p < 0.001$. Analyzing by stone location, smaller stone size was a predictor of treatment success for ureteric stones ($p < 0.001$) but not for renal stones ($p = 0.052$) and this is consistent with both the AUA and EAU guidelines[12–14] where the threshold for the treatment of ureteric stones is smaller than the limit for renal stones. The findings of this cohort support that stone size and stone surface area are important factors and should be considered when recommending SWL.

Stone attenuation on CT is highly correlated with stone composition[173]. Cystine stones are usually very hard stones and adult patients with cystinuria usually have poor results with SWL. Calcium oxalate monohydrate and calcium phosphate stones are less hard in comparison with cystine stones [174] but may also be relatively resistant to SWL. Uric acid stones are known to be soft stones, often breaking up easier during SWL than other stones, and their attenuation on CT is lower than cystine, calcium phosphate, and calcium oxalate stones[52]. Stone composition and stone attenuation on CT have been demonstrated to influence SWL success in many studies[52,54,56,93,94], and a threshold of attenuation of 1000HU has been identified, above which the chance of success following SWL treatment is significantly reduced[95,100,106]. Previous stone composition was unknown in a large proportion of the patients in this cohort (70.4%) and stone attenuation on CT was available for 74.5% of the patients who underwent a CT preoperatively as not all patients had the stone attenuation recorded in the database. Median attenuation on CT was 1018 HU (IQR 719 – 1239.5) and, in this cohort, lower stone attenuation on CT was a predictor of treatment success in the univariable ($p < 0.001$) and in the multivariable analysis ($p = 0.006$). Comparison between patients who underwent a successful treatment and patients who failed SWL showed a significant difference in the mean stone attenuation on CT (906.58 HU vs 1106.68 HU, respectively, $p < 0.001$). CT is currently the gold standard imaging modality for the diagnosis of urolithiasis and is becoming increasingly utilized. However, the use of the stone attenuation on CT as a predictive tool of SWL success should be considered carefully as patients with kidney stone disease have a high risk of recurrence[7] and may be exposed to large amounts of radiation due to this condition throughout their lives.

The success rates of SWL for renal calculi are often slightly lower than for stones located in the ureter[50]. Further to this, due to anatomic characteristics and gravity[53,112], stones located in the lower pole have poor stone clearance when compared to stones in other locations within the kidney[49]. In this cohort, a larger proportion of the patients presented with renal calculi (59%) and the majority of them were located in the lower pole (38.1%). Considering this, lower success rates for patients with renal stones were expected when compared to patients with ureteric stones however, in the analysis, stone location was not associated with treatment success ($p = 0.803$).

4.2.3 FACTORS RELATED TO THE TREATMENT

A systematic review and meta-analysis showed that lower shockwave frequencies of 1 Hz and 1.5 Hz were associated with higher SFR and these results were especially observed in the group of patients with larger stones[135]. Lowering the shockwave frequency impacts the treatment duration[62], contributing to higher levels of patient's discomfort[133] and could potentially decrease the number of procedures performed using the same lithotripter throughout the day. During the procedure, targeting is performed in real-time using fluoroscopy and changes in the stone can be frequently observed. If the stone size is <10 mm in size, patient toleration to the treatment is good and changes in the stone are observed with fluoroscopy, most urologists would use the default frequency of 2 Hz, which allows for a faster treatment than using lower frequency rates and could possibly result in the treatment of a larger number of patients on the same lithotripter, especially considering the scarcity of this resource. Although frequency of shocks was not a predictor of treatment success in the univariable or in the multivariable analysis for this cohort, a larger proportion of the procedures in this cohort was performed using 1.5 Hz (61.6%). Additionally, no difference was observed in the stone size when comparing different shockwaves frequencies.

There is no consensus in the literature regarding the highest energy level to be used during a SWL session that would result in both good success rates and low complication rates. To minimize complications, strategies such a stepwise approach have been described[139–141]. The median maximum energy level used in the cohort was 5 (IQR 4.5 – 6.0). The Storz Modulith® SLX-F2 lithotripter has varied energy levels according to the focus used (precise or extended)[175] and the output can be adjusted by 26 levels in its control center[176]. Both the maximum energy level and the SMLI, which is a measure calculated by the lithotripter of the total energy during a procedure, were not predictors of treatment success in the univariable or in the multivariable analysis. Higher energy levels were used for ureteric stones in comparison with renal stones ($p < 0.001$) reflecting the concern with complications such as perirenal hematoma when higher energy levels are applied to the kidneys, and this probably correlates with the low number of serious complications observed in the study.

Patient position can influence the SWL results when the stone is located over the bony sacrum as it could serve as a barrier for the shockwaves that would reach the stone with lower energy levels. The prone position was proposed to overcome this issue and has been used since, although not without a few complications[125,126]. More recently, several studies showed good results for SWL in the supine position for patients with distal ureteric stones as the shockwaves would travel via the greater sciatic foramen[127,128]. In this cohort, prone position was used in 12.9% of the cases and only for stones located in the mid and distal ureter. Patient positioning was not a predictor of treatment success for such stones and both the prone and the supine positions could be used according to the treating urologist's preference.

Fluoroscopy is used to adjust the target in real-time during SWL. Fluoroscopy time was evaluated as a possible predictor of treatment success with higher fluoroscopy times being associated with higher success rates[177], although higher fluoroscopy times could also be an indicator of difficulty in targeting. In this cohort, fluoroscopy time was not a significant predictor of SWL success in the univariable or in the multivariable analyses. The urologists should be mindful though during the procedure to use only as much radiation as necessary to conduct the case as not to increase unnecessarily the patient's exposure to radiation.

4.3 COMPLICATIONS

The overall complication rate in the study was 22.8%, and in 82% of these were classified as Clavien-Dindo I. Eight patients (2.9% of the total cohort) needed to be admitted due to complications (five with pain, two with *steinstrasse* and one with pyelonephritis). In the literature, the overall complication rate after SWL is reported around 7%[153,154] with serious complications presenting even lower numbers[157]. Five patients (1.8%) were identified as having a steinstrasse in the postoperative imaging, and only two of them required management with URS. The three patients who passed the fragments and did not need intervention, were using alpha-blockers, which may have influenced the outcome. As a predictor of treatment success however, the use of alpha-blockers was not associated with higher stone free rates.

There were no reports of symptomatic perinephric or subcapsular hematomas in our cohort which is consistent with previous series using the same lithotripter[158]. A higher incidence of incidental perinephric or subcapsular hematomas were reported with routine postoperative cross sectional imaging but the number of symptomatic patients remained low[143]. Postoperative imaging was performed according to each centre's standard of care in our cohort and 7.3% of the patients underwent a postoperative CT, which could have underestimated our number of asymptomatic patients with perinephric or subcapsular hematoma. However, given that they were asymptomatic there is likely little clinical relevance to underestimating the rate of renal hematoma.

Following an SWL procedure most patients are expected to have some degree of pain and self-limited hematuria, and both should resolve without any intervention. Overall, in this multicenter study, serious complications requiring admission to the hospital were 2.9%, which is consistent with other series and reinforces the safety of SWL.

4.4 LIMITATIONS

Limitations of this study include the lack of a standard follow up as we intended to replicate each treatment site's standard of care. Also, the main follow up imaging modality was KUB which is less sensitive than CT[178] and could have overestimated the success rates. On the contrary, the short mean follow up time could have underestimated our overall success rates as longer follow up times are associated with higher SFR for SWL[32]. CT is also a more sensitive imaging modality to detect perinephric and subcapsular hematomas, and given the low rates of CT scans performed as the primary postoperative imaging, we may have underestimated our complications rates, although the majority of patients with this type of complications are asymptomatic and do not require clinical intervention[143].

Current guidelines do not recommend routine stent insertion for patients undergoing SWL,[12–15] and the impact of having a stent *in situ* on SWL outcomes are equivocal in the literature[179,180]. In our cohort, indications and date of the stent insertion were not recorded, therefore, stent insertion was not analyzed as a predictor of treatment success, and this could have influenced our results.

The option of considering the potential factors influencing the treatment success in the multivariable analyses in separated sections (related to the patient, related to the stone, and related to the treatment) instead of considering all them together was performed to try to identify predictors that could possibly be altered to achieve better results, such as the selection of patients with specific stones' characteristics or to apply a certain frequency of shocks during the SWL, instead of trying to find the perfect combination of this factors that could lead to better results. By not performing the analysis with all the possible predictors combined, an increase in the confounding factors in each of the separate analysis occurred and this could have altered the results found. In spite of this, factors related to stone characteristics were consistent predictors of treatment success in both the univariable and in the multivariable analyses performed, and these results are consistent with the literature[48,51,52,54,82,93,94,98–100]. Based on the analysis, stone characteristics had the strongest effect and are most likely to influence the SWL results and although the ideal patient for SWL can not determined, these findings should be considered when proposing a treatment modality, as well as the patients' preferences and expectations.

CHAPTER 5

CONCLUSION

In this cohort, the overall success rate after two SWL sessions was 58.3%, which is lower than has been demonstrated by previous series. Unlike those studies, the patients enrolled in this cohort were not subject to strict selection criteria, but rather they represented patients who, in the treating physicians' estimation, were best served by SWL. This choice aimed to reflect the real-world patients who are cared for in three different referral centres. The short follow up, the high stone attenuation on CT, a strict definition of overall success, and the nature of the patients included in the cohort could be contributing factors to the lower success rate. Analysis of predictors of treatment success demonstrated that stone related factors appear to be the most important to predict treatment success and should be carefully considered when recommending SWL. The low rate of serious complications reaffirms that SWL is a safe, minimally invasive procedure.

This study aimed to demonstrate outcomes that could be generalizable to other treatment centers. A takeaway message may also be to encourage other centers to analyze one's own data and not to solely rely on published clinical trials, which may reflect conclusions resulting from different patient populations.

Table 1: AUA[12,13] and EAU[14] guidelines for the surgical treatment of urolithiasis

Stone Location	Stone Size	AUA guideline[12,13]	EAU guideline[14]
Ureter (distal and mid)	< 10 mm	URS	SWL or URS
	> 10 mm	URS	1. URS 2. SWL
Ureter (proximal)	< 10 mm	URS or SWL	URS or SWL
	> 10 mm		1. URS 2. SWL
Kidney	10 – 20 mm	SWL or URS	SWL or URS (if lower pole stones, prefer URS over SWL depending on anatomic characteristics)
	> 20 mm	PCNL	PCNL

Table 2: Factors impacting lithotripsy success

Related to the patient	Body Mass Index (BMI)	• Higher BMI associated with SWL failure[51,95]
	Skin-to-stone distance (SSD)	• Lower SSD associated with SWL success[55,90,99] • No effect of SSD in SWL success[91]
	Anatomy	• Acute infundibulopelvic angle[53], longer and narrow infundibula associated with lower SFR following SWL[115,116]
	Age	• Older age associated with lower SFR following SWL, especially for renal stones[87,88] • No difference in SFR according to stone site[89]
Related to the stone	Size	• Smaller stone size, especially < 10mm, associated with higher SFR[48,82,99]
	Location	• Mid and lower ureteric calculi are associated with higher SFR when compared to renal and upper ureteric[71,109]
	Attenuation on CT	• Lower attenuation on CT, especially > 1000 UH, associated with higher SFR [52,54,56,93–95]
	Composition	• Uric acid stones have lower attenuation values on CT than calcium oxalate and calcium phosphate stones and are associated with higher SFR[52,102]

Related to the procedure/ lithotripter	Frequency of shocks	• Lower shockwave frequency associated with higher SFR, especially for larger stones[133,135,171]
	Total energy output	• Higher total energy associated with s higher rates of perinephric hematomas[143]
	Patient position	• Supine position associated with higher SFR for distal ureteric stones than prone position[60,127,128,132]

Table 3: Technical specifications of different types of lithotripters according to generation[48–51,63,64,72,73,77,83,85,181–184]

Generation	Examples	Energy Source	Focus (aperture)	Maximum focal depth	Coupling mechanism	Targeting System
First Generation	Dornier HM3	Electrode (80 nF)	Semi-ellipsoid (140 mm)		Water bath	• 2 under-couch X-ray tubes
Second Generation	Dornier HM3 (modified)	Electrode (40 nF)	Semi-ellipsoid (170 mm)	130 mm	Water bath	• 2 under-couch X-ray tubes
	Sonolith 2000/3000	Electrode (50,000 shockwaves/electrode set)	Semi-ellipsoid (260 mm/205 mm)		Partial water bath	• 1 lateral ultrasound • 1 coaxial ultrasound
	Dornier HM4	Electrode (40nF)	Semi-ellipsoid (170 mm)	130 mm	Water cushion	• 2 under-couch X-ray tubes
	Siemens Lithostar®	Electromagnetic (flat coil)	Acoustic lens (105 mm)	95 mm (115 mm with modified shock head)	Water cushion	• 2 over-couch X-ray rubes

	Wolf Piezolith 2300	3000 piezoelectric elements	Self-focusing (500 mm)	120 mm	Partial water bath	• 2 coaxial ultra-sound scanners
	Direx Tripter X1	Underwater electrode	Semi-ellipsoid (200 mm)		Water cushion	• External C-arm
Third Generation	Wolf Piezolith 3000	Double layer of piezoelectric elements arranged in a concave surface	Self-focusing (360 mm) Three focal sizes	165 mm	Water cushion	• Isocentric C-arm • Coaxial ultrasound
	Storz Modulith® SL-20	Electromagnetic cylinder	Paraboloid reflector (300 mm) Two focal sizes	150 mm	Water cushion	• Coaxial ultrasound integrated • External C-arm
	Dornier Compact Delta	Electromagnetic	Acoustic lens (140 mm)	150 mm	Water cushion	• X-ray • Lateral • ultrasound

	Siemens Lithoskop	Electromagnetic (flat coil, System Pulse)	158mm	160 mm	Water cushion	• In-line fluoroscopy • In-line ultrasound
	Dornier MPL 9000	Electrohydraulic	Ellipsoid reflector (210 mm)	80 mm (modified to 130 mm in 1988)	Water cushion	• X-ray • Coaxial ultrasound
	Siemens Lithostar® Plus	Electromagnetic flat coil + Overhead module	Acoustic lens (185 mm)	155 mm	Water cushion	• Coaxial ultrasound • 2 over-couch tubes
Fourth Generation	Sonolith Vision	Electroconductive shock-wave generator with an elliptical reflector	Spherical dish (219 mm)	250 mm	Water cushion	• Isocentric C-arm X-ray • Lateral ultrasonography

	Storz Modulith® SLX-F2	Electromagnetic	Parabolic reflector (300 mm) Two focal sizes	180 mm	Water cushion	• In-line fluoroscopy • In-line ultrasound

Table 4: Cohort demographics

Age (mean, SD)	48.5 years (± 14.95)
BMI (median, IQR)	27.09 Kg/m^2 (24.23 – 30.27)
Skin-to-stone distance (mean, SD)	108.4 mm (± 23.22)
Sex (n, %)	
Males	185 (68.3%)
Females	86 (31.7%)
Comorbidities	**99 (36.3%)**
Hypertension	46 (17%)
Hypercholesterolemia	39 (14.4%)
Ischemic Heart disease	43 (15.9%)
Diabetes Mellitus	41 (15.1%)
Hyperparathyroidism	16 (5.9%)
Gout	3 (1.5%)
History of bowel resection	11 (4.1%)
Obesity surgery or inflammatory bowel disease	18 (6.6%)
Neurological conditions	4 (1.1%)
Presence of anatomic variants	8 (2.9%)

Table 5: Stones' characteristics

Stone Size (mean, SD)	9.88 mm (± 3.38)
Stone Surface (median, IQR)	42 mm^2 (27.48 – 61.12)
Attenuation on CT (median, IQR)	1018 HU (719 – 1239.5)
Laterality (n, %)	
Right side	117 (43.2%)
Left side	154 (56.8%)
Location (n, %)	
Kidney	**160 (59%)**
Upper calyx	13 (8.1%)
Middle calyx	28 (17.5%)
Lower calyx	61 (38.1%)
Renal pelvis/ UPJ	58 (36.2%)
Ureter	**111 (41%)**
Proximal ureter	57 (51.3%)
Mid ureter	6 (5.4%)
Distal ureter	48 (43.2%)

Table 6: Treatment characteristics

Patient position (n, %)	
Supine	235 (86.7%)
Prone	35 (12.9%)
Number of shocks (median, IQR)	3000 (3000 – 4000)
Maximum energy (median, IQR)	5.0 (4.5 – 6.0)
SMLI (median, IQR)	188 (172.62 – 255.62)
Frequency (n, %)	
1 Hz	2 (0.7%)
1.5 Hz	167 (61.6%)
2 Hz	93 (34.3%)
Radiation dose (median, IQR)	733.12 $cGycm^2$ (452.46 – 1164.2)
Fluoroscopy time (median, IQR)	135 seconds (86.25 – 217.75)
Focus (n, %)	
Precise	231 (85.2%)
Extended	3 (1.1%)
Combination	11 (4.1%)

Table 7: Complications post shockwave lithotripsy

Clavien-Dindo	Complication	Management	Total (n, %)
I	Pain Hematuria Steinstrasse	none	54 (19.9%)
II	Pyelonephritis Pain	Admission for antibiotic therapy Admission for pain control	3 (1.1%)
IIIb	Pain Steinstrasse Pain	Stent insertion URS URS	5 (1.8%)
Total			**62 (22.8%)**

Table 8: Success rates according to treatment site after one and two sessions

Site	ONE SWL SESSION			Number of patients submitted to two SWL sessions	TWO SWL SESSIONS		
	Success Yes (n, %)	Success No (n, %)	Total (n, %)		Success Yes (n, %)	Success No (n, %)	Total (n, %)
London	66 (52.8%)	59 (40.4%)	125 (46.1%)	19	77 (48.7%)	48 (42.5%)	125 (46.1%)
Vancouver	13 (44.8%)	16 (55.1%)	29 (10.7%)	2	13 (44.8%)	16 (55.1%)	29 (10.7%)
Oman	46 (36.8%)	71 (48.6%)	117 (43.2%)	57	68 (58.1%)	49 (41.8%)	117 (43.2%)
Total	**125 (46.1%)**	**146 (53.9%)**	**271 (100%)**	**78**	**158 (58.3%)**	**113 (41.7%)**	**271 (100%)**

Success rate was defined as the percentage of patients who had complete clearance of their treated stone on postoperative imaging, or presence of residuals fragments within the kidney with a cumulative size of less than 4 mm without need for further treatment following one or two SWL sessions.

Table 9: Univariable analysis for predictors of treatment success

Variable	SE	Wald	Sig	OR	95% CI	
					Lower	Upper
Related to the patient						
Age	0.008	4.649	**0.031**	0.982	0.966	0.998
Sex (reference: females)	0.270	2.392	0.122	1.519	0.894	2.580
BMI	0.028	0.395	0.530	0.983	0.930	1.038
SSD	0.007	0.312	0.576	0.996	0.984	1.009
Related to the stone						
Stone size	0.040	10.834	< **0.001**	0.876	0.810	0.948
Attenuation on CT	0.000	15.845	< **0.001**	0.998	0.997	1.000
Stone surface area	0.005	15.128	< **0.001**	0.982	0.973	0.991
Laterality (reference: left)	0.252	2.837	0.092	0.655	0.400	1.072
Stone location (kidney vs ureter) (reference: ureter)	0.251	0.103	0.748	1.084	0.663	1.773
Related to the procedure						
Number of shocks	0.000	0.081	0.776	1.000	1.000	1.000
Frequency of shocks (reference: 1.5 Hz)	0.267	2.176	0.140	0.675	0.400	1.138
Energy level	0.076	0.316	0.574	0.958	0.826	1.111
Total energy (SMLI)	0.002	0.261	0.610	1.001	0.998	1.004
Fluoroscopy time	0.001	0.016	0.898	1.000	0.998	1.003

SE: standard error; Wald: Wald Chi-Square test; Sig: significance; OR: odds ratio; CI: confidence interval

Table 10: Multivariable analysis for factors predictive of treatment success related to the patient

Variable	SE	Wald	Sig	OR	95% CI	
					Lower	Upper
Age	0.013	2.675	0.102	0.980	0.956	1.004
Sex (reference: females)	0.413	2.686	0.101	1.967	0.876	4.418
BMI	0.048	0.396	0.529	0.970	0.883	1.066
SSD	0.009	0.025	0.875	0.999	0.981	1.016

SE: standard error; Wald: Wald Chi-Square test; Sig: significance; OR: odds ratio; CI: confidence interval

Table 11: Multivariate analysis for factors predictive of treatment success related to the stone

Variable	SE	Wald	Sig	OR	95% CI	
					Lower	Upper
Stone size	0.063	8.654	**0.003**	0.832	0.735	0.940
Attenuation on CT	0.001	7.196	**0.006**	0.998	0.997	1.000
Laterality (reference: left)	0.315	1.513	0.219	0.679	0.366	1.258
Stone location (kidney vs ureter) (reference: kidney)	0.342	1.399	0.237	1.499	0.767	2.930
Attenuation on CT	0.001	7.568	**0.006**	0.999	0.998	1.000
Stone surface area	0.003	7.174	**0.007**	0.983	0.971	0.995
Laterality (reference: left)	0.314	0.824	0.364	0.752	0.407	1.391
Stone location (kidney vs ureter) (reference: kidney)	0.341	0.751	0.386	1.344	0.689	2.623

SE: standard error; Wald: Wald Chi-Square test; Sig: significance; OR: odds ratio; CI: confidence interval

Table 12: Multivariable analysis for factors predictive of treatment success related to the procedure

Variable	SE	Wald	Sig	OR	95% CI	
					Lower	Upper
Number of shocks	0.000	0.208	0.648	1.000	0.999	1.000
Frequency of shocks (reference: 1.5 Hz)	0.339	1.608	0.205	0.651	0.335	1.264
Energy level	0.105	2.057	0.152	0.860	0.699	1.057
Fluoroscopy time	0.001	0.354	0.552	0.999	0.996	1.002
Number of shocks	0.000	0.372	0.542	1.000	0.999	1.000
Frequency of shocks (reference: 1.5 Hz)	0.356	2.670	0.102	0.559	00.278	1.123
Total energy (SMLI)	0.002	0.222	0.638	1.001	0.997	1.004
Fluoroscopy time	0.002	1.052	0.305	0.998	0.995	1.001

SE: standard error; Wald: Wald Chi-Square test; Sig: significance; OR: odds ratio; CI: confidence interval

Figure 1: The Dornier HM3 lithotripter and a patient being prepared for treatment in the Dornier HM3. ***Source: Dornier Medtech***

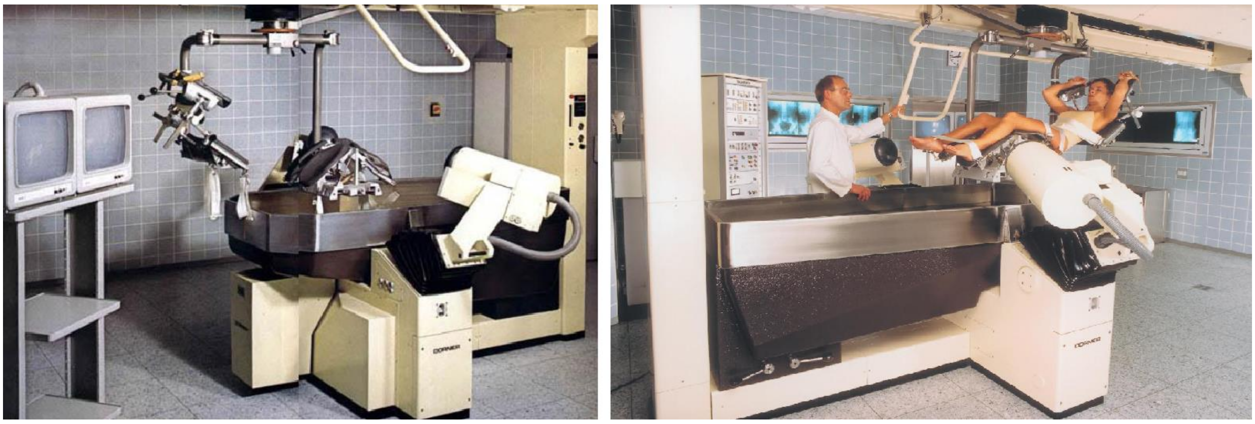


Figure 2: Storz Modulith® SLX-F2 lithotripter on the left and Storz Modulith® SLX-F2 Connect lithotripter on the right. ***Source: Storz Medical AG***

Figure 3: Cohort built

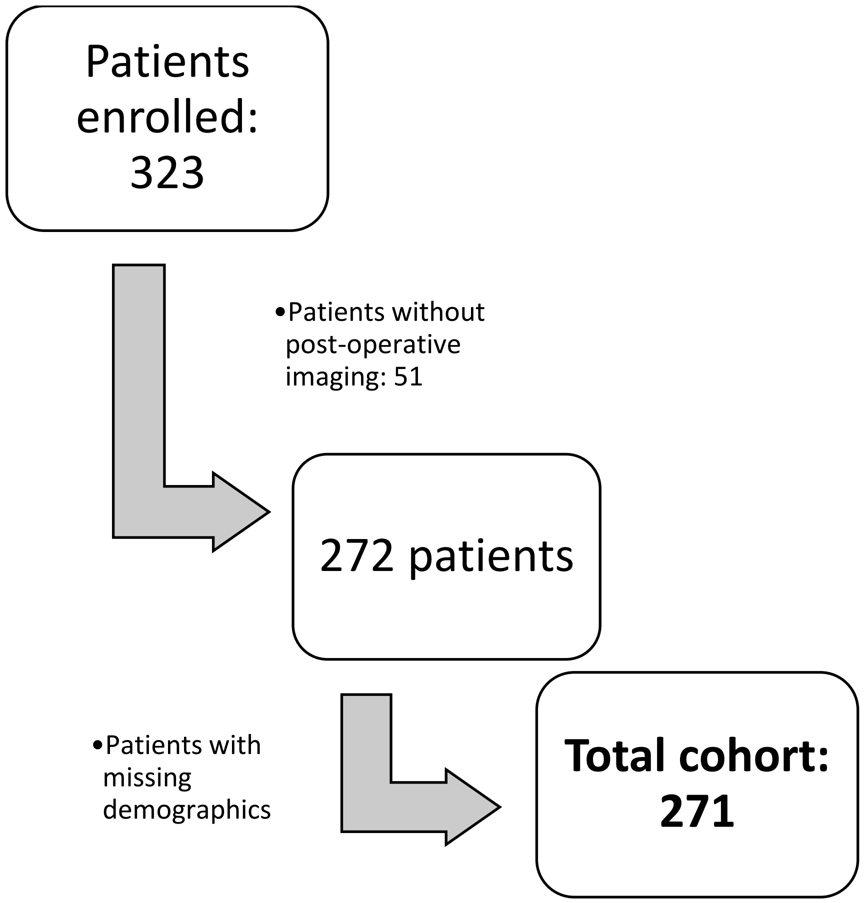


Figure 4: Previous stone composition in the cohort

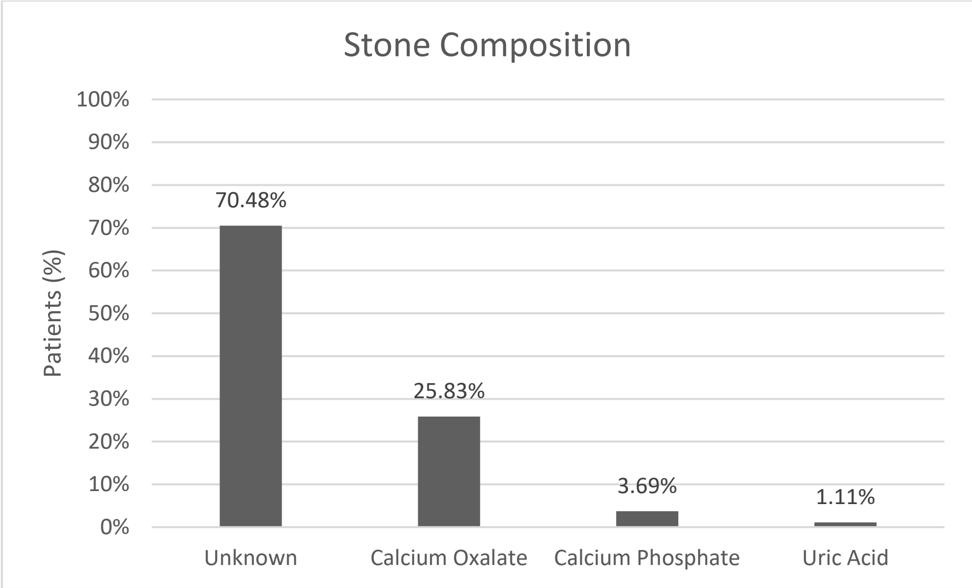
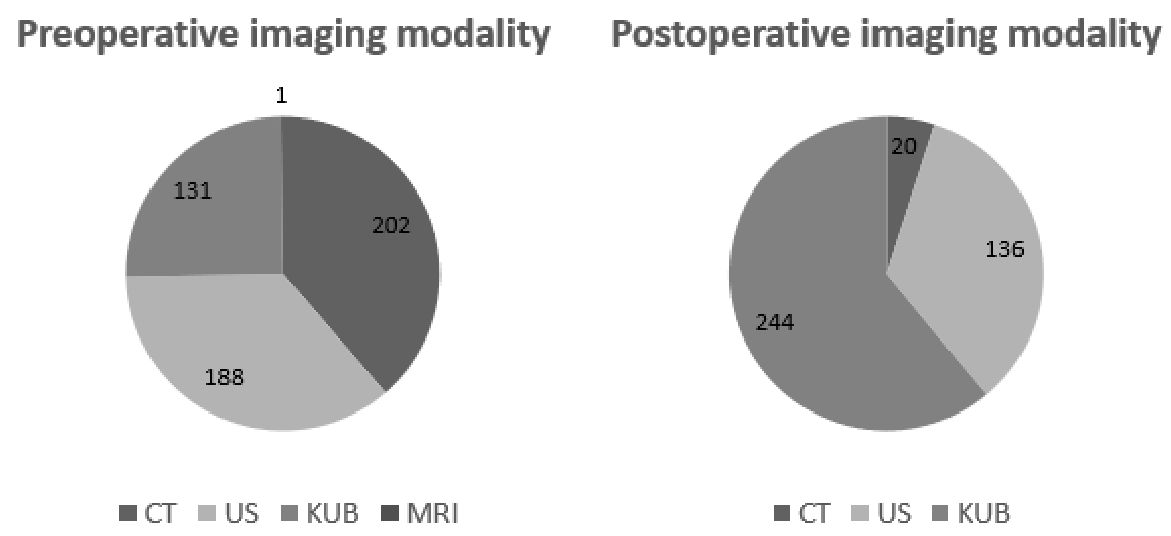
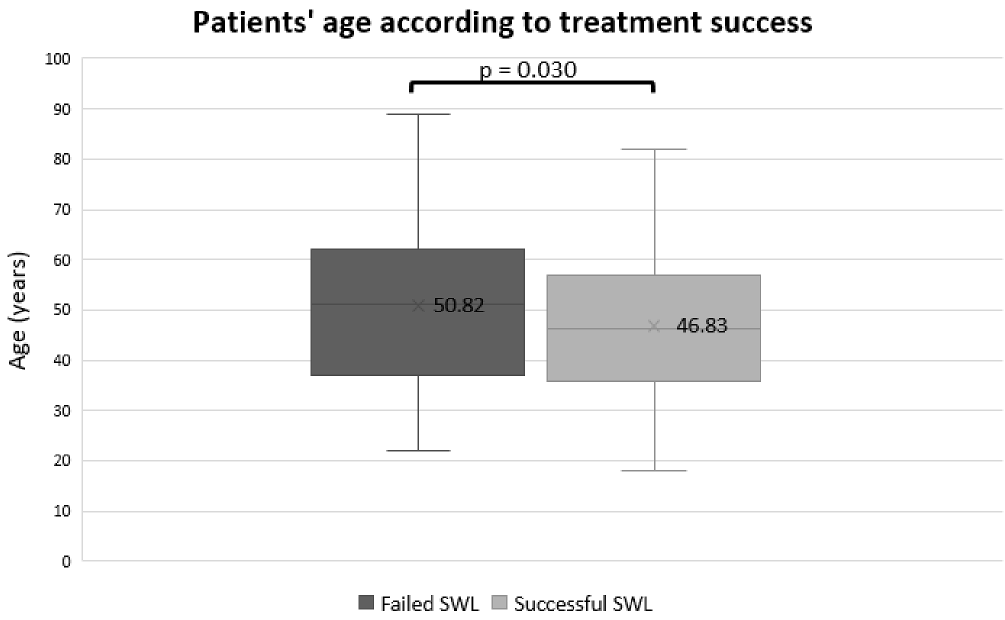


Figure 5: Number of patients according to the preoperative and post operative imaging modalities



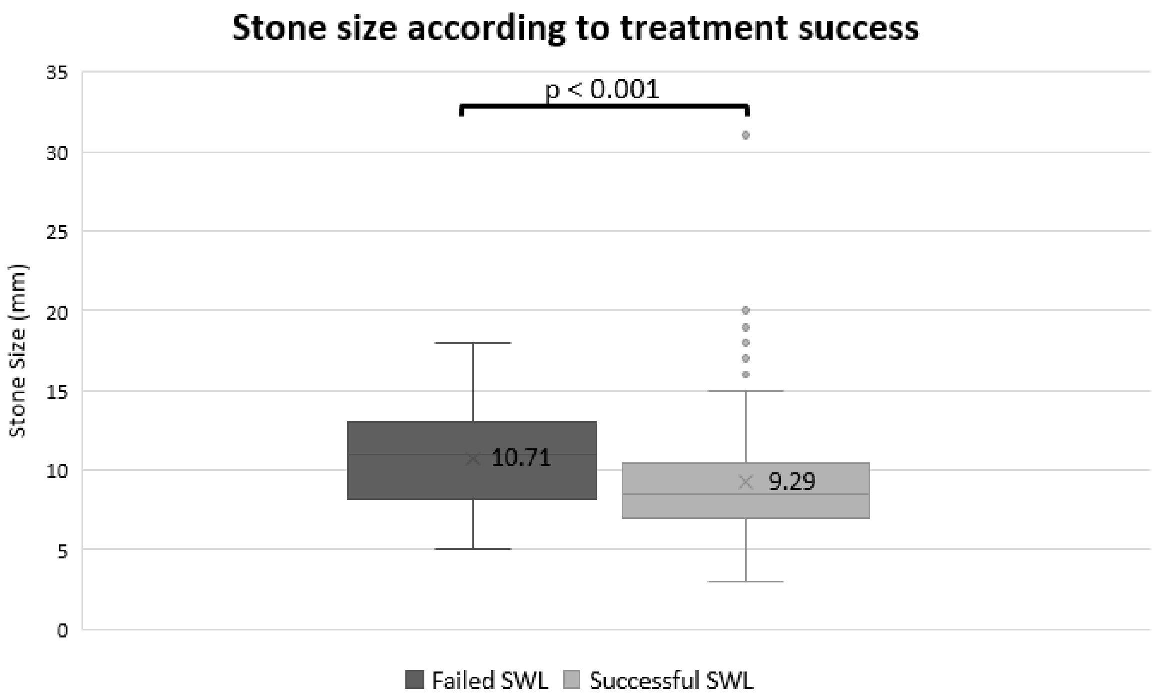
CT: computerized tomography; US: ultrasound; KUB: kidneys, ureters, and bladder plain-film X-ray; MRI: Magnetic Resonance Imaging

Figure 6: Box plot of age in patients who failed shockwave lithotripsy compared to patients who underwent a successful shockwave lithotripsy



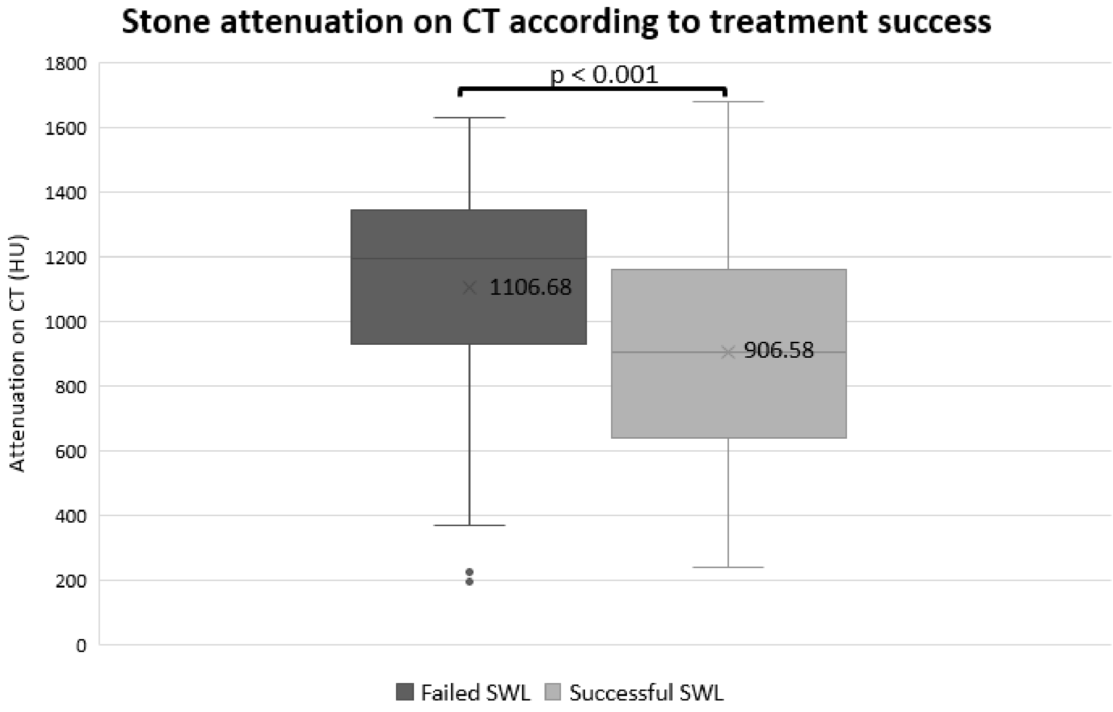
SWL: Shockwave lithotripsy

Figure 7: Boxplot of stone size in patients who failed shockwave lithotripsy compared to patients who underwent a successful shockwave lithotripsy



SWL: Shockwave lithotripsy

Figure 8: Boxplot of stone attenuation on CT in patients who failed shockwave lithotripsy compared to patients who underwent a successful shockwave lithotripsy



CT: computerized tomography; HU: Hounsfield units; SWL: Shockwave lithotripsy

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APPENDICES

Appendices 1: Data Collection Form

Shock Wave Lithotripsy
Outcomes in a Multicentric Prospective Observational Study

1) Basic Demographic Data

Study ID _______ __________

Age:________

Initials: _____ _____ _____

Sex: □ Male / □ Female

ASA:__________

For those patients whose referring urologist is not in London:

Phone Numbers: Daytime:__________________Evening:____________________________

Ethnicity: □ White or Caucasian/ □ Indigenous or Native / □ Black or African American / □ Asian or Pacific Islander / □ Hispanic or Latino / □ Multiracial or BIracial / □ Other, specify:________________

Weight (kg):________________Height (cm):_____________________= BMI _______

2) Current Stone Episode/ Stone History

Did patient present with pain with the current stone(s)? □ Y/ □ N

If no, how did patient present? □ Incidental Finding on Imaging/□ Haematuria, □ Macro or □ Micro /

□ Other, specify:____

Hydronephrosis?

□ Unspecified / □ No / □ Very Mild / □ Mild / □ Mild to Moderate / □ Moderate / □ Severe

With what imaging was current stone diagnosed? □ CT/□ IVU /□ US/ □ KUB / □ Other

If other, specify:____

Number of independent stone episodes (including today)? (#):__________

Previous Shock Wave Lithotripsy?	□ N / □ Y	How many times (#):________
Previous Ureteroscopy?	□ N / □ Y	How many times (#):________
Previous PCNL?	□ N / □ Y	How many times (#):________

Previous stone composition

□ Unknown
□ Calcium oxalate monohydrate
□ Calcium oxalate dihydrate
□ Uric acid
□ Calcium phosphate
□ Cystine
□ Struvite
□ Other

3) Other Medical History

Ischaemic heart disease? □ N / □ Y Gout? □ N / □ Y
Hypertension? □ N / □ Y Hyperparathyroidism □ N / □ Y
Diabetes? □ N / □ Y Significant bowel resection? □ N / □ Y
Obesity surgery? □ N / □ Y, specify: □ Roux-en-Y / □ Duodenal switch / □ other
if other, specify:____
Inflammatory bowel disease? □ N / □ Y
Known anatomical variants? □ N / □ Y, □ horseshoe kidney / □ duplex system / □ UPJ obstruction
□ other, specify:____
Existing neurological condition including spinal cord injury? □ N / □ Y
Other condition? □ N / □ Y, specify:____

4) Drug History

Taking or have taken prolonged courses of any of the following:

Steroids (ie: prednisolone, dexamethasone) □ N / □ Y

Chemotherapy □ N / □ Y

Diuretics □ N / □ Y

Alpha-Blockers □ N / □ Y

Regular consumption of Vitamin C supplements □ N / □ Y

Regular consumption of indigestion tablets □ N / □ Y

Other ____

5) Periop Details

Date of Initial Presentation / Imaging:________________________

Creatinine (umol/L): __________

Analgesia in department? □ none / □ paracetamol / □ diclofenac / □ tramadol /□ pethidine /

□ morphine / □ other, specify:____

Antibiotics? □ none / □ trimethoprim / □ nitrofurantoin / □ ciprofloxacin /□cefazolin /

□ gentamycin / □ other,specify:____

Antiemetics? □ none/ □ cyclizine □ metoclopramide/ □ ondansetron/ □ prochlorperazine stemetil /

□ other, specify:____

6) Lithotripsy Treatment

Date Treatment:____________________________________Side: □ Left / □ Right / □ Bilateral

Anaesthesia: □ General / □ IV or IM Sedation (Neurolept) / □ Analgesics, only / □ Other

If other, specify:____

Position: □ Prone / □ Supine
Total number of stones visible on recent imaging (#):____ Size of stones treated (mm, total size if more than one stone):_____________________________________

COMPLETE FOR FIRST TARGET STONE

Maximum stone diameter (mm):______indicate field of view: □ Axial / □ Sagittal / □ Coronal

Minimum stone diameter (mm):_______indicate field of view: □ Axial / □ Sagittal / □ Coronal

3rd stone diameter (mm), if CT was done:____indicate field of view: □ Axial / □ Sagittal / □ Coronal

Stone surface area on axial imaging:_______mm^2 Hounsfield Units (if preop CT) or n/a: ______

Skin to Stone (SSD) distance (mm):_____

Site of stone: □ upper calyx / □ middle calyx / □ lower calyx /□ renal pelvis / □ UPJ upper ureter (above SI joint) / □ mid ureter (on iliac crest) □ lower/distal ureter (below SI joint) / □ UVJ / □ uretero-enteric anastomosis / □ unknown / □ other:___

Is the stone visible on fluoroscopy? □ N / □ Y

Stent? □ N / □ Y

Patient treated by: □ Radiographer / □ Urologist / □ Technical Nurse / □ Other, specify:____________

Number of shocks (#):__________________Hz: □ 2.0 / □ 1.5 / □ 1.0 □ other, specify:_

Maximum energy reached:______________Storz Medical Lithotripsy Index (SMLI) : __

Focus: □ precise (narrow) / □ extended (wide) / □ combination

Imaging: □ KUB X Ray / □ Ultrasound/ □ CT / □ IVP /□ Other:____________________

Fluoroscopy Time:________Radiation dose (cGy-cm2):_______AV distraction (Gated)? □ N / □ Y

How was targeting during the procedure? □Unknown / □ 1 (poor) / □ 2 / □ 3 / □ 4 / □ 5 (excellent)

Any previous SWL for this stone? □ N / □ Y how many **previous** SWL for this stone?________

COMPLETE ONLY IF SECOND STONE TREATED

Maximum stone diameter (mm):______indicate field of view: □ Axial / □ Sagittal / □ Coronal

Minimum stone diameter (mm):_______indicate field of view: □ Axial / □ Sagittal / □ Coronal

3rd stone diameter (mm), if CT was done:____indicate field of view: □ Axial / □ Sagittal / □ Coronal

Stone surface area on axial imaging:________mm^2 Hounsfield Units (if preop CT) or n/a: ______

Skin to Stone (SSD) distance (mm):_____

Site of stone: □ upper calyx / □ middle calyx / □ lower calyx /□ renal pelvis / □ UPJ

□ upper ureter (above SI joint) / □ mid ureter (on iliac crest) □ lower/distal ureter (below SI joint) / □ UVJ / □ uretero-enteric anastomosis / □ unknown /

□ other:____

Is the stone visible on fluoroscopy? □ N / □ Y

Stent ? □ N / □ Y

Number of shocks (#): ___________________________

Hz: □ 2.0 / □ 1.5 / □ 1.0 □ other, specify:_______

Storz Medical Lithotripsy Index (SMLI) : ________

Maximum energy reached: ___________________________

Focus: □ precise (narrow) / □ extended (wide) / □ combination

Imaging : □ KUB X Ray / □ Ultrasound/ □ CT / □ IVP /□ Other:____________________

Fluoroscopy Time:________Radiation dose (cGy-cm2):_______AV distraction (Gated)? □ N / □ Y

How was targetting duirng the procedure? □Unknown / □ 1 (poor) / □ 2 / □ 3 / □ 4 / □ 5 (excellent)

Any previous SWL for this stone? □ N / □ Y how many **previous** SWL for this stone?________

Alpha-blocker prescribed after the procedure? □ Y/ □ N

General Comments:____

7) Follow-up: □ **London /** □ **Other**, specify:____

Imaging obtained following SWL: □ N / □ Y, date:________________________________ (dd/mon/yy)

Type of Imaging; □ CT / □ US / □ KUB / □ IVP / □ Other, specify:______________________________

Discrepancy between different types of imaging? □ N / □ Y

COMPLETE FOR FIRST TARGET STONE

Residual stones on followup imaging?

□ No change

□ Residual fragments present Number of residual fragments:_____

□ Dust or small fragments, not requiring further treatment

Round up /down accordingly:

Total cumulative fragment size of the target stone (mm):

□ < 2mm / □ 2-4mm / □ 4-6mm / □ 6-10mm / □ > 10mm

Size of largest residual fragment (greatest dimension): □ < 2mm / □ 2-4mm / □ >4mm

□ No residual fragments (stone free)

8) Further management

□ None

□ Discharge with complete stone clearance on imaging

□ Discharged with insignificant residual fragments without planned further therapy

□ Return to clinic appointment to discuss alternative treatments

□ Return to out of area referrer

□ Re-treatment with SWL

□ Re-treatment with URS

□ PCNL

□ Other, specify:____

□ Return for further follow-up with imaging to evaluate target stone

Second treatment? □ N / □ Y or third treatment? □ N / □ Y, indicate:

□ SWL Date(s):______________________________________

□ URS Date(s):______________________________________

FOLLOW-UP REGARDING THE STONE TREATED IN OTHER LOCATION, if applicable

Residual stones on followup imaging?

□ No change

□ Residual fragments present   Number of residual fragments:_____

□ Dust or small fragments, not requiring further treatment

Round up /down accordingly:

Total cumulative fragment size of stone:

□ < 2mm / □ 2-4mm / □ 4-6mm / □ 6-10mm / □ > 10mm

Size of largest residual fragment (mm) – greatest dimension: □ < 2mm / □ 2-4mm / □ >4mm

□ No residual fragments (stone free)

Further management

□ None

□ Discharge with complete stone clearance on imaging

□ Discharged with insignificant residual fragments without planned further therapy

□ Return to clinic appointment to discuss alternative treatments

□ Return to out of area referrer

□ Re-treatment with SWL

□ Re-treatment with URS

□ PCNL

□ Other, specify:____

Second treatment? □ N / □ Y or third treatment? □ N / □ Y, indicate:

9) COMPLICATIONS Related to Treatment(s)

□ N / □ Y, if yes describe the complication(s) with laterality, treatment(s) and outcome(s):

____

____