

**ASSOCIATION BETWEEN HOUNSFIELD UNIT
DENSITY AND STONE SIZE WITH STONE FREE
STATUS POST URETEROSCOPY LITHOTRIPSY**

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LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

URSL	Ureteroscopy lithotripsy
HU	Hounsfield unit
ESWL	Extracorporeal shockwave lithotripsy
PCNL	Percutaneous nephrolithotomy
CT	Computed tomography
KUB	Kidney, ureter, bladder
PACS	Picture archiving and communication system
IVU	Intravenous urography
MET	Medical expulsion therapy
EHL	Electrohydraulic lithotripsy
COM	Calcium oxalate monohydrate
RIRS	Retrograde intrarenal surgery

ABSTRAK

Latar belakang: Ureteroscopy lithotripsy (URSL) ialah kaedah rawatan penting untuk batu ureter yang kini digunakan untuk semua saiz batu, pada pelbagai lokasi di dalam ureter. Umum diketahui bahawa saiz batu dan nilai HUnya adalah faktor utama yang mempengaruhi kejayaan pembedahan ESWL dan PCNL bagi pesakit batu karang. Nilai HU adalah ukuran radiografi yang mudah dan berkorelasi baik dengan komposisi kimia batu. Memandangkan ada bukti keberkesanan meramalkan komposisi batu dan menentukan saiznya sebelum pembedahan menggunakan imbasan CT KUB, ia dapat membantu dan memainkan peranan penting dalam pemilihan jenis rawatan oleh pakar bedah urologi. Model ramalan berasaskan CT menggunakan faktor-faktor ini membolehkan anggaran kadar bebas batu selepas URSL dalam pesakit batu karang dan dengan ini memudahkan perancangan rawatan. Tujuan kajian ini adalah untuk menilai perkaitan antara ketumpatan HU dan saiz batu dengan masa operasi dan status bebas batu.

Metod: Ini adalah kajian kohort retrospektif dan telah dijalankan di Hospital USM, Kota Bharu, Kelantan, Malaysia. Sejumlah 204 pesakit yang menjalani pembedahan URSL elektif di Hospital USM dan telah didiagnosis dengan batu ureter tunggal di dalam imbasan CT KUB sebelum pembedahan, telah dikenal pasti dan didaftarkan dalam kajian ini. Ketumpatan HU dan saiz batu diukur daripada pangkalan data PACS. Radiograf KUB pada hari pertama selepas pembedahan akan disemak untuk memastikan sama ada pemecahan batu telah dilakukan secara total atau terdapat sisa batu karang. Perkaitan antara ketumpatan HU dan saiz batu dengan masa operasi dan status bebas batu telah dijalankan menggunakan ujian pekali korelasi Pearson.

Keputusan: Sejumlah 204 pesakit dengan diagnosis batu ureter tunggal telah menjalani pembedahan elektif URSL. Kira-kira 86% (n=176 pesakit) daripada pesakit telah menjalani pembedahan URSL dengan jayanya dan mempunyai status bebas batu pada hari pertama selepas pembedahan. Purata umur pesakit tanpa mengira jantina adalah 53.7 tahun ($\pm$ 14.862 tahun). Purata saiz batu pula berukuran 13.086mm ($\pm$ 5.568mm). Nilai purata HU batu ureter dengan pemecahan yang berjaya ialah 886.114HU ($\pm$ 347.416HU) dengan purata ketumpatan HU 78.996 HU/mm ($\pm$ 44.944 HU/mm). Purata masa pembedahan URSL ialah 1.156 jam ($\pm$ 0.052 jam). Kolerasi yang signifikan secara statistik antara ketumpatan HU dan masa operasi telah dicatatkan dengan nilai $p=0.047$. Walau bagaimanapun, tiada korelasi yang ketara dilihat antara saiz batu dan masa operasi ($p=0.084$), ketumpatan HU dengan status bebas batu ($p=0.391$) dan saiz batu dengan status bebas batu ($p=0.438$).

Kesimpulan: Komposisi batu ureter yang diwakili oleh nilai HU adalah faktor utama kejayaan pembedahan URSL. Kajian kami menunjukkan bahawa terdapat korelasi negatif yang signifikan secara statistik bagi masa operasi URSL dengan ketumpatan HU bagi batu ureter. Pesakit dengan ketumpatan HU yang lebih tinggi dijangka mempunyai masa operasi URSL yang lebih pendek. Oleh itu, pengukuran ketumpatan HU dapat memberi maklumat tambahan kepada pasukan pembedahan Urologi dalam membuat keputusan tentang cara pembedahan dan kaunseling pesakit, terutamanya di mana pelbagai pilihan rawatan mungkin digunakan.

Kata kunci: batu ureter, CT KUB, lithotripsy ureteroscopy, ketumpatan HU, masa operasi, status bebas batu

ABSTRACT

Background: Ureteroscopy lithotripsy (URSL) is an essential treatment modality for ureteral stones that is currently used for stones of all sizes, present at any location within the ureter. It is well established that stone size and its HU value are the main factors that influence the success of other type of surgery in patient with nephrolithiasis such as ESWL and PCNL. HU value is a convenient radiographic measurement that correlated well with the stone chemical composition. Given the effectiveness of predicting stone composition and determining its size preoperatively using plain CT KUB, it may play a role in the selection of treatment by the surgeon. A CT-based predictive model using these factors could enable estimation of the stone-free rate after URSL in individual patients and thus facilitate treatment planning. The purpose of this study is to evaluate the association between HU density and stone size with operative time and stone free status.

Methods: This is a retrospective cohort study and was conducted in Hospital USM, Kota Bharu, Kelantan, Malaysia. A total of 204 patients who underwent elective URSL in Hospital USM and was diagnosed with a single ureteric stone in preoperative plain CT KUB prior to the surgery were identified and enrolled in this study. HU density and stone size were measured from PACS database. Plain KUB radiograph on post operative day 1 will be reviewed to look for any residual stone or complete stone clearance. The association between HU density and stone size with operative time and stone free status had been carried out using Pearson's correlation coefficient test.

Results: A total of 204 patients underwent elective URSL for a single ureteric stone. About 86% (n=176 patient) of the patient had a successful URSL with stone free status on post operative day 1. Mean age of the patient regardless of gender was 53.7-year-old ($\pm$ 14.862-year-old). Mean stone size measures 13.086mm ($\pm$ 5.568mm). Mean HU value of the ureteric stone with successful fragmentation was 886.114HU ($\pm$ 347.416HU) with mean HU density of 78.996 HU/mm ($\pm$ 44.944 HU/mm). Mean URSL operative time was 1.156-hour ($\pm$ 0.052) A statistically significant correlation between HU density and operative time noted with p value of 0.047. However, there is no significant correlation seen between stone size and operative time.(p=0.084), HU density with stone free status (p=0.391) and stone size with stone free status (p=0.438).

Conclusion: Composition of a ureteric stone being represented by HU value are the cornerstone in URSL success. Our study shows that there is statistically significant negative correlation of URSL operative times with HU density of calculi. Patients with higher HU density were expected to have shorter URSL operative time. Thus, the HU density measurement may give extra information to the managing team in making future decisions on mode of surgery and patient counselling, especially where multiple treatment options might apply.

Keywords: ureteric stone, CT KUB, ureteroscopy lithotripsy, HU density, operative time, stone free status

CHAPTER 1: BACKGROUND

1.1 Introduction

Urolithiasis is a global problem that has become increasingly prevalent with a high rate of recurrence. It is a notable health problem with pain, risk of renal obstruction, and loss of renal function, and it is responsible for the yearly increment of total medical expenditure (Curhan, 2009). The epidemiology of urolithiasis differs according to geographical area in terms of prevalence and incidence, age and sex distribution, stone composition, and location. In Asia, about 1% to 19.1% of the population was diagnosed with urolithiasis (Liu et al., 2018).

Ureteral stone is one of the urologic conditions reported and treated widely. Most patients presented to casualty with acute flank pain and symptoms of obstruction causing renal deterioration requiring urgent diagnosis and treatment. A ureteral stone is a stone lodged in the ureter and obstruct the flow of urine. It may have arisen from the kidney and travelled down into the ureter. If the stone is small enough, it can be extricated and pass through the ureter and out of the body unnoticed. In cases where it is too large, it will not just cause severe pain, as it may also cause obstruction and subsequently deterioration of renal function if left untreated promptly.

The most appropriate imaging modality will be determined by the clinical situation, which will defer depending on if a ureteral or a renal stone is suspected. Standard evaluation includes a detail medical history and physical examination. Immediate evaluation is indicated in patients with solitary kidney, fever or when there is a doubt regarding a diagnosis of renal colic.

Urine pH, presence of crystals, urease-positive bacteria in urine, plain radiographs and history of urinary stones have long been utilized to predict the composition of stones. Recently, Hounsfield units (HU) of the stone on CT scan was proposed to be used for the same purpose. HU, a parameter used to quantify the number of X-rays that pass through or are absorbed by tissues which resulted in a radiodensity scale. CT images are made up of pixels, in which has gray scale value from 1 (black) to 256 (white). This value corresponds to the number of X-rays that pass through the structure and are conveyed in HU.

Non-contrast-enhanced computed tomography (CT) has become the standard for diagnosing acute flank pain, replacing intravenous urography (IVU). Non-contrast-enhanced CT can determine stone diameter, density, inner structure of the stone, skin-to-stone distance and surrounding anatomy; all of which affect selection of treatment approach. Few studies have shown the sensitivity and the specificity of CT for the diagnosis of ureteral stones ranges from 94 to 100% (Miller et al., n.d.; Pfister et al., 2003). Routine use of non-contrast CT has transformed the imaging evaluation of urolithiasis, nearly completely replacing other imaging methods for the diagnosis of acute ureteral obstruction. In addition, non-contrast CT is superior in its ability to detect non-urolithiasis causes of flank pain and to differentiate calculi from other ureteral abnormalities such as neoplasm, stricture and blood clot (Dalrymple et al., 1998). It is not only confined to help in making accurate diagnosis in patients with urolithiasis; it is also useful in the assessment of stone burden, composition, and fragility.

According to earlier studies performed, there seems to be a good correlation between urinary stone composition and Hounsfield Unit (HU) of non-contrasted CT as it can be used to assess the density of stones. The HU has been used to predict the

type and opacity of stones during diagnosis and the usefulness has been assessed using methods including extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), ureteroscopic ureterolithotripsy (URSL) and medical expulsive treatment (MET). Ascertaining the composition of the stones is the key role in choosing the most appropriate treatment mode.

There are different ways to manage urolithiasis depending on different factors such as fragility of calculi. By knowing the composition of the stone, it can help in choosing suitable treatment and avoid waste of sanitary costs due to inefficient treatment. The exact understanding of the type of stones is a necessity of any medical therapy for urinary calculus. Information regarding composition of a stone is vital because it correlates concerning the pathogenesis of the disease, including metabolic abnormalities, presence of infection, possible artefacts and even drug metabolism. Accurate high-quality stone analysis is a crucial requirement for this approach to patient management, allowing possible causes to be identified, logical treatment strategies to be applied and avoidance of stone recurrence.

Ureteroscopy lithotripsy (URSL) is an essential modality for the treatment of ureteral stones that is currently used for stones of all sizes present in any location within the ureter. The size and location of the stone are the key factors that determine the success of URSL. A successful URSL or stone free status is defined as absence of stones or residual stone fragments < 2mm by ureteroscopy and plain abdominal radiograph (Wook, Ji, Chae, & Wook, 2014).

1.2 Problem statement

Some studies suggested that stone fragmentation failure may be caused by variations of stone component and their sizes. Size of calculus is the main factor that influence the success of URSL. HU value is a convenient radiographic measurement that correlated well with the chemical composition of a stone. The determination of stone composition using its density by CT is not new; however, there are some controversies and limitations in the previous report. In 2014, a study by Torricelli concluded that there is an overlap in radiographic profiles of cystine and uric acid stones, making a definitive differentiation more challenging. However, Nakada et al in a study with 99 subjects (82 with calcium oxalate stones and 17 with uric acid stones), showed a substantial difference between the absolute HU of calcium oxalate and uric acid stones, concluding that it is possible to differentiate between these 2 stone compositions. Stone component has directly influenced the mean operating time which was significantly longer in the uric acid group than in the calcium oxalate group (Song et al., 2012).

The exact knowledge regarding stone composition and its density reflected by HU value in CT stones affords significant information to urologists for selecting the appropriate treatment and imaging modality to use during follow-up. Determining the composition of stone preoperatively via HU density value in a CT before they are subjected to URSL is rational if it is proven to have correlation with outcome of URSL. Better pre-operative planning and decision for choices of treatment can be made i.e more energy might be needed and/or the procedure might be prolonged to fragments stones with a higher HU using URSL.

1.3 Objectives

1.3.1 General Objective

To study the correlation between the size and HU density of ureteric stone with the outcome of ureteroscopy lithotripsy.

1.3.2 Specific Objectives

1. To measure the size and HU density value of ureteric stone in a non-contrasted CT.
2. To correlate between size and HU density of stone with URSL operative time.
3. To find association between HU density of stone with stone free status of URSL.

1.4 Hypothesis

The size and HU density of stone will have statistically significant correlation with the outcome of ureteroscopy lithotripsy. In addition to that, there is also statistically significant association between HU density of stone with stone free status post URSL.

1.5 Research Questions

- 1.What is the mean size measurement and HU density of lower ureteric stone among patient subjected for URSL in HUSM ?
- 2.What is the effect of size and HU density of stone on operative time ?
- 3.Are HU density and stone size associated with stone free status post URSL?

CHAPTER 2: LITERATURE REVIEW

2.1 Urolithiasis

2.1.1 Epidemiology

The worldwide prevalence, incidence and composition of urinary calculi varies and have changed in the last several decades, with prevalence ranging from 7% to 13% in North America, 5%–9% in Europe, and 1%–5% in Asia (Sorokin et al., 2017). A greater incidence of stone appear to be more common across the West Asia, Southeast Asia, South Asia as well as several developed countries, including South Korea and Japan, with prevalence ranging from 5% to 19.1% (Liu et al., 2018). However, due to variations in socio-economic status and geographic locations, the prevalence and incidence have changed in different countries or regions over the years and notably increased in most of the countries of Asia over the last several decades. The incidence of urolithiasis reaches its peak in population aged over 30 years and decreased afterwards (Ghole et al., 2014). When it comes to gender, the recurrence rate of urolithiasis in male is twice than that in female (Iguchi et al., 1996).

2.2 Diagnostic Imaging in Urolithiasis

The most appropriate imaging modality will be determined by the clinical situation, which will defer depending on if a ureteral or a renal stone is suspected. Standard evaluation includes a detail medical history and physical examination.

Immediate evaluation is indicated in patients with solitary kidney, fever or when there is a doubt regarding a diagnosis of renal colic.

Computed tomography (CT) is broadly accepted as one of the best imaging modalities for the detection and evaluation of urolithiasis. Numerous studies have shown the sensitivity and specificity of plain CT KUB for the diagnosis of ureteral stones to be 94-96 and 94-100% respectively (Miller et al., n.d.; Pfister et al., 2003). Since the introduction of plain CT KUB in 1995 by Smith et al (1995) it has been the golden standard for the diagnosis of urolithiasis, and because of its high sensitivity and safety, it has completely replaced radiography and excretory urography (Hidas et al., 2010). In addition, CT is not just superior in its ability to detect non-urolological causes of flank pain, it can also differentiate calculi from other ureteral abnormalities such as neoplasm, stricture and blood clot (Dalrymple et al., 1998). It is also useful in the assessment of stone burden, composition, and fragility.

2.3 Stone composition

2.3.1 Common profiles of stones

In most countries of Asia, calcium oxalate (75% to 90%) is the most common component of urolithiasis, followed by uric acid (5% to 20%), calcium phosphate (6% to 13%), struvite (2% to 15%), apatite (1%) and cystine (0.5% to 1%) (Memon et al., 2012; Wu et al., 2014; Iguchi et al., 1996). Since 1960s, the proportion of calcium oxalate and uric acid stones have risen, which is the typical pattern in the countries, like China, Japan, India and Indonesia (Iguchi et al., 1996; Thalut et al., 1976; Pendse et al., 1986). Besides, there are several differences between developed and developing

countries. The calcium oxalate (90% vs. 75%) and uric acid calculi (15% vs. 5%) are more common in developed countries than in developing countries, while the reverse is true for struvite stones (7% vs. 14%) (Alatab et al., 2016).

2.3.2 *HU and stone composition*

Mostafavi et al. performed an in-vitro study and reported that stone composition could be predicted with high accuracy using HU (Mostafavi, Ernst, & Saltzman, 1998). In a study to differentiate among subtypes of calcium stones reported by Torricelli, Fabio Cesar Miranda, et al., calcium stones could be identified with high accuracy using HU values, but there was similarity between the HU values of cystine and uric acid stones, making it difficult to differentiate these types of stones (Cesar et al., 2014). Spettel et al. designed an in-vivo study to predict uric acid stones using urine pH and HU and reasoned that using the two parameters together were more effective for predicting uric acid stones than either one alone. Specifically, for a stone > 4 mm, $HU \leq 500$ and $pH \leq 5.5$, had a positive predictive value of 90% for uric acid composition. Current studies also suggested that HU and their variants are useful for predicting the composition of stone (Spettel, Shah, Sekhar, Herr, & White, 2013). Hameed et al. reported that successful fragmentation using ESWL was decreased in stone with $HU > 1350$, which required usage of more shock waves (Hameed et al., 2013). El-Assmy et al. used the Hounsfield value of stones to predict stone composition and density, and the fragmentation success using ESWL, and selected $HU > 1000$ as their cut off value (El-assmy, Abou-el-ghar, El-nahas, Refaie, & Sheir, 2011). Foda et al demonstrated that stone disintegration failed if the stone density was

> 934 HU;therefore they did not recommend ESWL in this group of patients(Foda, Abdeldaeim, Youssif, & Assem, 2013).

2.3.3 HU density

Motley et al. tried to determine stone composition using HU density, calculated by dividing HU and largest transverse diameter of a stone (in mm), and recommended that HU density was more effective than HU alone (Motley, 2001). This study testified that there is a broad range of overlapping radiodensities. They considered that the possibility of broad range of stone sizes (1 to 19mm) have obscured significant differences among the stones. Mean HU was plotted against the stone size in millimetres, a statistically significant positive correlation between radiodensity and stone size ($R = 0.469$, $P = 0.001$) was observed; that is, higher mean HU was discovered in bigger stone, regardless of its composition. The analysis was repeated, taking into consideration of the effect of stone size on radiodensity, by measuring the ratio of mean HU of each stone to its greatest transverse diameter. The resultant value was termed as “Hounsfield unit density” (HU/mm). The mean HU density of calcium stone was found to be statistically different from uric acid stone.

2.3.4 Role of HU in ESWL, PCNL and MET

Extracorporeal shock wave lithotripsy (ESWL) can effectively eradicate approximately 90% of renal stones in adults (Miller, 2007). Data showed that the

energy of the shock wave needed for fragmentation was related to stone density, and that the higher the stone density, the stronger the shock wave energy needed to reach fragmentation in ESWL (Gupta, 2005; Pareek, 2005). Hameed et al. stated that successful fragmentation using ESWL was reduced in stones with HU of more than 1350, which required usage of more shock waves. El-Assmy et al. used the Hounsfield value to study the correlation of stone composition and density with the fragmentation success using ESWL and select HU of more than 1000 as their cut off value. Foda et al. proved that stone disintegration failed if the stone density was more than 934 HU; therefore, they did not recommend ESWL in this group of patients. Gücük et al. investigated on the outcome of 179 percutaneous nephrolithotomy (PCNL) patients and concluded that the HU value was an independent factor that affected the success of PCNL. Specifically, an HU value of more than 677.5 reduced the success rate of PCNL by 2.65-fold.

Medical expulsive treatment (MET) is frequently used to help the passage of ureteral stones in the absence of severe renal colic, infection, and obstruction. The spontaneous passage ratio can be as high as 98%, particularly in stones smaller than 5 mm. The most important factors that affect spontaneous passage are the size and location of the stone (Erturhan, 2000). Erturhan et al. studied the effect of HU value on the success of MET and showed that stones with a high HU would pass through the ureter slowly and with difficulty because of their compact structure.

2.4 HU value and URSL relationship

The only previous study of the relationship between HU value and URSL success was presented by Kim et al. They observed the size, location, impaction, and HU value of stones using plain CT KUB, as well as the effect of these parameters on the success of URSL. Their results revealed that the HU value did not affect the success of treatment using URSL. However, this study failed to retrieve several important parameters, such as the duration of the operation and duration of lithotripsy. As with ESWL, more energy might be needed and/or the procedure might be prolonged to fragment stones with high HU using URSL. Kim et al. also stated that stone free status was defined as the absence of stone or residual stone fragments <2mm by ureteroscopy and plain KUB radiography at post-operative day 1 (Wook et al., 2014)

2.4.1 *Ureteroscopy Lithotripsy (URSL)*

URSL is an essential treatment modality for ureteral stones that is currently used for stones of all sizes present at any location within the ureter. According to Moon, Young Joon, et al., the upper ureter and vesicoureteral junction are two peak sites at which stone lodge. The location and size of the stone, including the longest diameter, longest transverse diameter, height, and stone volume are the most important factor that determine the success of URSL. Other secondary signs such as hydronephrosis, perinephric edema, and tissue rim sign are also important in predicting the success of USRL (Moon, Kim, Kim, Kim, & Chang, 2015). In a study conducted by Zheng et al. in 2020, its purpose is to determine the factors that may

affect the success rate of holmium laser ureterolithotripsy (HLU). From this study, they concluded that surgical success was achieved in 338 patient (87.8%). Univariate analysis of this study revealed that the degree of hydronephrosis, stone impaction, stone location and previous extracorporeal shock wave lithotripsy were risk factors for surgical failure. Most urinary stones can be treated with extracorporeal shock wave lithotripsy (ESWL), but ureteroscopic removal of stones (URS) by use of intracorporeal lithotripsy devices has also been widely used as a valid, minimally invasive alternative to ESWL (Basar et al.,1997 & Verze et al., 2010). A gradual reduction in ureteroscope size and the development of effective lithotripters are the most important technical advances in URS (Mugiya et al., 2000). Smaller ureteral stones can be removed intact with endoscopic baskets or grasping devices after ureteral dilation, if necessary. However, larger ureteral stones require lithotripsy for the safe removal of the stone fragments. Up till now, four techniques are available for intracorporeal lithotripsy: electrohydraulic lithotripsy (EHL), laser lithotripsy, ultrasonic lithotripsy, and ballistic lithotripsy (Defarges et al., 2008). Operating time was defined as the time interval between ureteroscope insertion and complete removal of ureteral stones (Song et al., 2012).

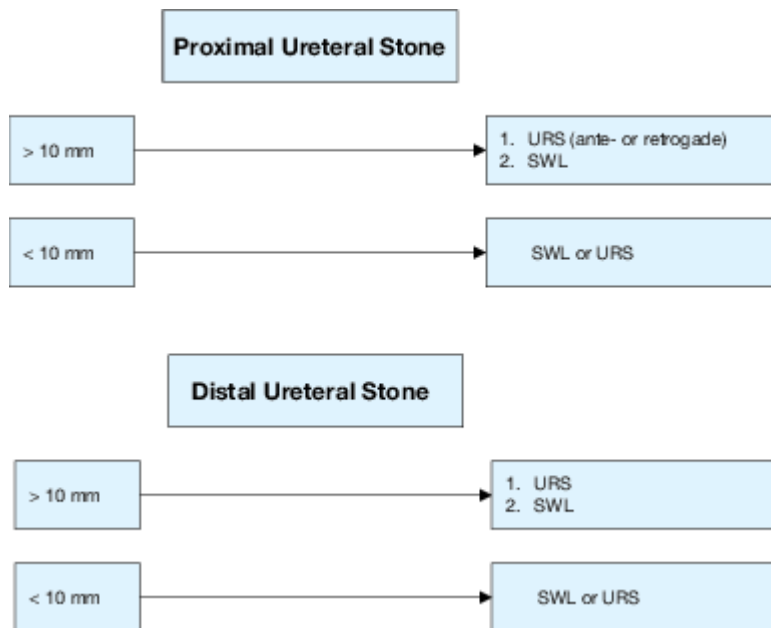


Figure 1 Treatment algorithm for ureteral stones (if active stone removal is indicated)

Adapted from European Association of Urology Guidelines

EAU Guidelines. Edn. presented at the EAU Annual Congress Barcelona 2019. ISBN 978-94-92671-04-2.

2.4.2 Stone free status

Patient underwent URSL will be monitored in ward for any post operative complications and monitoring of vital signs. As intraoperatively, a ureteric stent will be inserted in the affected ureter to prevent ureteric obstruction secondary to mucosal edema post instrumentation. A plain abdominal radiograph will be ordered by attending doctors to confirm placement of the ureteric stent and to observe residual stone fragments. Kim et al. stated that stone free status was defined as the absence of

stone or residual stone fragments <2mm by plain abdominal radiography at post-operative day 1 (Wook et al., 2014).

2.5 Conceptual framework

Component of ureteric stone

Multiple biochemical component of the stone will be reflected by HU density in CT

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dehydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

EAU Guidelines. Edn. presented at the EAU Annual Congress Barcelona 2019. ISBN 978-94-92671-04-2.



Predicted by **HU density**



Plain CT KUB



Optimal treatment modality



ESWL/URSL



Follow-up imaging modality



Radiograph/CT Urography

2.6 Rationale of the study

Given the effectiveness of predicting stone composition and determining its size preoperatively using plain CT KUB, better surgical planning, and decision for choices of treatment can be made by urologist i.e more lithotripter energy might be needed and/or the procedure might be prolonged to fragments stones with a higher HU value. It is well established that stone size and its HU value are the main factors that influence the success of other type of surgery in patient with nephrolithiasis such as ESWL and PCNL (Gupta et al., 2005; Pareek et al., 2005; Gücük et al.,2012). HU value is a convenient radiographic measure that correlated well with the chemical composition of a stone. The prediction of stone types and its composition would also lead to a better selection of medical treatment and prophylactic approach. CT-derived parameters including the stone diameter and HU density, are independent predictors of the outcome of URSL. A CT-based predictive model using these factors could enable estimation of the stone-free rate after URSL in individual patients and thus facilitate treatment planning.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This will be a retrospective cohort study using data images in Picture Archiving and Communication System (PACS) from plain CT KUB performed preoperatively in patients scheduled for elective URSL in HUSM from the period of 1st January 2018 until 1st Feb 2022. HU density and stone size will be measured from PACS. Plain KUB radiograph on post operative day 1 will be reviewed by urologist to look for any residual stone or complete stone clearance. A successful URSL is defined as absence of stones or residual stone fragments < 2mm on post operative (Day 1) plain KUB radiograph.

3.2 Sample Population

- i. Reference population : Patient diagnosed with ureteric stone, reviewed in Urology clinic and planned for URSL by respective surgeon.
- ii. Source population : Patient diagnosed with ureteric stone and underwent URSL in Hospital USM.
- iii. Target population – Patient with single ureteric stone who electively admitted and underwent URSL in Hospital USM.
- iv. Sampling frame – Eligible patients according to inclusion and exclusion criteria from the target population

3.3 Sample Size Calculation

Sample size estimation was calculated using Sample Size Calculator v2.0 software, prepared by Dr Wan Nor Ariffin, Unit of Biostatistics and Research Methodology, School of Medical Sciences, Health Campus, University Sains Malaysia.

1. For specific objective 1, based on the previous study in 2015 by Moon, Young Joon, et al. with probability (power) 0.8, significance level of 0.05, the minimum sample size is 175. With an additional 10% dropout rate, the corrected sample size is 195.

1 mean - Estimation	
Standard deviation (σ):	33.700
Precision ($\pm$ mean):	5.000
Confidence level $100(1 - \alpha)$:	95 %
Expected dropout rate:	10 %
Calculate	Reset
Sample size, $n =$	175
Sample size (with 10% dropout), $n_{drop} =$	195

2. For specific objective 2, based on the previous study in 2014 by Kim, Jong Wook, et al. with probability (power) 0.8, significance level of 0.05, the minimum sample size is 181. With an additional 10% dropout rate, the corrected sample size is 202.

Pearson's Correlation - Hypothesis Testing¹

Expected correlation (r):	0.3	
Significance level (α):	0.001	Two-tailed
Power ($1 - \beta$):	80	%
Expected dropout rate:	10	%
Calculate Reset		
Sample size, $n =$	181	
Sample size (with 10% dropout), $n_{\text{drop}} =$	202	

3. For specific objective 2, based on the previous study in 2012 by Song, Hyeong Cheol, et al. with probability (power) 0.8, significance level of 0.05, the minimum sample size is 179. With an additional 10% dropout rate, the corrected sample size is 199.

2 means - Hypothesis Testing

Standard deviation (σ):	33.700	
Expected difference:	10.000	
Significance level (α):	0.05	Two-tailed
Power ($1 - \beta$):	80	%
Expected dropout rate:	10	%
Calculate Reset		
Sample size, $n =$	179	
Sample size (with 10% dropout), $n_{\text{drop}} =$	199	

3.4 Sampling Method

All consecutive patients who were electively admitted and underwent elective URSL, who fulfil the inclusion and exclusion criteria from 1st January 2018 until 1st Feb 2022 were recruited for the study and was assigned with numbers. Demographic data of the subject is obtained from the case notes and computerised general information system (VIARAD). CT images will be reviewed in PACS system and HU density, and stone size measured.

3.5 Subject criteria

The subject selection was done if inclusion and exclusion criteria were fulfilled. The patient who was subjected to elective URSL by urologist and diagnosed with a single ureteric radio-opaque stone by preoperative plain CT KUB and preoperative KUB radiograph, irrespective of age were included in this study.

3.5.1 Inclusion Criteria

1. Patient planned for URSL who had preoperative plain CT KUB done
2. Patient diagnosed with unilateral single radio-opaque ureteric stone

3.5.2 Exclusion Criteria

1. Patient with history of ureteral stricture
2. Patient with bilateral ureteral stones
3. Patient with multiple unilateral ureteral stones

3.6 Research Tools

- i. Radiology Information System (RIS) – PACS version 6.0 (GE Healthcare) for image acquisition and demographic/clinical data information.
- ii. Diagnostic workstation with 3 MegaPixel monitor- (Barco E-3620 MA monitor– resolution 2048 x 1536) for image viewing and analysis.
- iii. SPSS version 26 was used for data analysis.

3.7 Operational Definition

Stone size : Measurement of widest diameter of stone (mm) in plain CT KUB

HU density : Mean HU value divide by widest diameter of stone (HU/mm)

Stone free status: Absence of radio-opaque stone or stone fragment less than 2mm in widest diameter by plain KUB radiograph on post operative day 1.

3.8 Data Collection

3.8.1 Patient Cohort

This is a retrospective cohort study that was conducted in Hospital USM, Kota Bharu, Kelantan, Malaysia. This study had obtained approval from the Human Research Ethics Committee of USM (USM/JEPeM/20020129). We included 204 patients who underwent elective URSL in Hospital USM and was diagnosed with a single ureteric stone in preoperative plain CT KUB prior to the surgery. The patients were identified through an operative census established by Urology team of Hospital USM. HU density and stone size will be measured from PACS. Plain KUB radiograph on post operative day 1 will be reviewed to look for any residual stone or complete stone clearance. A successful URSL is defined as absence of radio-opaque stones or residual stone fragments < 2mm on plain KUB radiograph.

3.8.2 Image acquisition

Plain CT KUB was performed using computed tomography system model Toshiba Aquillion Prime 160 Multislice. Patient is in supine position with arms above their head. Scout images were taken above the diaphragm to the below pubic symphysis and scan extension is planned from above the kidneys to below symphysis pubis at 120 kV with 200-400 mA. Images was then reconstructed at 1 mm and 5 mm thickness into soft tissue and bone algorithm which can be used to create multiplanar images.

3.8.3 Data collection method

Preoperative KUB radiograph and selected CT scan images were obtained from PACS workstation using Barco E-3620 MA, 20.8-inch 3 Megapixel display with a screen resolution of 2048 x 1536. Preoperative KUB radiograph is reviewed to ascertain stone radiopacity. Size of stone is measured from selected CT scan images using electronic workstation cursor in its greatest diameter. Stone radiodensity will be measured in HU (mean HU) and diameter in millimetre (mm). Post operative (Day 1) KUB radiograph were also reviewed via PACS workstation. Residual stone fragments are measured using electronic workstation cursor in its greatest diameter. Demographic data such as age, race and occupation were collected from patient's medical record. All data collected will be recorded on the data collection sheet. Data is analysed for mean and standard deviation of stone size and HU density value using descriptive analysis.

3.9 Statistical analysis

All data were collected, tabulated, and statistically analysed using Statistical Product and Service Solutions (SPSS) for Windows, SPSS Inc.© (Version 26, SPSS Inc., Chicago, IL, USA). The descriptive statistics for discrete variables were presented as n=frequency (%). Most data were expressed as mean $\pm$ standard deviation (SD). Statistical analyses were presented in tables. *Pearson's correlation coefficient* test was used to examine the association between stone size and HU density with operative time and stone free status.

3.10 Confidentiality and Privacy

Unique serial research numbers identified the subjects. No individual patient identifiable data were shared publicly. Upon completion of the study, all data were stored in a password-protected computer. This computer was only able to be accessed by the research team members. The researchers retained the data for knowledge purposes only. After completion of the study, the data in the computer have been copied to CDs, and the data in computer was erased. The CDs is stored in a locked office of the investigator and maintained for a minimum of three years after the completion of the study. The CDs and data will be destroyed after that period of storage. Neither the name nor any identifying information was used in any publication or presentation resulting from this study. The subjects will not be allowed to view their study data, as the data will be consolidated into a database.

3.11 Ethical Consideration

The study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM USM Code: USM/JEPeM/20020129), which complies with the Declaration of Helsinki (see Appendix).