Factors associated with spontaneous stone passage in a contemporary cohort of patients presenting with acute ureteric colic. Results from the MIMIC Study (A Multi-centre cohort study evaluating the role of Inflammatory Markers In patients presenting with acute ureteric Colic)

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Abstract

Objectives:

There is conflicting data on the role of white blood cell count (WBC) and other inflammatory markers in spontaneous stone passage in patients with acute ureteric colic. The aim of the study was to assess the relationship of WBC and other routinely collected inflammatory and clinical markers including stone size, stone position and Medically Expulsive Therapy use (MET) with spontaneous stone passage (SSP) in a large contemporary cohort of patients with acute ureteric colic.

Subjects and Methods:

Multi-centre retrospective cohort study coordinated by the British Urology Researchers in Surgical Training (BURST) Research Collaborative at 71 secondary care hospitals across 4 countries (United Kingdom, Republic of Ireland, Australia and New Zealand). 4170 patients presented with acute ureteric colic and a computer tomography confirmed single ureteric stone. Our primary outcome measure was SSP as defined by the absence of need for intervention to assist stone passage. Multivariable mixed effects logistic regression was used to explore the relationship between key patient factors and SSP.

Results:

2518 patients were discharged with conservative management and had further follow up with a SSP rate of 74% (n = 1874/2518). Sepsis after discharge with conservative management was reported in 0.6% (n = 16/2518). On multivariable analysis neither WBC, Neutrophils or CRP were seen to predict SSP, with an adjusted OR of 0.97 [95% CI 0.91 to 1.04, p = 0.38], 1.06 [95% CI 0.99 to 1.13, p = 0.1] and 1.00 [95% CI 0.99 to 1.00, p = 0.17], respectively. Medical expulsive therapy (MET) also did not predict SSP [adjusted OR 1.11 [95% CI 0.76 to 1.61]). However, stone size and stone position were significant predictors. SSP for stones < 5mm was 89% [95% CI 87 to 90] compared to 49% [95% CI 44 to 53] for those ≥5 to 7mm and 29% [95% CI 23 to 36] for stones >7mm. For stones in the upper

ureter the SSP rate was 52% [95% CI 48 to 56], middle ureter was 70% [95% CI 64 to 76], and lower ureter was 83% [95% CI 81 to 85].

Conclusion:

In contrast to the previously published literature, we found that in patients with acute ureteric colic who are discharged with initial conservative management, neither WBC, Neutrophil count or CRP help determine the likelihood of spontaneous stone passage. We also found no overall benefit from the use of MET. Stone size and position are important predictors and our findings represent the most comprehensive stone passage rates for each mm increase in stone size from a large contemporary cohort adjusting for key potential confounders. We anticipate that these data will aid clinicians managing patients with acute ureteric colic and help guide management decisions and the need for intervention.

Introduction

Urolithiasis is a very common problem with a lifetime incidence of up to 19% in men and 8% in women. Recent evidence shows that in high-income countries the incidence is 58.4 to 1116 per 100,000 people with incidence increasing over time and 25% experiencing recurrence [1-4]. In patients who have uncontrollable pain, sepsis or renal impairment, immediate intervention is often necessary. In patients presenting with acute ureteric colic who are clinically stable without an indication for immediate intervention there is uncertainty as to the likelihood of the patient requiring active treatment for their stone. Randomised control trials assessing the use of medically expulsive therapy to improve spontaneous stone passage confirm that three-quarters of stones will pass without the need for any surgical intervention [5-7]. Allowing a stone to pass spontaneously avoids the need for intervention and its associated complications. Once an intervention is carried out this can often lead to a number of surgical procedures before the patient is stone and stent free, causing burden to patients and healthcare systems [8]. Conversely, managing a stone conservatively that may not pass can lead to re-admission due to pain, infection or a delay in definitive management, so intervention in some patients is important [6].

Key clinical parameters that may influence spontaneous stone passage include stone size, stone position and the use of medical expulsive therapy (MET) [5, 9, 10], though the influence of these factors on SSP has rarely been considered together in a contemporaneous study. A biomarker that could predict which patients will pass their stone spontaneously and which would likely require intervention would be useful in guiding patient management in those who are clinically stable at presentation. A biomarker that is routinely collected, cheap and widely available to urological centres managing patients with renal colic would be the ideal candidate.

WBC, Neutrophil count and CRP are blood tests that are routinely performed in patients on admission with acute ureteric colic and have attracted attention for their potential as such biomarkers. Previously Sfoungaristos et al assessed 156 patients and found an increased chance of SSP in patients with a raised WBC or neutrophil count [11]. Conversely, Park et al, assessed 187 patients and showed that the stone passage rate was 11.4% more frequent in those with a normal neutrophil count when compared to those with a raised count, defined as >74% of the total white cell count [12] . Others have also shown that a raised WBC or CRP was associated with decreased spontaneous stone passage and an increased need for intervention [13, 14] .

A proposed hypothesis for the observed association was that a stone that passes along the full ureter has an opportunity to cause ureteric wall inflammation and sub-mucosal oedema [11, 15], thus generating an inflammatory response resulting in higher inflammatory markers.

However, the conflicting nature of the evidence within the literature and the observation that conclusions on whether this inflammatory response might be improving or reducing likelihood of SSP were based on studies with very small sample sizes, without power to adjust for key confounding variables. This led to the development of the MIMIC study (Multi-centre cohort study evaluating the role of Inflammatory Markers In patient's presenting with acute ureteric Colic) [12- 14, 16].

Our aim was to establish the association of primarily WBC but also Neutrophil count, CRP and other routinely measured clinical parameters with SSP in an appropriately powered sample, adjusting for key confounders. Specific clinical parameters that we aimed to investigate included stone size, stone position and MET. Particularly for the role of MET, there is controversy on whether it aids SSP, with the publication of conflicting data between a high quality RCT, SUSPEND, and a robustly performed meta-analysis [5, 7].

Subjects and Methods

Study Design

We carried out a multi-centre retrospective cohort study according to the principles of the trainee- led collaborative research model [17, 18] coordinated by the British Urology Researchers in Surgical Training (BURST) research collaborative. We carried out the study in secondary care hospitals in the UK, Ireland, Australia and New Zealand. A secondary care hospital was any institution with an accident and emergency department that accepts patients with ureteric colic. We report results according to the STROBE guidelines [19], [supplementary data, appendix 1].

Inclusion criteria included patients presenting with acute ureteric colic who had a solitary ureteric stone diagnosed by non-contrast computer tomography (CT) (15). Exclusion criteria included patients presenting with non-obstructing renal stones, patients with more than one ureteric stone and patients who have second or subsequent presentation of a previously identified ureteric stone [20]. The primary analysis excluded patients admitted for immediate emergency intervention, for example, due to sepsis, renal failure or unmanageable pain. We mitigated for selection bias by including consecutive patients meeting the eligibility criteria identified from each participating institution. Each centre collected data on a minimum of 50 consecutive patients with a minimum of 6 months of follow-up from initial presentation.

We assessed emergency department records, follow-up records, imaging results and surgical operation notes. We followed up patients' records until spontaneous stone passage or the patient underwent intervention and in the absence of these events, for a minimum of 6 months. We defined follow-up data as a patient attendance to an outpatient clinic, telephone consultation, an imaging test or admission to hospital.

Within Australia and New Zealand formal ethical review board approval was granted. In the UK, as per UK NHS Health Research Authority and National Research Ethics Service guidance, ethical exemption applied, and local research and development or clinical audit department approval was granted at each participating site. In the Republic of Ireland local audit department approval was granted at each participating site. The full study protocol has been published previously [20].

Variables

White blood count (WBC) was the primary determinant of interest. Secondary variables included Neutrophils, CRP, Stone Size and Stone Position, Medical Expulsive Therapy, Creatinine, Hydronephrosis, Hydroureter, Perinephric Stranding, NSAID use and Antibiotic use. Variables were selected a priori on basis of putative association with SSP based on the literature and on basis of being routinely available in clinical practice.

The primary outcome was the occurrence of SSP during follow-up. As with other landmark studies in acute ureteric colic, we defined SSP as the absence of need for intervention to assist stone passage [7, 21]. This definition allowed either a clinical or radiological confirmation of stone passage. Due to the real-world nature of the data collection this pragmatic definition minimised selection bias that would be created by analysing only those patients who had follow-up imaging. The follow-up and need for intervention were determined by local practice and clinical discretion.

For stone position, we classified upper ureteric stones as stones from the renal pelvis to the top of the sacrum, middle ureteric as being from the top to the bottom of the sacrum and lower ureteric stones were classified as stones below the sacrum to the vesico-ureteric junction (VUJ). The local radiologist determined stone size, the presence of hydronephrosis, hydroureter and peri-nephric stranding.

We checked all data for the variables of interest and primary outcome for inconsistencies and outliers and in addition an independent central quality control team checked the full data records for sense and consistency in 10% of patients chosen at random from each site. We removed one site, due to poor quality data, who had submitted data on 10 patients.

Statistical Analysis

We powered the study as per the accepted minimum criteria of 10 events per variable (EPV) for logistic regression analyses [22]. With 18 variables and assuming a 75% SSP rate, the minimum sample size required was 720 patients [20, 22, 23]. We added interaction terms between MET and stone size and stone position based on prior clinical evidence [5].

We used univariable logistic regression to determine the association between variables of interest and SSP. Subsequently, a multivariable logistic regression model was constructed, where the outcome of interest was SSP using data from patients who did not undergo intervention at presentation. We used a random effect to account for clustering of patients within hospitals. The multivariable model included adjustments for gender and age as control variables. We report odds ratios, related to the probability of spontaneous stone passage for each variable. We treated stone size as a categorical variable with clinically important boundaries derived from the literature [6]. Analyses were performed with multiple imputation by chained equations to determine the effect, if any, from missing data. Data was assumed to be missing at random. Predictive mean matching was used for continuous data, logistic regression for binary variables and polytomous logistic regression for unordered categorical variables.

Statistical analyses were performed using R version 3.4.4 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna. Austria. URL https//www.R-project.org/.). The packages used were rms, nlme, lme4, and mice.

Results

Demographics

We collected data on 4170 patients across 71 sites between 2011 and 2017 with the median number of patients per site being 50 [range 43 to 101]. 65.1% (n = 2706) had stones of 0-5mm [95%CI 63.7% to 66.6%], 20.6% (n = 855) 5-7mm [95%CI 19.4% to 21.8%] and 14.2% (n = 593) >7mm [95%CI 13.2% to 15.4%]. 8.0% (n = 330) [95%CI 7.2% to 8.9%] had a negative urine dipstick despite a CT confirmed ureteric stone. 75% (n = 3117) of patients were discharged with conservative management for their ureteric stone and were included in our primary outcome analysis. The remaining 25% (n = 1045) of patients were admitted for immediate emergency intervention. Of the 3117 patients discharged with conservative management an outcome of either spontaneous stone passage or re-admission for intervention was recorded in 2518/3117 (81%). The median age of this group was 47 years [IQR 35 to 57], median stone size was 4 mm [IQR 3 to 5] [Figure 1] and median WBC was 10.4 $\times 10^9$/Litre [IQR 8.1 to 12.8] . 60% received a NSAID analgesic and 38% received MET which in all cases was Tamsulosin. The overall spontaneous stone passage rate was 74% (1874/2518) and sepsis after discharge with conservative management was reported in 0.6% (n = 16/2518), [Table 1].

Descriptive and univariate analyses
White Blood Count (WBC), Neutrophils, CRP

Both WBC [OR 1.03, 95% CI 1.00-1.06, P=0.04] and Neutrophil count [OR 1.03, 95% CI 1.01-1.06, P=0.02] were shown on the univariable analysis to be associated with SSP whilst CRP was not [OR 1.00, 95% CI 0.99-1.00, P=0.17]. A WBC value of $<4 \times 10^9$/L had a 92% (12/13) chance of SSP compared to a 73% (1239/1687) chance of SSP for a WBC value between 4 to 12×10^9/L and 76% (N=622/817) chance for a WBC value $>12 \times 10^9$/L. For every increase in WBC by 1.0×10^9/L, the odds of SSP decreased on average by 3% [95% CI 0-6%] (p=0.04) [Table 2]. Similarly, as neutrophil count increased by each unit, the odds of SSP decreased by 3% [95% CI 1-6%] (P=0.02).

Stone Size and Stone Position

As stone size increased, SSP decreased. SSP for stones < 5mm was 89% [95% CI 87 to 90] compared to 49% [95% CI 44 to 53] for those ≥5 to 7mm and 29% [95% CI 23 to 36] for stones >7mm [Supplementary information].

As the presenting position of the stone was further down the ureter, the chances of SSP increased. For stones in the upper ureter the SSP rate was 52% [95% CI 48 to 56], middle ureter was 70% [95% CI 64 to 76], and lower ureter was 83% [95% CI 81 to 85] [Table 2 and Supplementary information].

Figure 2 shows the distribution of stones according to size and position whilst figure 3 shows the likelihood of SSP when stratified by both stone size and stone position and highlights the interaction between the two factors. Larger stones >7mm had a 47% chance of passing if in the lower ureter but this decreased to only 14% if in the upper ureter. Smaller, <5mm, stones had an 89% chance of passing in the lower ureter, decreasing to 71% if in the upper ureter.

Medically Expulsive Therapy

Data on MET use was available in 2182/2518 patients. A greater proportion of patients using MET had SSP (78% [95% CI 75 to 81]) compared to those that did not (72% [95% CI 70 to 75]). The odds of SSP in those who took MET were 31% greater than in those who did not take MET (p=0.02), [Table 2]. Of note, those who took MET had a greater proportion of lower ureteric stones (68% vs 65%, respectively) and fewer upper ureteric stones (21% vs 25% respectively) compared to those who did not [supplementary data appendix 2].

Hydronephrosis

Patients who had hydronephrosis reported on their initial CT scans had lower SSP compared those that did not (62% vs 69%, respectively). The odds of SSP in those who had hydronephrosis were 34% less than the odds of SSP in those who did not (p<0.0002), [Table 2].

Creatinine, Hydroureter, Perinephric Stranding, NSAID use, Antibiotic use.

Creatinine, presence of hydroureter, presence of perinephric stranding, NSAID use at presentation and antibiotic use at presentation did not appear to be associated with SSP on the univariable analysis [Table 2].

Multivariate logistic regression [Table 3].

Although WBC was initially seen to be associated with SSP on the univariable analysis this was not found to be the case on the multivariable analysis [Table 3]. The adjusted OR for WBC was 0.97 [95% CI 0.91 to 1.04, p = 0.39]. After adjustment stone size still predicted SSP. The adjusted odds of SSP for 5 to 7mm stones were 82% less than that of a 0 to 5mm stone and the adjusted odds of SSP for stones >7mm were 92% less than that of a 0 to 5mm stone. Stone position also predicted SSP after adjustment. The adjusted odds of SSP for mid ureteric stones were 38% less than that of a lower ureteric stone (p<0.07) and the odds of SSP for upper ureteric stones were 75% less than that of a lower ureteric stone (p<0.0001).

After adjustment, MET use [OR 1.11 [95% CI 0.76 to 1.61], p<0.6) and the presence of hydronephrosis (OR 0.94 [95% CI 0.72 to 1.23], p<0.65) no longer predicted SSP. For stones > 7mm, the use of MET use was associated with greater SSP (OR 2.20 [95% CI 0.92-5.27], p < 0.08), though the 95% confidence intervals were wide and included no effect.

Missing Data and Multiple Imputation

Data was missing in 576 cases (23%) for the final multivariable model. As a sensitivity analysis, all the above analyses were repeated with multiple imputation to account for this missing data and only minor changes were seen in the presented ORs. The interpretation of the study findings did not change after imputation [supplementary data, appendix 3].

Patients not responding to routine care follow-up invitation

20% of patients did not respond to follow-up invitation by the clinical care team after being discharged with conservative management. These patients had similar demographics to the cohort that passed their stone spontaneously (SSP+) [supplementary data, appendix 2]. The median stone size was 4mm [IQR 3-5mm] in both groups with the majority of stones located in the lower ureter (70%).

Discussion

In contrast to the previous literature, in this large multicentre cohort study, we have shown that there was no association between WBC, Neutrophil count or CRP on admission and the likelihood of subsequent SSP in patients presenting with acute ureteric colic who were initially discharged with conservative management. The overall stone passage rate was 74% and only 0.6% of those discharged on initial conservative management developed an episode of sepsis, confirming that it is safe to conservatively manage patients with obstructing ureteric stones providing that they receive close follow up with urological assessment and/or imaging tests. In addition, stone size and stone position were strong predictors of SSP, and our dataset has confirmed the rate of SSP stratified for stone size and position in a contemporary cohort of patients where stone size was calculated from a CT scan rather than X-rays or intravenous urogram as was the case in many previously published series. This data can allow clinicians to better counsel their patients on the likelihood of SSP, which should help inform management decisions in acute ureteric colic. As this data is derived from a large multicentre sample of patients, and adjusts for key confounding variables, we anticipate that it will be a useful reference standard for the management of renal colic.

Our data has similar overall SSP rates as recent RCTs in this field, validating our findings. The overall SSP rate was 80-81% in SUSPEND, 79-86% in the Ye et al study and 82-87% in the Furyk et al study [6, 7, 24]. Whilst previous studies did show an association between inflammatory markers and SSP in one direction or the other, after adjustment for key confounding variables, the MIMIC study did not find an association between WBC, Neutrophils or CRP and SSP [11-14]. Although our univariable analysis showed that Hydronephrosis and MET was associated with SSP, after adjustment, we found no such association, which highlights the importance of adjusting for confounding variables. With regards to MET use, there is much debate in the medical community at this time on its role in acute ureteric colic, with a both a meta-analysis and recent RCTs giving conflicting results [5-7, 24]. Previous studies have suggested that in stones of a particular size or location there may be a role for MET, though many of these RCTs have not had adequate power to investigate associations in specific subgroups. Although we found no overall evidence in our dataset to support the role of MET in SSP, we acknowledge that there is some uncertainty about its role in the subgroup of stones greater than 7mm. Unlike the carefully controlled environment of RCTs, our data is likely to be more generalisable to clinical practice where patients acceptability of treatment and local follow-up protocols can differ substantially to those set out within a trial schema and thus should be used to complement the findings from the interventional studies [26, 27].

The current European Association of Urology [25] and American Urology Association [10] guidelines do not discuss the role of predictors for SSP beyond stone size. Their guidelines are primarily based on older studies or those with a small sample size, which may not be readily generalisable to current day practice [9, 26]. Data on time to stone passage are based on a 75-patient dataset from 1999 whereas the rates of SSP stratified for stone size are based on a paper from 1993 which pre-dates modern treatments and the quoted figures for SSP differ substantially from current practice with SSP for stones < 4 mm of 38% and SSP for stones > 6mm of 1.2% [9, 26]. Further, though the guidelines do differentiate SSP rates in “small” and “large” stones, they do not discuss the differences in SSP rates for increases in stone size by every mm. The AUA guidelines also specify that evidence for conservative management for mid and upper ureteric stones is lacking, which is addressed in this study.

The key strengths of this study include its multi-centre nature, large sample size and pragmatic nature. The large sample size allowed adequate power to investigate the association of a number of important patient factors whilst adjusting for key confounders, which was lacking from previous studies. As can be seen from the differences between the univariate and multivariate analysis these confounding factors were important to account for. Despite being a large multicentre study, due to the robust central independent quality control, missing data for the key variables of interest was infrequent, highlighted by the sensitivity analysis with multiple imputation which showed no substantial differences. A pragmatic study design was chosen in order to ensure that the results were generalizable to clinical practice.

Nevertheless, there are a number of limitations to this study. First, the data was observational in nature, although interventional studies to answer the question of interest may not be feasible. Randomised trials in acute ureteric colic are often underpowered to investigate associations of a number of key variables simultaneously [7, 24, 27]. We accept that there is the possibility of unmeasured confounding being present that could have influenced the associations seen. Second, the study was retrospective in nature, though we do not feel this limited the validity of the conclusions. We initially carried out a pilot phase of the study [20] and tested whether retrospective data collection would be suitable; the pilot phase confirmed that retrospective data collection provided accurate and reliable data and had the benefits of allowing significant follow up data to be obtained for a large sample of patients in a resource-efficient manner [20]. Third, we also accept that there are alternative valid definitions of SSP. We used a pragmatic definition as utilised in previous landmark studies in acute ureteric colic whereby “absence of the need for intervention” encompasses both an imaging and clinical judgement-based method for determining SSP. This is an outcome that is of importance to patients with ureteric colic and is thus a valid choice [7]. It is however entirely possible that such a definition could result in a higher proportion of patients being declared stone free, but it is in keeping with current clinical practice. Exposing patients to excessive radiation from repeated imaging tests not in keeping with clinical practice carries risk of harm to patients [28]. Fourth, 25% of patients were admitted for immediate intervention included in the current analyses which could be a potential confounder. As the decision to intervene at initial admission is often multifactorial based on local clinician preference and local policies including it in our analyses would in itself have led to bias. Thus, the current data is best applied to those patients who are deemed suitable for and have been discharged with conservative management rather than all patients presenting with acute ureteric colic. Finally, a proportion of patients had been lost to follow-up following initial presentation with ureteric colic. Although this was the case, loss to follow up was minimised as a result of the robust routine clinical follow up arranged for these patients who typically had outpatient clinic follow up or telephone follow up. When we compared the demographics of this group to the whole cohort we found that they were similar to patients who spontaneously passed their stone. This highlights the need for more robust follow-up pathways for patients discharged with ureteric colic. Further, the results of the study were consistent when carrying out multiple imputation to account for missing data as a sensitivity analysis.

Conclusions

In patients with acute ureteric colic who are discharge with initial conservative management, neither WBC, Neutrophil count nor CRP were associated with SSP and thus should not be used to help influence decisions on the likelihood that the patient will require future intervention. We also found no benefit from the use of MET in aiding spontaneous stone passage in our cohort of patients. Stone size and position are the most important determinants of the need for active stone treatment. Our findings represent the most comprehensive stone passage rates for each mm increase in stone size from a large contemporary cohort. We anticipate that these data will aid clinicians in managing patients with acute ureteric colic and help guide management decisions and the need for intervention.

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Tables

Variable	Discharged with Conservative Management	Discharged with Conservative Management and Outcome Available	SSP+	SSP-
N	3117	2518	1874	644
Age [IQR]	46 [35-57]	47 [35-57]	46 [35 - 57]	48 (37 - 59)
Male (%)	75	75	75	76
Female (%)	25	25	25	24
PMH (%)	27	28	27	29
WBC [IQR]	10.4 [8.2-12.8]	10.4 [8.1-12.8]	10.5 [8.3 - 12.9]	10.1 [7.8 - 12.5]
Neutrophils [IQR]	7.8 [5.4-10.2]	7.8 [5.4-10.2]	7.8 [5.5 - 10.3]	7.5 [4.9 - 10]
CRP [IQR]	3.4 [1.0-7.00]	4.0 [1.1-7.1]	3.1 [1 - 7]	4 [1.3 - 10]
Creatinine [IQR]	91 [77-107]	91 [77-108]	91 [77 - 107]	92 [76 - 110]
Stone Size, mm [IQR]	4 [3-5]	4 [3-5]	4 [3 - 5]	6 [5 - 7]
Side (left:Right)	53:47	53:47	52:48	55:45
Upper (%)	23	24	17	45
Middle (%)	10	10	9	12
Lower (%)	67	66	74	43
HN (%)	63	63	62	69
HU (%)	56	57	59	51
Perinephric stranding (%)	42	42	43	42
NSAIDS (%)	61	60	62	59
Opiod (%)	55	54	55	55
MET (%)	37	38	40	33
Antibiotics (%)	12	12	13	12

Table 1. Key patient group characteristics. SSP+ = those that were discharged with conservative management and subsequently achieved spontaneous stone passage; SSP- = those that were discharged with conservative management and did not achieve spontaneous stone passage (SSP-); PMH = Past medical history; WBC = White blood cell count; CRP = C-reactive protein; HN = hydronephrosis; HU = hydroureter; NSAIDS = Non-steroidal anti-inflammatory drugs; MET = medical expulsive therapy (tamsulosin).

Univariable Analysis				
Variable	OR	CI (Lower 95)	CI (Upper 95)	P-value
WBC	1.03	1.00	1.06	0.04
Age	0.99	0.99	1.00	0.02
Sex	0.96	0.78	1.20	0.45
Previous Stone History	0.90	0.73	1.11	0.31
Size 5-7mm	0.16	0.13	0.20	<0.0001
Size >7mm	0.07	0.05	0.10	<0.0001
Side	1.13	0.94	1.36	0.19
Middle ureter	0.46	0.34	0.63	<0.0001
Upper ureter	0.21	0.17	0.26	<0.0001
Neutrophils	1.03	1.01	1.06	0.02
CRP	1.00	0.99	1.00	0.17
Creatinine	1.00	1.00	1.00	0.56
Hydronephrosis	0.66	0.54	0.82	<0.0002
Hydroureter	1.14	0.91	1.42	0.26
Peri-nephric stranding	0.96	0.76	1.22	0.75
NSAID oral	1.25	0.95	1.64	0.11
NSAID rectal	1.12	0.87	1.45	0.38
MET	1.31	1.05	1.64	0.02
Antibiotics	1.06	0.79	1.43	0.68
factor(MET.interaction.middle ureter)	0.63	0.40	0.99	0.05
factor(MET.interaction.upper ureter)	0.39	0.28	0.54	<0.0001
factor(MET.interaction.5-7mm)	0.31	0.22	0.44	<0.0001
factor(MET.interaction.>7mm)	0.19	0.10	0.34	<0.0001

Table 2. Univariable analysis presented as odds ratio (OR) with their corresponding 95% confidence intervals (CI) and p-values. Hospital/institution was treated as a random effect.

OR = Odds Ratio; CI = Confidence Interval. WBC = White blood cell count; CRP = C-reactive protein; NSAID = Non-steroidal anti-inflammatory drug; MET = medical expulsive therapy (tamsulosin).

Multivariable model with interactions terms included				
Factor	OR	Lower 95	Upper 95	p-value
WBCx10^9/L	0.97	0.91	1.04	0.39
Age	1.00	0.99	1.00	0.34
Sex	0.82	0.62	1.08	0.15
Size 5-7mm	0.18	0.12	0.25	0.0001
Size>7mm	0.08	0.04	0.14	0.0001
MET	1.11	0.76	1.61	0.6
Middle ureter	0.62	0.37	1.04	0.07
Upper ureter	0.25	0.18	0.35	0.0001
Neutrophilsx10^9/L	1.06	0.99	1.13	0.11
Hydronephrosis	0.94	0.72	1.23	0.65
Size 5-7mm*MET	1.29	0.75	2.23	0.36
Size >7mm*MET	2.20	0.92	5.27	0.08
Middle ureter*MET	0.83	0.39	1.78	0.64

Figure 1. Histogram of stone size

Absolute frequency

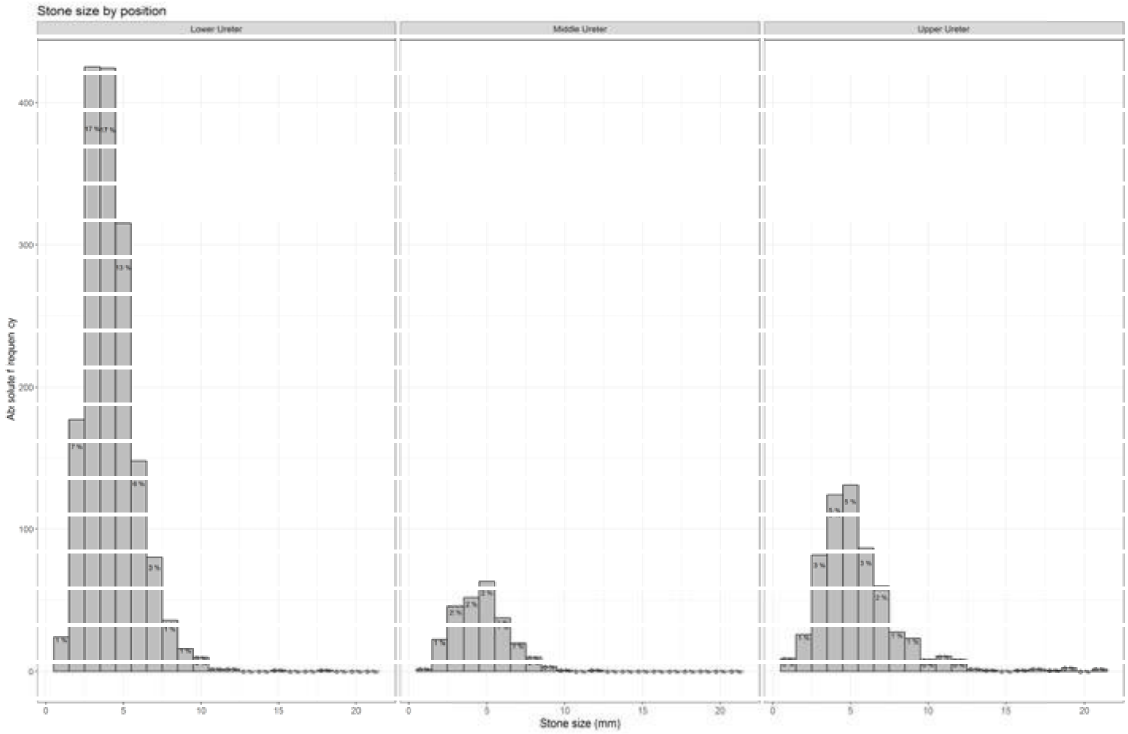

Figure 2. Histogram demonstrating the distribution of stones stratified by stone size (mm) and position.