






Original Article

Nomogram predicting the probability of spontaneous stone passage in patients presenting with acute ureteric colic

Chuanyu Gao¹ , Max Peters², Piet Kurver², Thineskrishna Anbarasan¹, Keerthana Jayaraajan¹, Todd Manning³ , Sophia Cashman¹, Arjun Nambiar¹, Marcus Cumberbatch^{1,4}, Benjamin W. Lamb^{1,5} , Robert Pickard⁶, Paul Erotocritou⁷, Daron Smith⁸ , Veeru Kasivisvanathan^{1,9}, Taimur T. Shah^{1,9,10,11} , and British Urology Researchers in Surgical Training (BURST) Collaborative MIMIC Study Group[†],

¹British Urology Researchers in Surgical Training (BURST), ²Department of Urology, Whittington Hospital, ³Department of Urology, University College London Hospital, ⁴Division of Surgery, and Interventional Science, University College London, ⁵Division of Surgery and Cancer, Imperial College London, ⁶Charing Cross Hospital, Imperial Health NHS Trust, London, ⁷Academic Urology Unit, University of Sheffield, Sheffield, ⁸Department of Urology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, ⁹Department of Urology, Newcastle University, Newcastle, UK, ¹⁰Department of Radiation Oncology, Cancer Centre, University Medical Centre Utrecht, Utrecht, the Netherlands and ¹¹Australian Young Urology Researchers Organisation (YURO), Melbourne, Vic., Australia

V.K. and T.T.S. joint senior authors.

[†]PubMed Indexed Collaborators (BURST Collaborative MIMIC Study Group) members are present in Appendix A.

Objectives

To develop a nomogram that could predict spontaneous stone passage (SSP) in patients presenting with acute ureteric colic who are suitable for conservative management.

Patients and Methods

A 2517 patient dataset was utilised from an international multicentre cohort study (MIMIC, A Multi-centre Cohort Study Evaluating the role of Inflammatory Markers In Patients Presenting with Acute Ureteric Colic) of patients presenting with acute ureteric colic across 71 secondary care hospitals in the UK, Ireland, Australia, and New Zealand. Inclusion criteria mandated a non-contrast computed tomography of the kidneys, ureters, and bladder. SSP was defined as the 'absence of the need for intervention'. The model was developed using logistic regression and backwards selection (to achieve lowest Akaike's information criterion) in a subset from 2009–2015 ($n = 1728$) and temporally validated on a subset from 2016–2017 ($n = 789$).

Results

Of the 2517 patients, 1874 had SSP (74.5%). The mean (SD) age was 47 (14.7) years and 1892 were male (75.2%). At the end of the modelling process, gender: male (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.64–1.01, $P = 0.07$), neutrophil count (OR 1.03, 95% CI 1.00–1.06, $P = 0.08$), hydronephrosis (OR 0.79, 95% CI 0.59–1.05, $P = 0.1$), hydroureter (OR 1.3, 95% CI 0.97–1.75, $P = 0.08$), stone size >5–7 mm (OR 0.2, 95% CI 0.16–0.25, $P < 0.001$), stone size >7 mm (OR 0.11, 95% CI 0.08–0.15, $P < 0.001$), middle ureter stone position (OR 0.59, 95% CI 0.43–0.81, $P = 0.001$), upper ureter stone position (OR 0.31, 95% CI 0.25–0.39, $P < 0.001$), medical expulsive therapy use (OR 1.36, 95% CI 1.1–1.67, $P = 0.001$), oral nonsteroidal anti-inflammatory drug (NSAID) use (OR 1.3, 95% CI 0.99–1.71, $P = 0.06$), and rectal NSAID use (OR 1.17, 95% CI 0.9–1.53, $P = 0.24$) remained. The concordance-statistic (C-statistic) was 0.77 (95% CI 0.75–0.80) and a nomogram was developed based on these.

Conclusion

The presented nomogram is available to use as an on-line calculator via www.BURSTurology.com and could allow clinicians and patients to make a more informed decision on pursuing conservative management vs early intervention.

Keywords

ureteric colic, predict, spontaneous stone passage, nomogram, multivariable, #KidneyStones, #EndoUrology, #UroStone, #Urology

Introduction

Ureteric colic is a common urological problem with a lifetime incidence of 8%–19% in males and 3%–5% in females in Western countries and its incidence has been increasing in recent decades [1,2]. In the UK, there is an estimated annual incidence of one to two cases/1000 people, and there is a lifetime incidence of 12% amongst men and 6% amongst women [3].

Although some variation is seen geographically in the management of ureteric colic, most guidelines including the European Association of Urology (EAU) guidelines recommend conservative management of 'small' ureteric stones of <6 mm in diameter [4]. The UK National Institute for Health and Care Excellence (NICE) recommends that stones <5 mm can be considered for watchful waiting, with surgical management considered on re-admission or in those with intolerable pain [5].

Data from randomised controlled trials (RCTs), meta-analyses and from our own previous cohort study (MIMIC, A Multi-centre Cohort Study Evaluating the role of Inflammatory Markers In Patients Presenting with Acute Ureteric Colic) showed a 70%–80% rate of spontaneous stone passage (SSP) in those presenting with acute ureteric colic [6–8]. Our data also showed that the proportion of patients having SSP tends to decrease with increasing stone size and a more proximal ureteric stone location. Thus, although conservative management may be suitable for most patients there are a subset of patients who are destined to fail to pass their stone and who will therefore require intervention either as an elective or emergency case.

Currently, clinicians utilise stone size and position, as well as patient preference, in determining whom to manage conservatively and in whom to intervene. Our aim was to utilise the data collected on patients from the MIMIC study cohort who were managed conservatively after admission with acute ureteric colic to develop a risk calculator that could predict the probability of stone passage with conservative management and conversely identify those patients that may benefit from early intervention due to a low probability of stone passage.

Patients and Methods

Study Design and Patients

Our aim was to develop a risk calculator to predict the probability of SSP in patients presenting with ureteric colic

utilising the MIMIC dataset. MIMIC was an international multicentre cohort study of 4170 patients presenting with acute ureteric colic across 71 secondary care hospitals in the UK, Ireland, Australia, and New Zealand, co-ordinated by the British Urology Researchers in Surgical Training (BURST) research collaborative. Inclusion criteria mandated a non-contrast CT confirmed solitary ureteric stone. The patient population for the predictive model development comprised 2517 patients who had a confirmed clinical outcome after being initially managed conservatively for ureteric colic.

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. Within Australia and New Zealand formal ethical review board approval was granted.

Variables

Variables were chosen based on an internal and external peer-review process including discussions with statisticians, clinicians, and methodologists that aimed to highlight clinically relevant variables that could be collected. Variables included in the first stage of the model were age, sex, previous stone history, side of stone disease, presence of hydronephrosis and hydroureter, presence of perinephric stranding, respiratory rate, heart rate, medical expulsive therapy (MET) use (α -blockers, e.g., tamsulosin used to enhance stone passage), NSAID use (oral or rectal), stone size (categories 0–<5, \geq 5–7, and >7 mm), and stone position (upper, middle or lower ureter) on CT. Furthermore, biochemical parameters such as white blood cell (WBC) count ($10^9/L$), neutrophils ($10^9/L$), C-reactive protein (CRP; mg/L), creatinine ($\mu\text{mol/L}$), and urine dipstick outcomes (blood, nitrites, and leucocytes) were included. Cut-offs for stone size were determined based on the Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial [8], which dichotomised stones to <5 and >5 mm, with the latter group further categorised at 7 mm as per the study by Ye *et al.* [9], which evaluated MET in stone sizes of 4–7 mm. To our knowledge relevant variables not collected/assessed were ureteric wall diameter and previous SSP history [8,9].

SSP was defined by the absence of the need for intervention in acute ureteric colic as per our previous publication and protocol [6].

Normally distributed variables are presented as mean (\pm SD) and skewed variables as median with corresponding interquartile range (IQR).

Model Development

The guideline ‘Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement’ was used for the creation of this prediction model and presentation of the results [10]. Correlations between variables were assessed before the first modelling step, where correlations of >0.7 of variance inflation factor (VIF) >5 were reasons for exclusion of one of the correlated variables from the first modelling step. Logistic regression was performed including all clinical variables. Odds ratios (ORs) with 95% CIs were obtained. The first modelling step included all variables, after which variables were deselected using a manual backwards stepwise selection. The subsequent model at each step was compared to its predecessor. Modelling stopped when the lowest value of Akaike’s information criterion (AIC) was achieved [11,12]. Adopting a traditional Wald-test P value cut-off of $P < 0.05$ has been known to miss important predictors. Using AIC as the model selection criteria (significance of $P = 0.157$) allows consideration of variables which, although independently only approached traditional statistical significance ($P < 0.05$), are in fact important predictors in the context of others [10, 13].

Model Internal and Temporal Validation, Calibration, and Assumptions

The C-statistic, corresponding to an area under the curve, was used to assess the final models’ discriminative ability. To obtain optimism corrected ORs, intercept and C-statistic, internal validation was performed in each of the 20 imputed datasets. All modelling steps were repeated on 2000 bootstrap resampled datasets of each of the 20 imputations. The optimism-corrected β s was used in further analyses. Deciles of predicted vs the observed probabilities for SSP were plotted to visually assess the models’ calibration. The linearity assumption with the log-odds of the outcome for continuous variables was visually assessed and the Hosmer–Lemeshow test for the final full model was performed.

As sensitivity analysis, the model was developed in a subset of patients from 2009–2015 ($n = 1728$) and temporally validated on a subset of patients from 2016 and 2017 ($n = 789$) to assess whether the model was sensitive to temporal trends.

Nomogram

The corrected β coefficients after internal validation were used for creation of a nomogram to assess an individual patients’ SSP probability.

Decision Curve Analysis

A decision curve analysis for SSP was performed to compute the net benefit of decisions based on the developed model. A separate curve illustrating net reduction in interventions with the use of the developed model against a range of threshold probabilities was generated.

Statistical Software

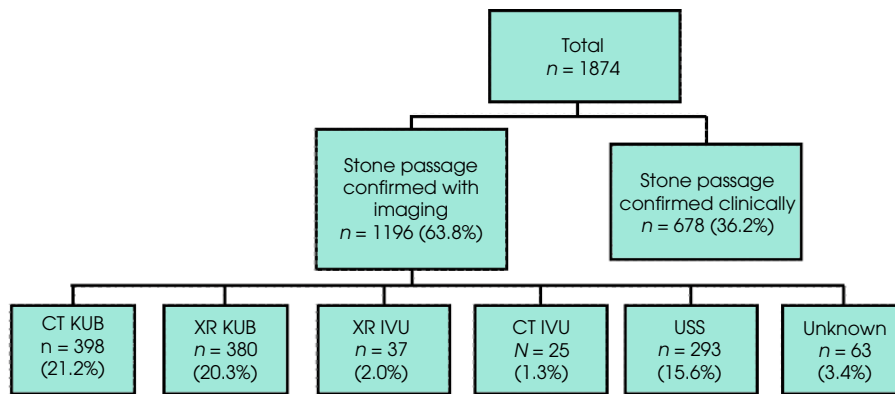
R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses (‘mice’ package for multiple imputation, ‘rms’ package for model development, internal and temporal validation, calibration, and nomogram construction and decision curve analysis) [14].

Results

Of the 2517 patients included from the MIMIC database, 1874 had SSP (74.5%). The median (IQR) age was 47 (35–57) years and 1892 were male (75.2%). The median (IQR) neutrophil count was 10.4 (8.1–12.8) $\times 10^9/L$. The proportion of hydronephrosis and hydroureter were 63% ($n = 1586$) and 57% ($n = 1435$), respectively. The proportion of patients with stone passage for stones sizes of 0–5 mm was 89% (95% CI 87–90) decreasing to 49% (95% CI 44–53) for stones measuring ≥ 5 –7 mm, and 29% (95% CI 23–36) for stones measuring ≥ 7 mm. In all, 56% ($n = 1410$) of patients had stones measuring 0–5 mm, 31% ($n = 781$) ≥ 5 –7 mm, and 11% ($n = 277$) ≥ 7 mm. Most stones were in the lower ureter with 66% ($n = 1662$), 10% ($n = 252$) and 24% ($n = 604$), in the lower, mid, and upper ureter, respectively. The lower the stone is in the ureter, the higher the likelihood of SSP. The SSP rate for lower ureteric stone was 83%, mid ureteric was 69%, and proximal ureteric stones was 51%. Amongst 1874 patients who were included in the model, 1196 patients (63.8%) had imaging-confirmed stone passage, which included CT of the kidneys, ureters, and bladder (KUB), X-ray KUB and X-ray IVU, CT IVU, and ultrasonography (Fig. 1). Missing data ranged from 0% to 31% for different variables and these are presented in Table S1. No significant change in proportion of patients having SSP was seen with respect to the year of patient presentation through the duration of the study (Fig. S1).

Modelling Process

Because there were no relevant correlations found between the variables included at the first step of the modelling process, no factors were excluded from the first step of model development. There was no significant interaction between stone size and position ($P = 0.18$ to 0.60) and these factors were therefore included in the model separately without

Fig. 1 Breakdown of stone passage confirmation with respect to imaging modality. USS, ultrasonography; XR, X-ray.**Table 1** Multivariable analysis of factors for highest predictive ability for SSP. Corrected OR refers to adjusted OR that controls for other input variables as part of the multivariable logistic regression model.

	Corrected OR	Corrected lower 95% CI	Corrected upper 95% CI	P
Intercept	5.49	3.74	8.04	
Male	0.8	0.64	1.01	0.07
Neutrophils	1.03	1	1.06	0.08
Hydronephrosis	0.79	0.59	1.05	0.1
Hydroureter	1.3	0.97	1.75	0.08
Stone size >5–7 mm	0.2	0.16	0.25	<0.001
Stone size >7 mm	0.11	0.08	0.15	<0.001
Middle ureter	0.58	0.42	0.8	<0.001
Upper ureter	0.31	0.25	0.39	<0.001
NSAID oral	1.3	0.99	1.71	0.06
NSAID rectal	1.17	0.9	1.53	0.24
MET	1.36	1.1	1.67	<0.001

interaction. At the end of the modelling process, the following variables were included in the model: male compared to female (OR 0.80, 95% CI 0.64–1.01, $P = 0.07$), neutrophil count (OR 1.03, 95% CI 1.00–1.06, $P = 0.06$), hydronephrosis (OR 0.79, 95% CI 0.59–1.05, $P = 0.1$), hydroureter (OR 1.30, 95% CI 0.97–1.75, $P = 0.08$), stone size >5–7 mm (OR 0.20, 95% CI 0.16–0.25, $P < 0.001$), stone size >7 mm (OR 0.11, 95% CI 0.08–0.15, $P < 0.001$), middle ureter stone position (OR 0.58, 95% CI 0.42–0.80, $P = 0.001$), upper ureter stone position (OR 0.31, 95% CI 0.25–0.39, $P < 0.001$), MET use (OR 1.36, 95% CI 1.1–1.67, $P = 0.001$), oral NSAID use (OR 1.3, 95% CI 0.99–1.71, $P = 0.06$), and rectal NSAID use (OR 1.17, 95% CI 0.9–1.53, $P = 0.24$) (Table 1 and Table 2).

Internal Validation

The apparent C-statistic of the uncorrected model was 0.78 (95% CI 0.75–0.80), which decreased to 0.77 (95% CI 0.75–0.80) after internal validation of the model, which indicates

Table 2 Corrected regression coefficients of multivariable analysis.

	Corrected regression coefficient	Corrected lower 95% CI	Corrected upper 95% CI	P
Intercept	1.703	1.32	2.085	
Male	−0.218	−0.45	0.014	0.07
Neutrophils	0.026	−0.003	0.056	0.08
Hydronephrosis	−0.239	−0.526	0.047	0.1
Hydroureter	0.262	−0.033	0.557	0.08
Stone size >5–7 mm	−1.609	−1.837	−1.382	<0.001
Stone size >7 mm	−2.221	−2.572	−1.869	<0.001
Middle ureter	−0.542	−0.857	−0.227	<0.001
Upper ureter	−1.175	−1.398	−0.952	<0.001
NSAID oral	0.263	−0.012	0.537	0.06
NSAID rectal	0.159	−0.105	0.423	0.24
MET	0.304	0.095	0.513	<0.001

good discrimination capacity. Calibration was good in the full development set over deciles of observed and predicted probabilities (Fig. 2).

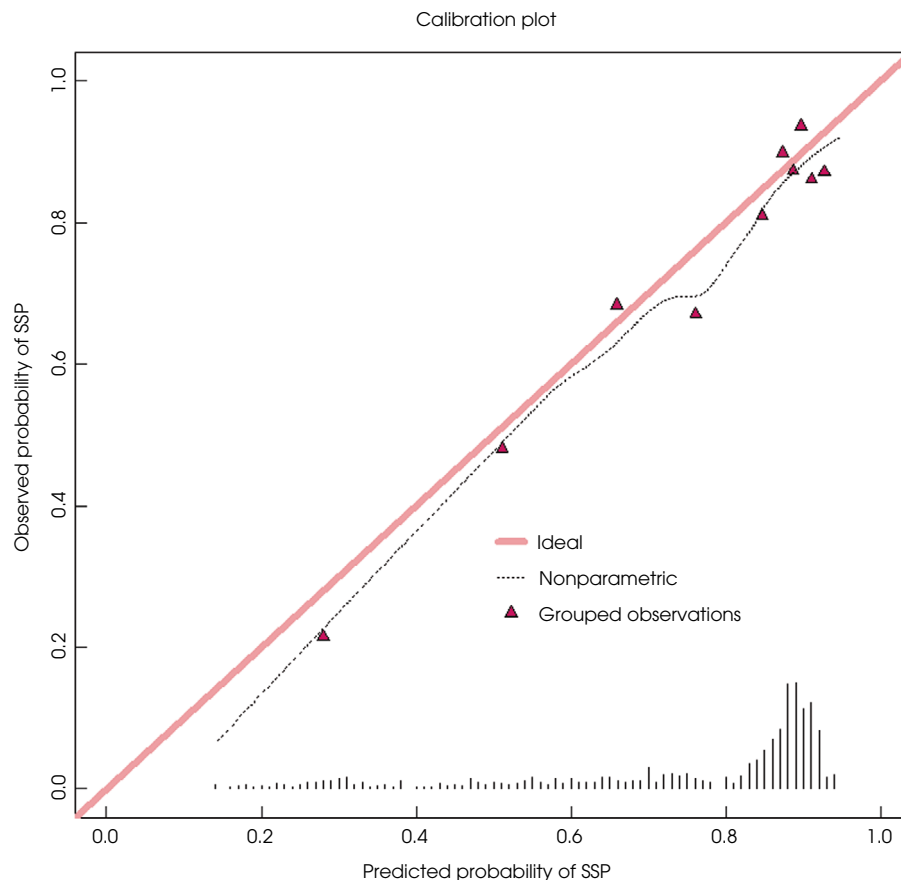
Model Assumptions

Model assumptions were met (linearity of predictors with logit of SSP, non-significant Hosmer–Lemeshow test of final model, $P = 0.09$).

Temporal Validation

Temporal splitting of the dataset was used for validation and showed that when applying the predictors from the full developmental set to the set from 2009–2015, the differences in corrected OR were minor (Table S2). This model resulted in an apparent C-statistic of 0.78 and corrected for optimism of 0.77, like the original model based on the full dataset. When calibration was performed on the dataset from 2016–2017 including 789 patients, with 576 (73%) experiencing SSP, calibration remained constant with deciles of predicted

Fig. 2 External validation calibration plot.



vs observed probabilities (Fig. 2). There was no evidence of a bad fit of the model (Hosmer–Lemeshow test, $P = 0.59$). The C-statistic was 0.76 (95% CI 0.72–0.80) demonstrating that the model was insensitive to temporal trends.

Nomogram

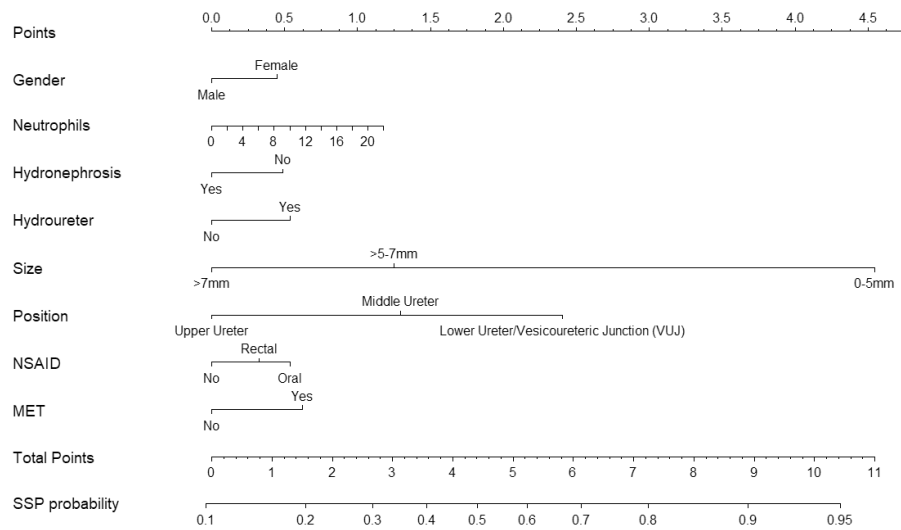
Subsequently a nomogram was created using each variable's β coefficient, depicted in Fig. 3, with which a patient's individual probability of SSP can be calculated based on their baseline characteristics. The nomogram utilises gender (male, female), stone size (0–5, ≥ 5 –7, > 7 mm), stone position (upper ureter, middle ureter, lower ureter), neutrophil count, hydronephrosis (yes, no), hydroureter (yes, no), MET use (yes, no) and NSAID use (no, oral, rectal) to determine a probability of SSP between 20% and 95%. The value of each β coefficient plotted on the nomogram can influence the chance of SSP. Furthermore, an on-line calculation tool has been created (<https://www.bursturology.com/Studies/Mimic/Calculator/calc/> and Fig. S2). For example, a female patient with a neutrophil count of $15 \times 10^9/L$, CT evidence of hydroureter without hydronephrosis, use of oral NSAID, no MET use and a confirmed stone of < 5 mm in the lower

ureter has a 93% chance of passing the stone spontaneously. In comparison a male patient with a neutrophil count of $6 \times 10^9/L$, no CT evidence of hydroureter or hydronephrosis, use of MET, use of oral NSAID and a stone size of 8 mm in the upper ureter has a 23% chance of spontaneously passing the stone.

Decision curve analysis for SSP (Fig. S3a) showed that net benefit with the model (compared to intervention-for-all strategy) was higher with increasing threshold probabilities from ~20%. The net benefit difference against an intervention-for-all strategy at 20% and 40% threshold probabilities, is one and four net reductions in interventions per 100 people, respectively (Fig. S3b).

Discussion

The presented analysis details the development and validation of a multivariable prediction model and nomogram for SSP in patients presenting with acute ureteric colic who are suitable for initial conservative management. It has been developed from a contemporary cohort of 2517 patients, with the model showing good discriminatory ability with a C-statistic of 0.77 after internal validation. On decision curve

Fig. 3 Nomogram of patient's individual probability of spontaneous stone passage.

analysis, the net benefit with the model (compared to intervention-for-all strategy) was higher with increasing threshold probabilities from ~20%. Reassuringly, model performance remained similar on temporal validation with only a marginal overestimation observed in the lower prediction ranges (0–30%). There is a paucity of similar data within the literature, with most publications based upon small sample sizes and to our knowledge there does not appear to be another contemporary peer-reviewed published nomogram predicting SSP based on a large dataset such as ours. The presented nomogram has been developed into a freely available on-line calculator and has the potential to significantly impact on clinical care as it can aid clinical decision making in determining which patients can be managed conservatively after presenting with acute ureteric colic. The positive sequelae of which could be to reduce emergency re-admissions and allow better planning of elective surgery.

Comparing our results to others, we found that many groups have tried to identify variables that can select patients who may achieve SSP, such as stone size [15,16], stone position [17], WBC count [18], neutrophil count [18], CRP [19], microscopic haematuria [20], perinephric stranding [21] but there appears to be a paucity of published nomograms thus limiting the use of these data in clinical practice. We ourselves recently published an analysis highlighting stone size and position as strong predictors of SSP but in developing the prediction model were able to identify additional variables such as gender, neutrophils, hydroureter, hydronephrosis, MET and NSAID use that have an additional discriminatory ability within the model [6]. The only similar publications are in abstract form. Ganesan *et al.* [22] developed a nomogram with stone size, position, previous

stone history and WBC count as the variables based on 661 patients. Yoshida *et al.* [23] developed a nomogram based on stone size, position and ureteric wall thickness based on 401 patients. Both these abstracts showed good discriminatory ability of the model with a C-statistic of 0.8 and 0.9, respectively; however, neither has been validated or been formally published, which limits a more detailed comparison. A finding unique to our dataset is the opposing relationship between hydronephrosis and hydroureter and SSP. A clinical explanation for this finding may be due to ureteric vermiculation aiding stone passage and thus causing hydroureter without significant hydronephrosis. However, we do stress that the degree of effect either hydroureter or hydronephrosis have on the probability of SSP is small. The relationship between NSAID use and SSP remains unclear. Mechanistically it has been postulated that NSAIDs may contribute to ureteric relaxation and promote SSP, but evidence is largely limited to *in vitro* studies with mixed findings in the clinical setting [24]. In our study, neutrophil count only approached statistical significance ($P = 0.06$) in multivariable logistic regression but was observed to have a relevant impact on SSP through the modelling process. Previously Sfoungaristos *et al.* [18] showed a significant association between neutrophilia and SSP which was not replicated in a more recent study [25]. Therefore, the exact predictive role of neutrophil count for SSP remains unclear. Nonetheless, it is postulated that increased initial circulating neutrophilia may be reflective of a more intense periureteric inflammatory response. This may aid SSP through pro-inflammatory cytokine-induced distal ureteric smooth-muscle relaxation [26].

The key strengths of our analysis come from the underlying large contemporary dataset that included data from 71

different secondary care institutions and thus should allow the data to be generalisable to the wider urological community. The dataset was predominantly formed by cases from UK sites but also included cases from Australia, New Zealand, and Ireland, where clinical practice remains similar. There are some limitations that we would like to highlight. First, due to the size of the dataset we were able to divide it temporally into development and validation cohorts. One could argue that a formal external validation is needed. As the majority of UK urological units were involved in this study, repeating the data collection within the UK would not achieve more than the already temporally split analysis. A pan-European or international patient population could be utilised and would allow external validation in varying healthcare systems with differing patient demographics. However, it is worth noting that practice with regards to ureteric colic across Europe is standardised in accordance with EAU guidelines and so we believe that the presented model is still generalisable across European centres. Nonetheless, until robust external validation in an independent population is completed, we acknowledge and emphasise this limitation with use of the model. Second, we understand that our definition of SSP may be pragmatic whereby 'absence of the need for intervention' signifies SSP. This definition is in keeping with the SUSPEND RCT and encompasses both an imaging- and clinical judgement-based method for determining SSP [8]. Next, we accept that only 63.8% ($n = 1196/1874$) of patients had imaging to confirm stone passage. Whether an initial X-ray KUB was performed to determine radio-opacity of the stone, was not determined as part of the study. Additionally, as only radiologist reported stone size was collected, one cannot exclude any influence from potential systematic differences (i.e., low-dose CT scanner underestimating stone size). Together these may consistently under/overestimate SSP. However, this is often the case in routine clinical practice upon which our pragmatic analysis is based. Concerns regarding heterogeneity stemming from various CT protocols may be somewhat mitigated, as a systematic review highlighted significant differences only for stones of <3 mm, which is smaller than the categorisation resolution of stone size for the nomogram (<5, 5–7, >7 mm) [27]. Next, the majority of patients included in this study had ureteric stones that were <5 mm and/or in the distal ureter, which limits generalisability to larger proximal stones. Lastly, in this analysis we did not evaluate time to SSP. This will be detailed in a separate report to help characterise the natural progression of stone passage and to provide guidance on time of intervention.

How to Best Utilise the Nomogram

This nomogram is an adjunctive tool developed to guide patient counselling on the predicted probability of SSP. It should not be used in isolation but as part of an overall

decision-making process involving multidisciplinary professionals. Interpretation of the nomogram output has to be taken in context of the following limitations; (i) it does not define probability thresholds to perform interventions; (ii) it does not provide estimations on time to SSP; (iii) it does not detail the opportunity cost (i.e., risk of complications from intervening or additional resource use) associated with treatment strategy at each prediction point; it has been developed and temporally validated on a dataset with cases only from the UK, Australia, Ireland and New Zealand. External validation in an independent population will be a future study.

Conclusion

This study presents a multivariable prediction model and nomogram for SSP in patients presenting with acute ureteric colic. Its use could allow clinicians and patients to make a more informed decision on pursuing conservative management vs early intervention at initial presentation. An on-line calculator is freely available for all clinicians to use via <https://www.bursturology.com/Studies/Mimic/Calculator/calculator/>.

Acknowledgement

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Disclosure of Interests

Benjamin W Lamb receives consulting fees from Digital Surgery Ltd, MDOutlook and East of England cancer alliance and receives speaker fees from Astra Zeneca. He is part of the Camprobe trial, Neurosafe Trial, trial management groups and is a Nuffield Health representative. Veeru Kasivisvanathan is an Academic Clinical Lecturer funded by the United Kingdom National Institute for Health Research (NIHR). Taimur T Shah sits on the CHRONOS trial, ATLANTA trial, MATTER Trial, PROSPECT Trial and PACIFIC Trial, trial management groups. All other authors have no conflicts of interests to disclose.

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Appendix A

PubMed Indexed Collaborators (BURST Collaborative MIMIC Study Group)

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Correspondence: Taimur Tariq Shah, Department of Urology Faculty Of Medicine, Imperial College London 5th Floor,

Charing Cross Hospital Fulham Palace Rd, London W6 8RF, UK.

e-mail: t.shah@imperial.ac.uk

Abbreviations: AIC, Akaike's information criterion; CRP, C-reactive protein; EAU, European Association of Urology; IQR, interquartile range; KUB, kidneys, ureters, and bladder; MET, medical expulsive therapy; MIMIC, A Multi-centre Cohort Study Evaluating the role of Inflammatory Markers In Patients Presenting with Acute Ureteric Colic; OR, odds ratio; RCT, randomised controlled trial; SSP, spontaneous stone passage; SUSPEND, Spontaneous Urinary Stone Passage Enabled by Drugs (trial); WBC, white blood cell.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary Tables and Figures.

Table S1. Table with percentage of missing values.

Table S2. Multivariable analysis corrected in development set.

Figure S1. Proportion of patients with SSP according to year of patient presentation.

Figure S2. Risk calculator interface (website version).

Figure S3. Decision curve analysis for SSP.