Development of a novel predictive model for a successful stone removal after flexible ureteroscopic lithotripsy based on ipsilateral renal function: a single-centre, retrospective cohort study in China

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ABSTRACT

Objectives The aims of this study were to investigate the effect of preoperative ipsilateral renal function on the success of kidney stone removal with flexible ureteroscopic lithotripsy and to develop a predictive model based on the results.

Design Retrospective cohort study.

Setting Data from the 2001–2012 period were collected from the electronic records of West China Hospital, Sichuan University.

Participants 576 patients who underwent flexible ureteroscopic lithotripsy were included in the study.

Primary outcome Stone-free rate (SFR) after the procedures.

Results In patients with suspected impaired kidney function, the overall SFR was 70.1%. Stone volume (OR 1.46; 95% CI 1.18 to 1.80), lower calyx stones (OR 1.80; 95% CI 1.22 to 2.65), age (OR 1.02; 95% CI 1.00 to 1.04), body mass index (OR 1.10; 95% CI 1.04 to 1.17) and estimated glomerular filtration rate of the affected kidney (OR 0.95; 95% CI 0.94 to 0.97) were identified as independent predictors of SFR. Lasso regression selected the same five predictors as those identified by univariate and multivariate logistic regression analyses, thus verifying our model. The mean area under the curve, based on 1000 iterations and 10-fold validation, was 0.715 (95% CI 0.714 to 0.716). The Hodges-Lehmann test and calibration curve analysis revealed no significant mismatch between the prediction model and the retrospective cohort.

Conclusion Ipsilateral renal function may be a novel independent risk factor for kidney stone removal with flexible ureteroscopic lithotripsy. A novel nomogram for predicting SFR that uses stone volume, lower calyx stones, age, body mass index and estimated glomerular filtration rate was developed, but remains to be externally validated.

INTRODUCTION

Kidney stone disease (KSD) is an increasingly prevalent and costly condition in the USA, affecting approximately 9% of the population. At present, extracorporeal shockwave lithotripsy, flexible ureteroscopy (fURS) lithotripsy and percutaneous nephrolithotomy are widely available as surgical treatment options for KSD. In the USA, the use of ureteroscopy combined with laser lithotripsy has risen over time. Although fURS is increasingly being used to treat KSD with low morbidity, residual fragments after fURS are of significant concern because they can significantly increase the risk of stone-related events and need for additional procedures. Many factors have been reported to affect the stone-free rate (SFR) after fURS, including size, number and location of stones. Studies of factors affecting SFR after fURS have mostly focused on stone load, stone location, abnormal anatomical structure and ureteral stricture; however, the driving force behind stone discharge has not been sufficiently considered. Together, glomerular filtration and tubule reabsorption constitute
the urination capacity of the kidney. Typically, when renal function is impaired and the glomerular filtration rate (GFR) is reduced, the urine production capacity of the kidney is also affected, leading to a decreased ability for the urine to wash away the residual stone, which further affects the efficiency of stone removal after fURS. However, at present, there is no discussion about renal function in relation to the stone clearance rate after fURS. Ipsilateral renal function can be accurately measured using nuclear medicine detection methods, such as renal imaging with single-photon emission CT. In this study, we analysed the effect of ipsilateral renal function on the stone clearance rate after fURS and constructed a clinical prediction model.

METHODOLOGY

Study design and participants
Data from patients who underwent fURS for renal stones were obtained from the database of the Department of Urology of West China Hospital, Sichuan University. Patients for whom information on the outcomes and predictors, described in the Outcomes and predictors section, was not available were excluded from the study. Patients with anatomical deformities of the kidney, such as a sponge kidney or a horseshoe kidney, were also excluded. Bilateral surgeries on the same patient were considered independently. There were 576 patients who met the criteria and were included in the study for further analysis.

Outcomes and predictors
In this study, stone-free (SF) status was based on kidney, ureter and bladder (KUB) X-rays performed approximately 4 weeks after treatment. ‘Stone free’ was defined as fragment sizes ≤2 mm because residual fragments >2 mm in size increase the risk of stone-related events and need for additional procedures. Research has shown that KUB is sufficient for evaluating SF status using a cut-off of residual components >2 mm. All KUB images were evaluated by two authors (YM, ZJ) according to standard procedures.

Potential factors affecting SFR were determined on the basis of a literature review and clinical experience. These factors were sex, age (years), body mass index (BMI; kg/m²), alcohol consumption (heavy drinker, defined as alcohol consumption ≥3 times/week), kidney side, GFR of the ipsilateral and contralateral kidney (mL/min), hypertension, diabetes, smoking, stone volume (cm³), stone location, ipsilateral hydronephrosis, and ureteral stricture history. The most crucial variable in the present study was GFR, which was measured by nuclear medicine studies. The preoperative stone volume was calculated based on Non-contrast CT (NCCT) using the following formula:

\[ \text{Volume} = \text{length} \times \text{width} \times \text{height} \times \frac{1}{6\pi}. \]

Statistical analysis
Based on the definition of SF above, patients were divided into SF and non-SF groups.

Normality of data distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as mean±SD and were compared between groups using t-test. Non-normally distributed data are presented as median with IQR and were compared between groups using Mann-Whitney test. Categorical variables are presented as numbers and percentages and were compared between groups using χ² or Fisher’s exact test.

Given that there were 29 variables included in this analysis and only 172 positive-end cases (ie, fragments >2 mm), the most useful predictive indicators were selected through the least absolute shrinkage and selection operator (lasso) regression, which is suitable for regression of high-dimensional data. As reported previously, the optimal λ for feature selection in lasso regression was identified by 10-fold cross-validation. The optimal λ was set via the minimum criteria and the minimum criteria—1 SE (‘1-SE criteria’). Univariate and multivariate logistic regression analyses were used to determine the effects of different variables on the outcome event. To ensure statistical power, only significant variables identified by univariate regression were included in the multivariate regression. After the effect of ipsilateral renal function on the SFR had been determined through logistic regression, the restricted cubic spline (RCS) method was used to further test the linear association between ipsilateral renal function and SFR. An RCS was plotted using the R package rms; 25%, 50% and 75% of GFR were chosen as fitting nodes, and reference points were determined using the univariate Youden index (YI).

All statistical analyses were performed using R V.3.6.2 (www.r-project.org). All reported p values are two-sided, with significance set at p<0.05.

Patient and public involvement
No patients or members of the public were involved in the design, conduct or reporting of this study. The study results were not disseminated to study participants.
RESULTS

According to the inclusion and exclusion criteria, of 2432 patients who underwent fURS for kidney stones at West China Hospital between 2001 and 2012, 1566 were excluded because they did not undergo a preoperative ipsilateral renal function test. A further 177 patients were excluded due to having anatomical deformities of the kidney or a history of ureteral stricture. Another 113 patients with other data missing were also excluded. Finally, 576 patients with preoperative nuclear medicine studies were included in the present study.

The characteristics of the patients included in this study are summarised in table 1. The SFR in this study was 70.1%. Postoperative fever, defined as a temperature >38°C within 72 hours after the procedure, occurred in 16 patients. No grade III or IV complications were observed.

The results of univariate and multivariate logistic regression analyses are presented in table 2. Stone volume (OR 1.46; 95% CI 1.18 to 1.80), lower calyx stones (OR 1.80; 95% CI 1.22 to 2.65), age (OR 1.02; 95% CI 1.00 to 1.04), BMI (OR 1.10; 95% CI 1.04 to 1.17) and GFR of the treated kidney (OR 0.95; 95% CI 0.94 to 0.97) were identified as independent predictors of SF status.

Tuning parameter ($\lambda$) selection in the lasso model using 10-fold validation is shown in figure 1A. A lasso coefficient profile of the included features with the primary $\lambda$ set to 100 is shown in figure 1B; the vertical line indicates the optimal $\lambda$ value ($\lambda=0.0416$, 1-SE criteria). The lasso regression selected the same five predictors as those determined in the univariate and multivariate logistic regression analyses, thus confirming the strength of the model based on logistic regression (online supplemental table 1).
Based on univariate logistic regression between the GFR of the treated kidney and the risk of stone removal failure, the YI was calculated and ranked. The largest YI was achieved when the cut-off GFR of the treated kidney was set at 49 mL/min. When the RCS was plotted using the set reference point of 49 mL/min (figure 2), a significant linear correlation was found between the GFR and the risk of stone removal failure ($\chi^2=24.30$, p<0.0001).

### Table 2 Factors associated with stone-free status after retrograde intrarenal surgery (RIRS) by univariate and stepwise multivariate logistics regression

<table>
<thead>
<tr>
<th>Patients without stone-free status</th>
<th>Univariate regression</th>
<th></th>
<th>Multivariate regression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>P value</td>
<td>Adjusted OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.907 (0.618 to 1.333)</td>
<td>0.621</td>
<td>–</td>
<td>0.651</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.030 (1.013 to 1.046)</td>
<td>&lt;0.001</td>
<td>1.018 (1.001 to 1.035)</td>
<td>0.039</td>
</tr>
<tr>
<td>BMI (per kg/m²)</td>
<td>1.091 (1.033 to 1.152)</td>
<td>0.002</td>
<td>1.100 (1.037 to 1.167)</td>
<td>0.002</td>
</tr>
<tr>
<td>Heavy drinker (yes)</td>
<td>1.359 (0.740 to 2.494)</td>
<td>0.322</td>
<td>–</td>
<td>0.346</td>
</tr>
<tr>
<td>Diabetes (yes)</td>
<td>1.389 (0.716 to 2.693)</td>
<td>0.331</td>
<td>–</td>
<td>0.833</td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td>1.341 (0.825 to 2.179)</td>
<td>0.237</td>
<td>–</td>
<td>0.979</td>
</tr>
<tr>
<td>Smoker (yes)</td>
<td>0.854 (0.581 to 1.255)</td>
<td>0.422</td>
<td>–</td>
<td>0.591</td>
</tr>
<tr>
<td>Previous upper urinary stone history (yes)</td>
<td>1.421 (0.845 to 2.389)</td>
<td>0.185</td>
<td>–</td>
<td>0.329</td>
</tr>
<tr>
<td>Treated side (left)</td>
<td>1.190 (0.832 to 1.704)</td>
<td>0.341</td>
<td>–</td>
<td>0.882</td>
</tr>
<tr>
<td>ESWL history within 12 months (yes)</td>
<td>0.516 (0.110 to 2.415)</td>
<td>0.401</td>
<td>–</td>
<td>0.798</td>
</tr>
<tr>
<td>GFR of treated kidney (per mL/min)</td>
<td>0.955 (0.939 to 0.971)</td>
<td>&lt;0.001</td>
<td>0.953 (0.936 to 0.970)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR of another kidney (per mL/min)</td>
<td>0.990 (0.978 to 1.002)</td>
<td>0.093</td>
<td>–</td>
<td>0.927</td>
</tr>
<tr>
<td>Ureteral access sheath (12 Fr/14 Fr)</td>
<td>0.901 (0.600 to 1.352)</td>
<td>0.615</td>
<td>–</td>
<td>0.433</td>
</tr>
<tr>
<td>Stone volume (per cm³)</td>
<td>1.414 (1.160 to 1.722)</td>
<td>0.001</td>
<td>1.458 (1.182 to 1.799)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Staghorn calculus (yes)</td>
<td>2.660 (1.311 to 5.397)</td>
<td>0.007</td>
<td>–</td>
<td>0.148</td>
</tr>
<tr>
<td>Largest stone diameter (per cm)</td>
<td>1.350 (1.054 to 1.729)</td>
<td>0.017</td>
<td>–</td>
<td>0.566</td>
</tr>
<tr>
<td>Number of stones</td>
<td>0.285</td>
<td>–</td>
<td>0.333</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; ESWL, extracorporeal shockwave lithotripsy; GFR, glomerular filtration rate.

**Figure 1** Lasso regression for candidate predictor selection. (A) A 10-fold cross-validation plot. Dotted line means the lambda values of best performance model and concise model. (B) Lasso coefficient profile of the included features. The vertical line was the optimal $\lambda$ value ($\lambda$=0.0416, 1-SE criteria). Lasso, least absolute shrinkage and selection operator.

**Figure 2** Restricted cubic spline (RCS) plot between glomerular filtration rate (GFR) and the OR for stone removal failure. Reference point: 49 mL/min.
This finding further supported the inclusion of lateral renal function as a continuous variable in the prediction model.

Subsequently, an SFR prediction model incorporating the five predictors (stone volume, lower calyx stones, age, BMI and GFR of the treated kidney) was built based on multivariate logistic regression and is shown as a nomogram in figure 3. The mean area under the curve was 0.715 (95% CI 0.714 to 0.716) based on 1000 iterations and 10-fold validation. The Hodges-Lehmann test ($\chi^2=8.73$, df=8, $p=0.3658$) and calibration curve (figure 4) revealed no significant mismatch between the prediction model and the retrospective cohort.

DISCUSSION

In this study, we found the GFR of the treated kidney to be a novel factor for predicting SF status after fURS. Based on this novel independent predictive factor, we developed a new nomogram for the prediction of SFR status in patients with KSD treated with fURS. This new nomogram, based on five variables (age, BMI, stone volume, GFR of the treated kidney and lower calyx stones), facilitated individualised preoperative prediction of residual fragments >2 mm at approximately 4 weeks after treatment.

Based on KUB X-rays conducted approximately 4 weeks after the treatment of patients with suspected kidney function impairment, the SFR (fragment size <2 mm) in this study was 70.1%. Ghani et al \cite{ghani2019} systematically reviewed studies that reported the SFR following fURS for KSD and found interstudy variation due to the different definitions and imaging methods used, as well as differences in time points. The most common definitions of SF are fragments <2 mm and fragments <4 mm. In this study, we defined SF as fragments <2 mm. The first reason for using this definition is that our hospital routinely uses KUB to detect residual fragments after fURS, which is sufficient for evaluating SF status when residual fragments are >2 mm. The second reason is that the risk of stone-related events and additional procedures increases with residual fragments >2 mm in size. \cite{ghani2019} The time point at which patients in this study underwent KUB after fURS was short (approximately 4 weeks after treatment), and this may have led to a lower SFR because most of the fragments were small enough to spontaneously pass through our dusting technique. Furthermore, preoperative nuclear medicine studies of renal function are not routinely required in West China Hospital, and doctors usually perform renal function scans only when stones are suspected to have caused renal damage. This practice may also explain, in part, the low rate of stone removal in this cohort.

Consistent with the literature, \cite{ghani2019, zhao2018} a lower pole location of stones was one of the independent predictors of SFR in this study. A lower pole location limits access to stones. Furthermore, the laser fibre used in fURS can result in a 10°–15° loss of deflecting ability. \cite{zhao2018} To reduce surgical difficulty and increase SFR, \cite{ghani2019} a basket displacement technique was routinely performed to remove lower-pole stones in other calyces in our patients. Performing a retrograde pyelogram is not a typical perioperative practice in our hospital; therefore, the influence of the infundibulopelvic angle could not be thoroughly evaluated in this study. However, the effect of renal anatomy on the SFR after fURS has not yet been definitively established. \cite{zhao2018, zhao2018b, zhao2018c} A recent prospective study with CT follow-up also reported that renal stone features are more critical than renal anatomy in predicting the outcomes of shockwave lithotripsy. \cite{zhao2018}

Stone volume ($\text{length} \times \text{width} \times \text{height} \times 1/6\pi$) based on NCCT was another independent predictor associated with SFR in our cohort. This finding is consistent with those of previous reports. \cite{ghani2019, zhao2018, zhao2018b, zhao2018c} A large stone burden contributes to a prolonged operating time, which can lead to an increased risk of sepsis. However, when the operating time is restricted, the SFR is lower among patients with larger stone burden. In the present study, a 14 Fr/16 Fr UAS was used in most patients to maintain lower intrarenal pressure, which allowed the operating time to be prolonged, thereby increasing the SFR. Furthermore, the
use of a 14 Fr/16 Fr UAS also improved the efficacy of basking fragments.

Age, BMI and GFR were identified as new independent predictors of SFR status after UIRS. KSD has been reported to be associated with an increased risk of loss of kidney function.\textsuperscript{21, 22} Moderate physical activity helps promote the expulsion of stone fragments. Therefore, for older patients and those with a higher BMI, who may be less physically active, the SFR is lower. Patients in our study were told to follow the American Urological Association guideline, which recommends that patients increase their water intake after IURS to reach a daily urine volume of 2.5 L/day to achieve optimal stone clearance.\textsuperscript{23}

We speculate that the amount of urine produced by kidneys with impaired function is reduced, which in turn decreases the efficacy of flushing stones out in the urine. In addition, patients with kidney stones with a decreased GFR may also have an extended history of KSD, have undergone repeated KSD surgery and have greater stone burden. However, these new factors require further investigation in other cohorts.

This study has several limitations. First, this was a retrospective study with expected biases. Second, all patients included were operated on by the same surgeon, which may have also introduced some bias. Third, due to limitations imposed by the retrospective study design, it was difficult to collect information on many vital variables, such as other surgical history related to kidney stones and postoperative eating habits. Therefore, the conclusions of this study need to be treated with caution. Fourth, although all patients underwent stone composition analysis, these data were held by another team at the Department of Urology, West China Hospital, and we did not have permission to use these data; consequently, this information is not presented in this study. Fifth, the use of KUB and CT to evaluate SFR is still associated with many problems. Although some studies support the accuracy of KUB for stone detection >2 mm, the potential for measurement bias is worth noting. KUB measurements are also affected by BMI and stone opacity. Although KUB evaluation is clinically relevant, the limited accuracy of KUB in evaluating residual fragments needs to be addressed.

In conclusion, this study found that ipsilateral renal function may be a novel independent risk factor for kidney stone removal using URS lithotripsy. A novel nomogram for predicting SFR status using stone volume, lower calyx stones, age, BMI and GFR was developed and internally validated in our retrospective cohort using a 10-fold validation method. This predictive model still lacks external cohort validation and we look forward to checking its performance using other data sources.

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Contributors Study concept and design: YM, ZJ, K-JW. Acquisition of data: YM, ZJ. Analysis and interpretation of data: YM, ZJ, LX. Drafting of the manuscript: YM, ZJ. Critical revision of the manuscript for important intellectual content: LZ, DL.

Statistical analysis: YM. ZJ. Administrative, technical or material support: LX, LZ, XJ, K-JW. Supervision: K-JW, HL. Guarantor: K-JW

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the West China Hospital of Sichuan University Medical Research Ethics Committee (202000508). According to local policy, informed consent is not required in a retrospective research.

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Data availability statement Data are available upon reasonable request.

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