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# A novel predicting model for stone removal after flexible ureteroscopic lithotripsy based on Ipsilateral renal function: A retrospective analysis.

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**Title**：A novel predicting model for stone removal after flexible ureteroscopic lithotripsy based on Ipsilateral renal function: A retrospective analysis.

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**Abstract**

**Objective:** To introduce a convenient model for predicting the stone removing success after flexible ureteroscopic lithotripsy based on easily accessible clinical information.

**Design** Retrospectively designed cohort study of data collected in West China hospital.

**Setting** Cohort study. Data were mainly analyzed by using multivariate regression.

**Participants** Patients received fURS between 2012 and 2018 for kidney stones were screened. A total of 855 patients in our center underwent both preoperative SPECT renal scan and fURS. After the screening according to the inclusion and exclusion criteria, a total of 576 patients were finally enrolled.

**Main outcome measures** Odds ratio (OR) for included variables

**Results:** After the screening, 576 patients were finally enrolled in retrospective analysis. In patients whose kidney function were suspected to be impaired, the overall SFR was 70.1%. Stone volume (OR=1.46, 95%CI 1.18-1.80), lower calyx stone (OR=1.80, 95%CI 1.22-2.65), age (OR=1.02, 95%CI 1.00-1.04), BMI (OR=1.10, 95%CI 1.04-1.17), and GFR (OR=0.95, 95%CI 0.94-0.97) were identified as independent predictors. LASSO regression selected five predictors the same as univariate and multivariate logistic regression analyses, thus consolidating our model. The mean AUC was (AUC = 0.715, 95%CI: 0.714-0.716) based on 10000 times 10-fold validation. Hodges-Lehmann test and calibration curve revealed that there was no significant mismatch between the prediction model and the retrospective cohort.

**Conclusion:** Ipsilateral renal function might be a novel independent risk factor for kidney stone removal for flexible ureteroscopic lithotripsy. A novel nomogram for SFR prediction using stone volume, lower calyx stone, age, BMI, and the GFR was developed.

**Strengths and limitations of this study**

1. We used almost all available data from a large hospital and analyzed it using two types of regression models. Our findings have statistical and clinical significance.

2. There are several limitations in this study. Firstly, this was a retrospectively designed study with inevitable biases. Secondly, all patients included were operated by the same surgeon, this also brings selection bias.

3. Conclusion of this analysis should be interpreted with caution and further validation was needed.

## Introduction

Kidney stone disease (KSD) is an increasingly prevalent and costly condition in the United States, affecting approximately 9% of the population[1, 2]. At present, extracorporeal shockwave lithotripsy (SWL), flexible ureteroscopy (fURS) lithotripsy, and percutaneous nephrolithotomy (PCNL) are widely available surgical treatment options for KSD. In the USA, the use of ureteroscopy (URS) combined laser lithotripsy was reported increasing over time [3]. Though fURS is increasingly being used to treat KSD with a low morbidity 4, residual fragments after fURS are a significant concern because it can significantly increase the risk of stone-related events and additional procedures [4].

At present, there are several clinically based scores for predicting the stone-free rate (SFR) after fURS treatment of KSD. Rescorlu et al. reported a Resorlu-Unsal Stone Score (RUSS) based on a retrospective analysis of 207 patients [5]. Jung et al. developed a scoring system incorporating 88 patients called modified Seoul National University Renal Stone Complexity (S-ReSC) score [6]. Although both score systems' sample size was relatively small, external validation and evaluation were done in other larger cohorts [7, 8].

Another model (Ito score) without renal anatomy factors reported by Ito et al. showed a reliable prediction based on characteristics including stone volume, lower pole calculi, operator experience, hydronephrosis, and the number of stones [9]. The role of renal anatomy on SFR after fURS is not well concluded yet [10-12]. A recent prospective study with CT follow-up also reported that renal stone features are more critical than renal anatomy to predict SWL outcomes [13]. Besides, renal anatomy information, including infundibulopelvic angle (IPA), needs to be measured on pyelogram [14], which is not routinely performed in our center.

Therefore, we aimed to derive and internally validate a predicting model without renal anatomy factors to evaluate SFR after fURS for KSD in one large cohort of patients.

## Methods

### Study design and participants

This study was approved by local health ethics at west china hospital and was retrospectively designed. Patients received fURS between 2012 and 2018 for kidney stones were screened. Those without information on outcomes and predictors described below were excluded. Besides, patients with kidney anatomical deformities such as sponge kidney and horseshoe kidney were also excluded. Bilateral surgeries of the same patient were considered independently. A total of 855 patients in our center underwent both preoperative SPECT renal scan and fURS. After the screening according to the above conditions, a total of 576 patients were finally enrolled.

### Outcomes and predictors

Based on kidneys-ureters-bladder X-ray (KUB) at approximately four weeks after treatment, stone-free (SF) was defined as size ≤ 2mm because residual fragments >2 mm increases the risk of stone-related events and additional procedures [4]. Besides, KUB is enough to evaluate SF when residual components> 2mm compared with non-contrast computed tomography (NCCT) [15].

We included the potential factors through literature review and clinical experience. These factors were described as follows: gender, age (year-old), body mass index (BMI, kg/m$^2$), kidney side, glomerular filtration rate of the ipsilateral kidney (GFR, ml/min), GFR of the contralateral kidney (ml/min), hypertension, diabetes mellitus (DM), smoking, alcohol consumption, stone volume (cm$^3$), stone location, and ureteral stricture history. Preoperative stone volume was calculated based on NCCT with formula: volume=length*width*height *1/6*π [16]. In this study, the most important variable is GFR and it was measured by nuclear medicine tests [17].

## Surgical techniques

Surgical techniques have been described in our previous study [18, 19]. Briefly, a double-J stent was generally placed approximately two weeks before surgery in our institute because it was reported associated with higher SFR [20]. Because of this, 14/16 Fr ureteral access sheaths (UAS) could be used among most of our patients to reduce the intrarenal pressure, which will also help facilitate stone extraction without compromising ureteral injury. fURS with holmium laser lithotripsy were performed with active basket retrieval of fragments, followed by the dusting technique. If the stone is located in the lower pole, basket displacement would decrease the surgical difficulty, which was also associated with the increased SFR[4]. All patients were stented postoperatively for about two weeks. Tamsulosin was routinely used to reduce the related symptoms during this period.

**Statistical analysis**

Based on the definition described above, patients were classified as SF and none-SF (NSF) groups. If the continuous variables were normality distribution examined by the Kolmogorov-Smirnov test, they were presented with the mean (standard deviation, SD). Otherwise, the median (interquartile range, IQR) was applied. T-test and Mann–Whitney test was used to testing for continuous variables with normally distributed and non-normally distributed, respectively. Categorical variables were presented with the number (percentage) and tested by Chi-square test or the Fisher's exact test.

Given that there were 29 variables enrolled in this analysis and only 172 positive-end cases (fragments > 2mm), the most useful predictive indicators were selected through the least absolute shrinkage and selection operator (LASSO) regression [21], which is fit for the regression of high-dimensional data. As previously reported [22], the optimal λ for feature choosing in the LASSO regression was identified by the 10-fold method. Optimal λ was set via the minimum criteria and the minimum criteria' 1 standard error (the 1-SE criteria).

Based on the multivariable logistic analysis, all of the identified significant ($P < 0.05$) clinical candidate predictors were pooled into a clinical prediction nomogram. The mean area under the curve (AUC) was used to assess the model's discriminative performance, calculated by using 10-fold cross-validation. A calibration curve was plotted based on 10000 times bootstrap resampling, accompanied by the Hosmer-Lemeshow test.



All statistical analyses above were achieved through R v.3.6.2 (www.r-project.org).

## Results

According to the inclusion and exclusion criteria, out of 2432 patients, 1566 patients were excluded because they did not receive preoperative ipsilateral renal function test. 177 cases were excluded for deformities or with history of ureteral stricture. 123 patients were removed because any other data were missing. 576 patients with preoperative nuclear medicine tests were finally included in this study. Patient characteristics were summarized in Table 1, and the SFR in our study was 70.1%. The results of univariate and multivariate logistic regression analyses were demonstrated in Table 2. Stone volume (OR=1.46, 95%CI 1.18-1.80), lower calyx stone (OR=1.80, 95%CI 1.22-2.65), age (OR=1.02, 95%CI 1.00-1.04), BMI (OR=1.10, 95%CI 1.04-1.17), and GFR of the treated kidney (OR=0.95, 95%CI 0.94-0.97), were identified as independent predictors.

The tuning parameter (λ) selection in the LASSO model used 10-fold validation was shown in Figure 1A. When the primary λ was set as 100, a LASSO coefficient profile of included features was plotted as Figure 1B, and the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria). In conclusion, LASSO regression selected the same five predictors described above, thus strengthening the model based on logistic regression (Supplementary Table 1).

A subsequent SFR predicting model incorporating these five predictors was built based on multivariate logistic regression and shown as a nomogram (Figure 2). The mean AUC was 0.715 (95%CI: 0.714-0.716) based on 10000 times10-fold validation. Hodges-Lehmann test (Chi-square = 8.73， DF = 8, P = 0.3658) and calibration curve (Figure 3) revealed that there was no significant mismatch between the prediction model and the retrospective cohort.

## Discussion

This study developed a new, clinically based nomogram for SFR in patients with KSD treated with fURS therapy. The new Nomogram, based on the five variables; age, BMI, stone volume, GFR of the treated kidney, and lower calyx stone, facilitated the individualized preoperative prediction of residual fragments > 2mm at approximately four weeks after treatment.

SFR (fragment size < 2mm) in our study was 70.1% based on KUB at approximately four weeks after treatment for patients whose kidney function were suspected to be impaired before operation. Ghani et al. systematically reviewed the SFR following fURS for KSD and reported that variations exist in the published studies because of the different definitions, imaging methods used, and time point[4]. No of fragments size < 2mm, and fragments < 4mm were the most common definitions. We choose fragments size < 2mm as the SFR definition mainly by referring to the following two aspects: On the one hand, KUB was routinely used to detect residual fragments after fURS in our center. NCCT was recommended if endoscopic evaluation showed no fragments or residual fragments between 0-2 mm, while KUB is enough to evaluate SFR when residual fragments > 2mm [15]. On the other hand, residual fragments >2 mm increases the risk of stone-related events and additional procedures [4]. The time point at which patients were undergoing KUB was relatively short (approximately four weeks after treatment) might lead to a lower evaluated SFR because most of the fragments were pieced small enough to pass spontaneously through our dusting technique. At the same time, in our center, the preoperative nuclear medicine test of renal function is not a routinely required item. That is to say, doctors usually perform renal function scans when they suspect that stones may have caused renal damage. This may also partly explain the low rate of stone removal in this cohort.

Paralleling the literature [4, 10], lower pole location was one of the independent predictors in our series. The scope of access to stone would be limited by lower-pole location. Additionally, the laser fiber would result in 10-15°

loss of deflecting ability in fURS use [23]. To decrease the surgical difficulty and increase the SFR[4], a basket displacement technique would be performed to remove lower-pole stones to other calyxes, routinely performed in our study. Retrograde pyelogram is not typical perioperative practice in our center. The influence of IPA could not be thoroughly evaluated in this study. However, the role of renal anatomy on SFR after fURS is not well concluded yet [10-12]. A recent prospective study with CT follow-up also reported that renal stone features are more critical than renal anatomy to predict SWL outcomes [13].

Stone volume (length*width*height *1/6*π [16]) based on NCCT was another independent predictor associated with SFR in our cohort. This finding was consistent with previously reported studies[4, 10, 24, 25]. Stone burden contributed to the prolonged operating times, leading to an increased risk of sepsis. Therefore, SFR among larger stone burden patients would be lower due to the limited operating times. In our study, 14/16Fr UAS was used in most patients to maintain lower intrarenal pressures, then prolonging the operating time, thereby increasing the SFR. Besides, 14/16Fr UAS was a benefit to improve the efficacy of basketing fragments.

Age, BMI, and GFR were found to be new independent predictors for SFR after fURS. It was reported that KSD was associated with increased risks of kidney function loss [26, 27]. To our knowledge, moderate physical activities helped promote the expulsion of stone fragments. Patients with older age and higher BMI might be associated with decreased physical activity, leading to a lower SFR. Patients were told to follow the AUA guideline, which recommended that patients increase the amount of water supply after fURS to reach a daily urine volume of 2.5 L/d to get the optimal SFR [28].

On the one hand, we speculated that the amount of urine produced by impaired kidneys would be reduced, and the urine-flushing efficacy on this side will be weakened. On the other hand, stone patients accompanied by deceased GFR might be associated with a more extended history of KSD, repeated KSD surgery, and stone burden. However, these new factors should be further studied in other cohorts.

There are several limitations in this study. Firstly, this was a retrospectively designed study with inevitable biases. Secondly, all patients included were operated by the same surgeon, this also brings selection bias.

## Conclusion

Ipsilateral renal function might be a novel independent risk factor for kidney stone removal for flexible ureteroscopic lithotripsy. A novel nomogram for predicting SFR using stone volume, lower calyx stone, age, BMI, and the GFR was developed and validated with a 10-fold validation method in our retrospective cohort.

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**Competing interests** None declared

**Patient consent for publication** Not required

**Ethics approval** The study was approved by the West China Hospital of Sichuan University Medical Research Ethics Committee (20200508).

**Data sharing statement** All data used in this analysis can be obtained by contacting the corresponding author.

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

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## Figure legends

Figure 1. LASSO regression for candidate predictor selection. 1A. 10-fold cross-validation plot, dotted line means lambda values of best performance model and concise model. 1B. LASSO coefficient profile of included features, the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria).

Figure 2. Nomogram based on the significant predictors selected by multivariate logistic regression model.

Figure 3. Calibration plot of nomogram based on the bootstrap method.

Table 1 Baseline characteristics of the SF and NSF groups. BMI: Body mass index; ESWL: Extracorporeal shock wave lithotripsy; GFR: glomerular filtration rate. *: T-test and Mann–Whitney test was used for continuous variables with normally distributed and non-normally distributed, respectively. Categorical variables were tested by $\chi^2$ test or the Fisher's exact test if the requirements for the $\chi^2$ test were not satisfied.

| Variables | N(%), median(IQR) or mean±SD (n=576) | NSF group (n=172, 29.9%) | SF group (n=404, 70.1%) | P* |
|---|---|---|---|---|
| Gender (Female, n, %) | 186 (32.3) | 53 (30.8) | 133 (32.9) | 0.621 |
| Age (years) | 49 (40, 57) | 51 (42, 60) | 48 (39, 58) | **0.001** |
| Plateau people (Yes, n, %) | 39 (6.8) | 9 (5.2) | 30 (7.4) | 0.340 |
| BMI (kg/m2) | 23.92±3.31 | 24.59±3.77 | 23.64±3.07 | **0.001** |
| Heavy drinker (Yes, n, %) | 50 (8.7) | 18 (10.5) | 32 (7.9) | 0.322 |
| Diabetes (Yes, n, %) | 41 (7.1) | 15 (8.7) | 26 (6.4) | 0.331 |
| Hypertension (Yes, n, %) | 85 (14.8) | 30 (17.4) | 55 (13.6) | 0.237 |
| Smoker (Yes, n, %) | 188 (32.6) | 52 (30.2) | 136 (33.7) | 0.422 |
| Chronic kidney disease history (Yes, n, %) | 4 (0.7) | 1 (0.6) | 3 (0.7) | 0.832 |
| Previous upper urinary stone history (Yes, n, %) | 71 (12.3) | 26 (15.1) | 45 (11.1) | 0.185 |
| Treated side (left, n, %) | 304 (52.8) | 96 (55.8) | 208 (51.5) | 0.341 |
| ESWL history within 12-month (Yes, n, %) | 11 (1.9) | 2 (1.2) | 9 (2.2) | 0.401 |

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|---|---|---|---|---|
| GFR of treated kidney (ml/min) | 38 (31, 47) | 35 (28, 42) | 39.8 (32, 48.4) | **<0.001** |
| GFR of another kidney (ml/min) | 40.9 (32.7, 48.8) | 40 (30.7, 47.4) | 41.1 (33.3, 49.3) | 0.072 |
| Preoperative urinary tract infection (Yes, n, %) | 129 (22.4) | 42 (24.4) | 87 (21.5) | 0.448 |
| Ureteral Access Sheath (12/14F, n, %) | 19 (3.3) | 4 (2.4) | 15 (3.7) | 0.615 |
| Stone volume ($cm^3$) | 0.73 (0.42, 1.23) | 0.99 (0.49, 1.57) | 0.67 (0.39, 1.16) | **<0.001** |
| Staghorn calculus (Yes, n, %) | 33 (5.7) | 17 (9.9) | 16 (4.0) | **0.007** |
| Largest stone diameter (cm) | 1.46 (1.05, 1.90) | 1.58 (1.20, 2.00) | 1.40 (1.00, 1.80) | **<0.001** |
| Stone number (n, %) | | | | 0.285 |
| One | 213 (37.0) | 60 (34.9) | 153 (37.9) | |
| Two | 159 (27.6) | 48 (27.9) | 111 (27.5) | |
| Three | 79 (13.7) | 18 (10.5) | 61 (15.1) | |
| Four | 40 (6.9) | 15 (8.7) | 25 (6.2) | |
| More or equal to five | 85 (14.8) | 31 (18.0) | 54 (13.4) | |
| Lower calyx stone (Yes, n, %) | 232 (40.3) | 83 (48.3) | 149 (36.9) | **0.011** |
| Multiple stone (Yes, n, %) | 288 (50) | 94 (54.7) | 194 (48.0) | 0.146 |
| Ipsilateral hydronephrosis (Yes, n, %) | 393 (68.2) | 118 (68.6) | 275 (68.1) | 0.900 |
| Postoperative infection (Yes, n%) | 15 (2.6) | 5 (2.9) | 10 (2.5) | 0.766 |

Table 2. Factors associated with stone-free status after RIRS by univariate and stepwise multivariate logistics regression. BMI = Body mass index; ESWL= Extracorporeal shock wave lithotripsy; GFR = glomerular filtration rate; OR =Odds ratio.

| | Patient without stone-free status | | | |
|---|---|---|---|---|
| | **Univariate regression** | | **Multivariate regression** | |
| | Crude OR (95% CI) | ***P*-value** | Adjusted OR (95% CI) | ***P*-value** |
| Gender (Female) | 0.907 (0.618, 1.333) | 0.621 | / | 0.651 |
| Age (per year) | 1.030 (1.013, 1.046) | **<0.001** | 1.018 (1.001, 1.035) | **0.039** |
| Plateau people (Yes) | 0.688 (0.320, 1.483) | 0.340 | / | 0.488 |
| BMI (per kg/m2) | 1.091 (1.033, 1.152) | **0.002** | 1.100 (1.037, 1.167) | **0.002** |
| Heavy drinker (Yes) | 1.359 (0.740, 2.494) | 0.322 | / | 0.346 |
| Diabetes (Yes) | 1.389 (0.716, 2.693) | 0.331 | / | 0.833 |
| Hypertension (Yes) | 1.341 (0.825, 2.179) | 0.237 | / | 0.979 |
| Smoker (Yes) | 0.854 (0.581, 1.255) | 0.422 | / | 0.591 |
| Chronic kidney disease history (Yes) | 0.782 (0.081, 7.568) | 0.832 | / | 0.934 |
| Previous upper urinary stone history (Yes) | 1.421 (0.845, 2.389) | 0.185 | / | 0.329 |
| Treated side (left) | 1.190 (0.832, 1.704) | 0.341 | / | 0.882 |
| ESWL history within 12-month (Yes) | 0.516 (0.110, 2.415) | 0.401 | / | 0.798 |
| GFR of treated kidney (per ml/min) | 0.955 (0.939, 0.971) | **<0.001** | 0.953 (0.936, 0.970) | **<0.001** |
| GFR of another kidney (per ml/min) | 0.990 (0.978, 1.002) | 0.093 | / | 0.927 |
| Preoperative urinary tract infection (Yes) | 1.177 (0.773, 1.794) | 0.448 | / | 0.752 |
| Ureteral Access Sheath (12/14F) | 0.901 (0.600, 1.352) | 0.615 | / | 0.433 |
| Stone volume (per cm3) | 1.414 (1.160, 1.722) | **0.001** | 1.458 (1.182, 1.799) | **<0.001** |
| Staghorn calculus (Yes) | 2.660 (1.311, 5.397) | **0.007** | / | 0.148 |
| Largest stone diameter (per cm) | 1.350 (1.054, 1.729) | **0.017** | / | 0.566 |
| Stone number | | 0.285 | / | 0.333 |

| | | | | |
|---|---|---|---|---|
| One | Ref. | / | / | |
| Two | 1.103 (0.702, 1.732) | 0.161 | / | |
| Three | 0.752 (0.411, 1.377) | 0.318 | / | |
| Four | 1.530 (0.755, 3.101) | 0.057 | / | |
| More or equal to five | 1.464 (0.859, 2.495) | **0.911** | / | |
| Lower calyx stone (Yes) | 1.596 (1.112, 2.290) | 0.011 | 1.802 (1.223, 2.654) | **0.003** |
| Multiple stones (Yes) | 1.305 (0.912, 1.866) | 0.146 | / | 0.548 |
| Ipsilateral hydronephrosis (Yes) | 1.025 (0.698, 1.505) | 0.900 | / | 0.650 |
| Postoperative infection (Yes) | 1.180 (0.397, 3.504) | 0.766 | / | 0.780 |

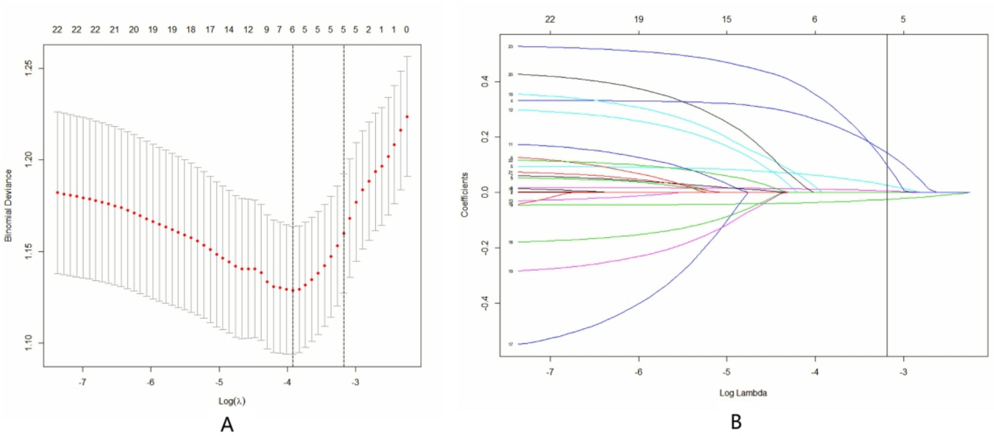



Figure 1. LASSO regression for candidate predictor selection. 1A. 10-fold cross-validation plot, dotted line means lambda values of best performance model and concise model. 1B. LASSO coefficient profile of included features, the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria).

524x228mm (300 x 300 DPI)

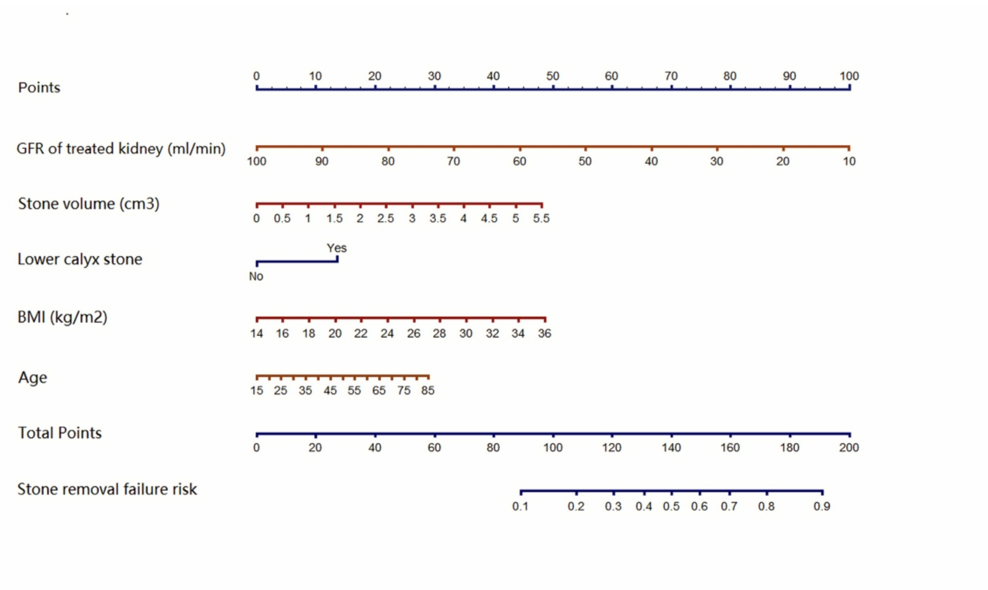



Figure 2. Nomogram based on the significant predictors selected by multivariate logistic regression model.

385x228mm (300 x 300 DPI)

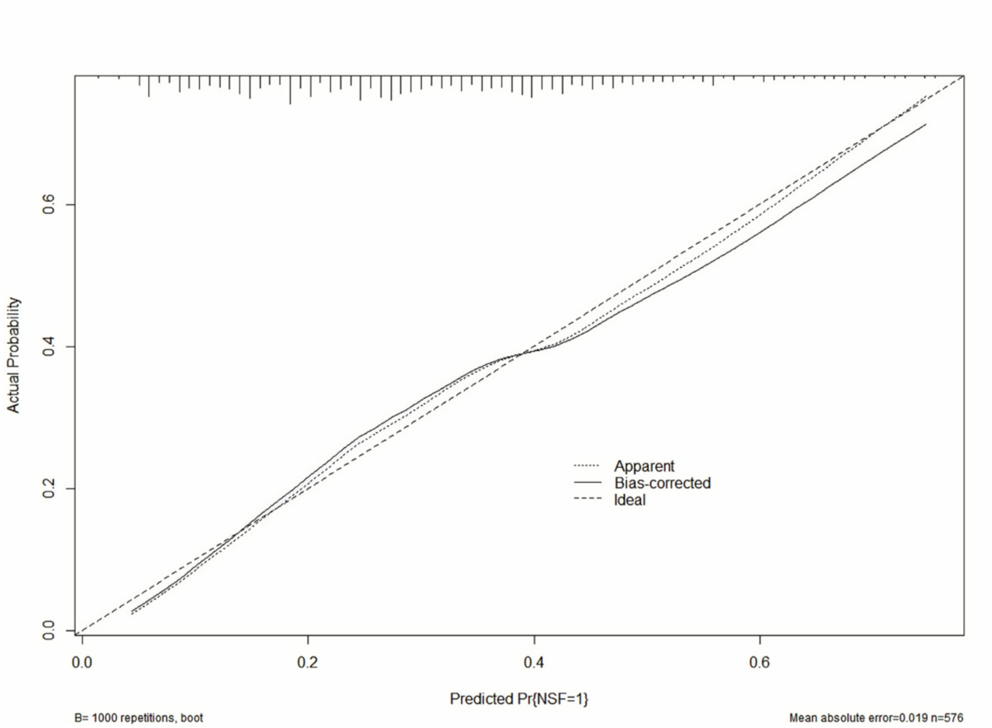



Figure 2. Nomogram based on the significant predictors selected by multivariate logistic regression model.

315x228mm (300 x 300 DPI)

## STROBE Statement—checklist of items that should be included in reports of observational studies

| Section/item | Item No | Recommendation | Reported on Page Number/Line Number | Reported on Section/Paragraph |
|---|---|---|---|---|
| **Title and abstract** | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | | |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | | |
| **Introduction** | | | | |
| Background/ rationale | 2 | Explain the scientific background and rationale for the investigation being reported | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | | |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | | |
| Participants | 6 | (a) ***Cohort study***—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>***Case-control study***—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants | | |
| | | (b) ***Cohort study***—For matched studies, give matching criteria and number of exposed and unexposed<br>***Case-control study***—For matched studies, give matching criteria and the number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | | |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | | |
| Bias | 9 | Describe any efforts to address potential sources of bias | | |
| Study size | 10 | Explain how the study size was arrived at | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | | |

| | | | |
|---|---|---|---|
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | |
| | | (b) Describe any methods used to examine subgroups and interactions | |
| | | (c) Explain how missing data were addressed | |
| | | (d) ***Cohort study***—If applicable, explain how loss to follow-up was addressed<br>***Case-control study***—If applicable, explain how matching of cases and controls was addressed<br>***Cross-sectional study***—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (e) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) ***Cohort study***—Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | ***Cohort study***—Report numbers of outcome events or summary measures over time | |
| | | ***Case-control study***—Report numbers in each exposure category, or summary measures of exposure | |
| | | ***Cross-sectional study***—Report numbers of outcome events or summary measures | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (b) Report category boundaries when continuous variables were categorized | |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | |

| | | | |
|---|---|---|---|
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | |

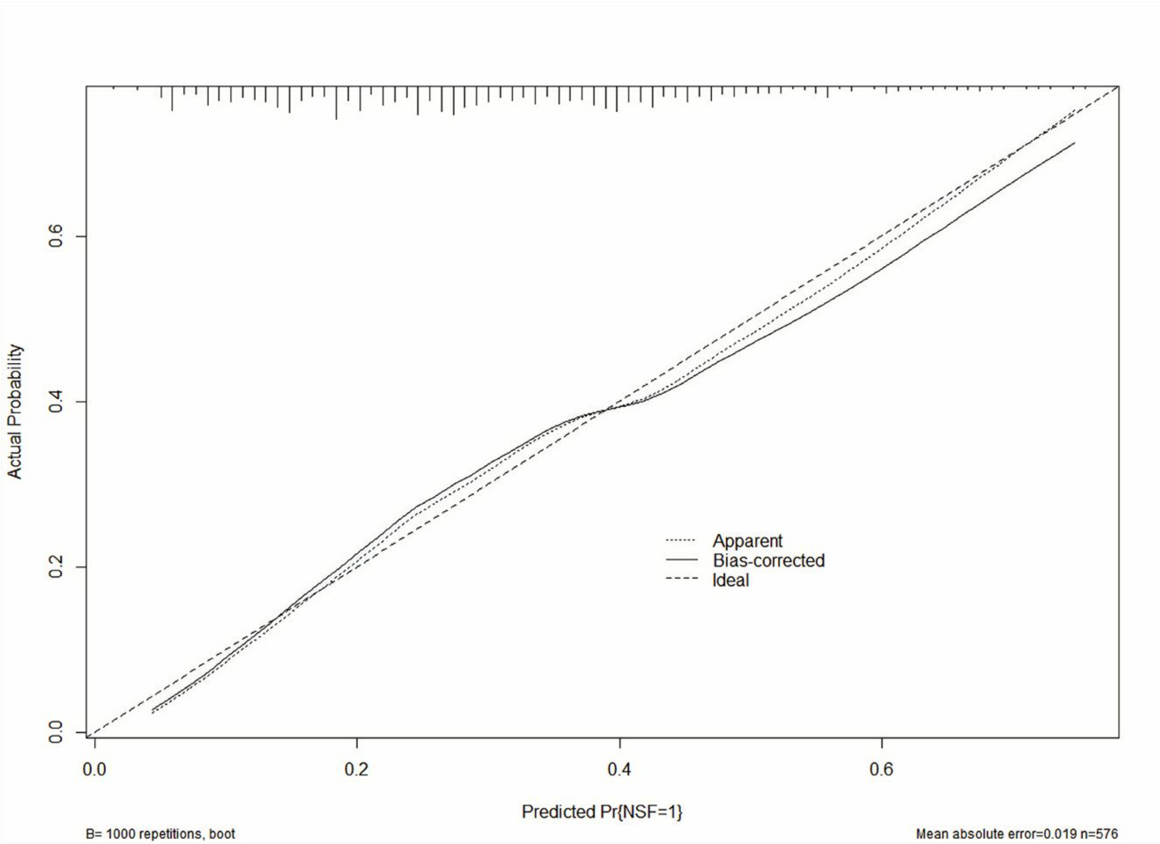
*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplementary Table 1. Variables identified according to the leave-one cross validation LASSO regression and stepwise multivariate logistics regression. The 1-SE criteria were chosen to build a concise model. LASSO: Least absolute shrinkage and selection operator regression; GFR: glomerular filtration rate; BMI: Body mass index.

| Variables identified by LASSO | Intercept | GFR of treated kidney (ml/min) | Stone volume (cm3) | BMI (kg/m2) | Age (years) | Lower calyx stone (Yes) |
|---|---|---|---|---|---|---|
| LASSO coefficients (λ=0.0416) | -0.887 | -0.025 | 0.141 | 0.025 | 0.005 | 0.095 |
| Logistics coefficients | -2.854 | -0.048 | 0.377 | 0.095 | 0.018 | 0.589 |

Supplementary Figure 1. Calibration plot of nomogram based on the bootstrap method.


Actual Probability
0.0
0.2
0.4
0.6
Predicted Pr{NSF=1}
Apparent
Bias-corrected
Ideal
B= 1000 repetitions, boot
Mean absolute error=0.019 n=576

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

| | |
|---|---|
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| | |

SCHOLARONE™ Manuscripts

**Title：** Development of a novel predictive model for the success of stone removal after flexible ureteroscopic lithotripsy based on ipsilateral renal function: a singe-centre, retrospective cohort study in China

**Authors:**

Yu-cheng Ma[1], Zhong-Yu Jian[1], Liyuan Xiang, Liang Zhou, Xi Jin， Deyi Luo, Hong Li, Kun-Jie Wang.

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**Keywords:** Stone-free Status; Flexible Ureteroscopic lithotripsy; Risk Factors.

**Abstract word count:** 255

**Manuscript word count:** 2383

**Number of figures:** 4

**Number of tables:** 2

**Abstract**

**Objectives:** The objective of this study was to investigate the effect of preoperative ipsilateral renal function on stone removing success for flexible ureteroscopic lithotripsy and develop a predictive model based on it.

**Methods:** A retrospective cohort of kidney stone patients in West China Hospital were screened. The predictive indicators from demographic factors, clinical characteristics, and imaging features were obtained through the least absolute shrinkage and selection operator (LASSO) regression. Univariate and multivariate logistic regression were also applied to select independent predicting factors. Then the prediction model was also derived using multivariate logistic regression. Calibration, discrimination, and clinical usefulness of the Nomogram were evaluated.

**Results:** After the screening, 576 patients were finally enrolled in retrospective analysis. In patients whose kidney function were suspected to be impaired, the overall SFR was 70.1%. Stone volume (OR=1.46, 95%CI 1.18-1.80), lower calyx stone (OR=1.80, 95%CI 1.22-2.65), age (OR=1.02, 95%CI 1.00-1.04), BMI (OR=1.10, 95%CI 1.04-1.17), and eGFR of the affected kidney (OR=0.95, 95%CI 0.94-0.97) were identified as independent predictors. LASSO regression selected five predictors the same as univariate and multivariate logistic regression analyses, thus consolidating our model. The mean AUC was

(AUC = 0.715, 95%CI: 0.714-0.716) based on 10000 times 10-fold validation. Hodges-Lehmann test and calibration curve revealed that there was no significant mismatch between the prediction model and the retrospective cohort.

**Conclusion:** Ipsilateral renal function might be a novel independent risk factor for kidney stone removal for flexible ureteroscopic lithotripsy. A novel nomogram for SFR prediction using stone volume, lower calyx stone, age, BMI, and the GFR was also offered.

**Strengths and limitations of this study**

1. This study is based on a large sample database focused on impaired kidney function patients who received flexible ureteroscopic lithotripsy.
2. This study found that ipsilateral renal function was an independent predictor of stone clearance rate after flexible ureteroscopic lithotripsy.
3. Due to the popularity of nuclear medicine detection methods, this study provides a convenient prediction model for stone removal after flexible ureteroscopic lithotripsy.
4. This study is retrospectively designed, further prospectively designed study is needed to validate this model.

## Introduction

Kidney stone disease (KSD) is an increasingly prevalent and costly condition in the United States, affecting approximately 9% of the population[1, 2]. At present, extracorporeal shockwave lithotripsy (SWL), flexible ureteroscopy (fURS) lithotripsy, and percutaneous nephrolithotomy (PCNL) are widely available surgical treatment options for KSD. In the USA, the use of ureteroscopy (URS) combined laser lithotripsy was reported increasing over time [3]. Though fURS is increasingly being used to treat KSD with a low morbidity 4, residual fragments after fURS are a significant concern because it can significantly increase the risk of stone-related events and additional procedures [4].

Many risk factors such as stone size, stone number and stone position for stone free rate after the fURS have been reported[5, 6]. However, in the current studies on the influence of SFR after the fURS, the factors considered mostly focus on the stone load, stone location, abnormal anatomical structure, ureteral stricture etc., while the driving force of stone discharge is still not considered enough. The glomerular filtration and tubule reabsorption together constitute the urination capacity of the kidney. It is expected that when the renal function of patients is impaired and the glomerular filtration rate is reduced, the urine production capacity of the kidney will also be affected, leading to a reduced ability of urine to wash the residual stone, which will further affect the stone removal efficiency after fURS. However, there is currently no discussion of renal function in relation to the cleavage rate after fURS. At present, nuclear medicine detection methods such as SPECT renal imaging have been able to measure the ipsilateral renal function more accurately. Therefore, this study will analyze the effect of ipsilateral renal function on the stone clearance rate after fURS based on the database of renal stone patients who received fURS in the Urology Department of West China Hospital, and further construct a clinical prediction model.

## Methods

### Study design and participants

This study was approved by local health ethics at west china hospital and was retrospectively designed. Patients who received fURS for kidney stones were screened. Those without information on outcomes and predictors described below were excluded. Besides, patients with kidney anatomical deformities such as sponge kidney and horseshoe kidney were also excluded. Bilateral surgeries of the same patient were considered independently. The remaining 576 cases met the criteria and were further analyzed.

### Patient and Public Involvement

Patients or the public were not involved in the study design, or conduct, or reporting in this study. The study results were not disseminated to study participants.

### Outcomes and predictors

Based on kidneys-ureters-bladder X-ray (KUB) at approximately four weeks after treatment, stone-free (SF) was defined as size ≤ 2mm because residual fragments >2 mm increases the risk of stone-related events and additional procedures [4]. Besides, KUB is enough to evaluate SF when residual components> 2mm compared with non-contrast computed tomography (NCCT) [7].

We included the potential factors through literature review and clinical experience. These factors were described as follows: gender, age (year-old), body mass index (BMI, kg/$m^2$), alcohol consumption (heavy drinker defined as alcohol consumption more than three times per week), kidney side, glomerular filtration rate of the ipsilateral kidney (GFR, ml/min), GFR of the contralateral kidney (ml/min), hypertension, diabetes mellitus (DM), smoking, stone volume ($cm^3$), stone location, ipsilateral hydronephrosis, and ureteral stricture history. In this study, the most crucial variable is GFR, and it was measured by nuclear medicine tests [8]. The volume of pre-operative stone was calculated based on NCCT with formula: volume=length*width*height *1/6*π [9].

**Surgical techniques**

Surgical techniques have been described in our previous study [10, 11]. Briefly, a double-J stent was generally placed approximately two weeks before surgery in our institute because it was reported associated with higher SFR [12]. Because of this, 14/16 Fr ureteral access sheaths (UAS) could be used among most of our patients to reduce the intrarenal pressure, which will also help facilitate stone extraction without compromising ureteral injury. fURS with holmium laser lithotripsy were performed with active basket retrieval of fragments, followed by the dusting technique. If the stone is located in the lower pole, basket displacement would decrease the surgical difficulty, which was also associated with the increased SFR[4]. All patients were stented postoperatively for about two weeks. Tamsulosin was routinely used to reduce the related symptoms during this period.

**Statistical analysis**

Based on the definition described above, patients were classified as SF and none-SF (NSF) groups. If the continuous variables were normality distribution examined by the Kolmogorov-Smirnov test, they were presented with the mean (standard deviation, SD). Otherwise, the median (interquartile range, IQR) was applied. T-test and Mann–Whitney test was used to testing for continuous variables with normally distributed and non-normally distributed, respectively. Categorical variables were presented with the number (percentage) and tested by Chi-square test or the Fisher's exact test.

Given that there were 29 variables enrolled in this analysis and only 172 positive-end cases (fragments > 2mm), the most useful predictive indicators were selected through the least absolute shrinkage and selection operator (LASSO) regression [13], which is fit for the regression of high-dimensional data. As previously reported [14], the optimal λ for feature choosing in the LASSO regression was identified by the 10-fold method. Optimal λ was set via the minimum criteria and the minimum criteria' 1 standard error (the 1-SE criteria).

Univariate and multivariate logistic regression analysis would be applied to determine the effect of different variables on the outcome event and only significant variable identified by univariate regression should be included in multivariate regression to ensure statistical power. After using a logistic regression to determine the effect of ipsilateral renal function on SFR, we further tested the linear association between them using restricted cubic spline method. Restricted cubic spline was plotted based on R package rms, 25%, 50% and 75% of GFR were chosen as fitting nodes and reference points are determined using the univariate Youden index.

All statistical analyses above were achieved through R v.3.6.2 (www.r-project.org). All the reported P values were 2-sided, and significance was indicated as $P<0.05$.

## Results

According to the inclusion and exclusion criteria, out of 2432 patients, 1566 patients were excluded because they did not receive preoperative ipsilateral renal function test. 177 cases were excluded for deformities or with a history of ureteral stricture. 123 patients were removed because any other data were missing. 576 patients with preoperative nuclear medicine tests were finally included in this study. Patient characteristics were summarized in Table 1, and the SFR in our study was 70.1%. Postoperative fever (POF) is defined as the temperature of the patient higher than 38 ℃ within 72 h after operation and there was 16 patients had POF in this analysis. No other Clavien grade III or IV complication was found. The results of univariate and multivariate logistic regression analyses were demonstrated in Table 2. Stone volume (OR=1.46, 95%CI 1.18-1.80), lower calyx stone (OR=1.80, 95%CI 1.22-2.65), age (OR=1.02, 95%CI 1.00-1.04), BMI (OR=1.10, 95%CI 1.04-1.17), and GFR of the treated kidney (OR=0.95, 95%CI 0.94-0.97), were identified as independent predictors.

The tuning parameter (λ) selection in the LASSO model used 10-fold validation was shown in Figure 1A. When the primary λ was set as 100, a LASSO coefficient profile of included features was plotted as Figure 1B, and the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria). In conclusion, LASSO regression selected the same five predictors described above, thus strengthening the model based on logistic regression (Supplementary Table 1).

Based on the uni-variable logistic regression between GFR of treated kidney and stone removing failure risk, Youden index (YI) was calculated and ranked. It was found that when set cut-off GFR value of 49ml/min of treated kidney, the largest YI could be achieved. RCS was plotted when set reference point as 49ml/min (Figure 2), significant linear correlation between GFR and stone removing failure risk was found (Chi-Square: 24.30, P<0.0001). This finding further supported that we should include lateral renal function as a continuous variable in subsequent prediction model construction.

A subsequent SFR predicting model incorporating these five predictors was built based on multivariate logistic regression and shown as a nomogram (Figure 3). The mean AUC was 0.715 (95%CI: 0.714-0.716) based on 1000 times10-fold validation. Hodges-Lehmann test (Chi-square = 8.73， DF = 8, P = 0.3658) and calibration curve (Figure 4) revealed that there was no significant mismatch between the prediction model and the retrospective cohort.

## Discussion

In this study we have found a novel predicting factor for SFR after the fURS, GFR of the treated kidney, which has not been reported so far. Based on this novel independent predicting factor, we also offered a new nomogram for SFR in patients with KSD treated with fURS therapy. The new Nomogram, based on the five variables; age, BMI, stone volume, GFR of the treated kidney, and lower calyx stone, facilitated the individualized preoperative prediction of residual fragments > 2mm at approximately four weeks after treatment.

SFR (fragment size < 2mm) in our study was 70.1% based on KUB at approximately four weeks after treatment for patients whose kidney function were suspected to be impaired before operation. Ghani et al. systematically reviewed the SFR following fURS for KSD and reported that variations exist in the published studies because of the different definitions, imaging methods used, and time point[4]. No of fragments size < 2mm, and fragments < 4mm were the most common definitions. We choose fragments size < 2mm as the

SFR definition mainly by referring to the following two aspects: On the one hand, KUB was routinely used to detect residual fragments after fURS in our center. NCCT was recommended if endoscopic evaluation showed no fragments or residual fragments between 0-2 mm, while KUB is enough to evaluate SFR when residual fragments > 2mm [7]. On the other hand, residual fragments >2 mm increases the risk of stone-related events and additional procedures [4]. The time point at which patients were undergoing KUB was relatively short (approximately four weeks after treatment) might lead to a lower evaluated SFR because most of the fragments were pieced small enough to pass spontaneously through our dusting technique. At the same time, in our center, the preoperative nuclear medicine test of renal function is not a routinely required item. That is to say, doctors usually perform renal function scans when they suspect that stones may have caused renal damage. This may also partly explain the low rate of stone removal in this cohort.

Paralleling the literature [4, 15], lower pole location was one of the independent predictors in our series. The scope of access to stone would be limited by lower-pole location. Additionally, the laser fiber would result in 10-15° loss of deflecting ability in fURS use [16]. To decrease the surgical difficulty and increase the SFR[4], a basket displacement technique would be performed to remove lower-pole stones to other calyxes, routinely performed in our study. Retrograde pyelogram is not typical perioperative practice in our center. The influence of IPA could not be thoroughly evaluated in this study. However, the role of renal anatomy on SFR after fURS is not well concluded yet [15, 17, 18]. A recent prospective study with CT follow-up also reported that renal stone features are more critical than renal anatomy to predict SWL outcomes [19].

Stone volume (length*width*height *1/6*π [9]) based on NCCT was another independent predictor associated with SFR in our cohort. This finding was consistent with previously reported studies[4, 15, 20, 21]. Stone burden contributed to the prolonged operating times, leading to an increased risk of sepsis. Therefore, SFR among larger stone burden patients would be lower due to the limited operating times. In our study, 14/16Fr UAS was used in most patients to maintain lower intrarenal pressures, then prolonging the operating time, thereby increasing the SFR. Besides, 14/16Fr UAS was a benefit to improve the efficacy of basketing fragments.

Age, BMI, and GFR were found to be new independent predictors for SFR after fURS. It was reported that KSD was associated with increased risks of kidney function loss [22, 23]. To our knowledge, moderate physical activities helped promote the expulsion of stone fragments. Patients with older age and higher BMI might be associated with decreased physical activity, leading to a lower SFR. Patients were told to follow the AUA guideline, which recommended that patients increase the amount of water supply after fURS to reach a daily urine volume of 2.5 L/d to get the optimal SFR [24].

On the one hand, we speculated that the amount of urine produced by impaired kidneys would be reduced, and the urine-flushing efficacy on this side would be weakened. On the other hand, stone patients accompanied by deceased GFR might be associated with a more extended history of KSD, repeated KSD surgery, and stone burden. However, these new factors should be further studied in other cohorts.

Several limitations should be mentioned in this study. Firstly, this was a retrospectively designed study with expected biases. Secondly, all patients included were operated on by the same surgeon, which may bring some bias. Third, due to the limitations of the retrospective study design, many vital variables were difficult to collect, such as other surgical history related to kidney stones, postoperative eating habits, etc. Therefore, the conclusions of this study need to be treated with caution. Fourth, although all stone patients in our center underwent stone composition analysis, however, because the data of the stone composition analysis results were saved by another team of the Department of Urology of West China Hospital, we did not have permission to use this part of the data, so this study did not present the relevant data. Fifth, using KUB and CT as SFR evaluation methods still brings many problems. Although some studies support that the accuracy of KUB in detecting stones larger than 2 mm can still meet the needs, the measurement bias caused by different influence methods is still worth noting. Meanwhile, KUB measurement is affected by patients' BMI and stone opacity. Although KUB evaluation is clinically relevant, the limited accuracy of KUB to evaluate residual fragments should be addressed.

289 After all, in this study, we found that Ipsilateral renal function might be a novel independent risk factor for kidney stone removal for flexible ureteroscopic lithotripsy. A novel nomogram for predicting SFR using stone volume, lower calyx stone, age, BMI, and the GFR was developed and internally validated with a 10-fold validation method in our retrospective cohort. This predictive model still lacks external cohort validation, so we look forward to re-check from other data sources as well.

## Disclosure

### Contributors

Study concept and design: YM, ZJ, KW

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,KW

Supervision: KW, HL

Other: None.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

### Approval of the research protocol by an Institutional Reviewer Board

N/A

## Informed Consent

N/A

## Registry and the Registration No. of the study/trial

N/A

## Animal Studies

N/A


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## Ethical Statement

The study was approved by the West China Hospital of Sichuan University Medical Research Ethics Committee (20200508) and individual consent for this retrospective analysis was waived.

## Data availability statement

Data are available upon reasonable request

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## Figure legends

Figure 1. LASSO regression for candidate predictor selection. 1A. 10-fold cross-validation plot, dotted line means lambda values of best performance model and concise model. 1B. LASSO coefficient profile of included features, the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria).

Figure 2. Restricted cubic spline plot between GFR and OR for stone removing failure. Reference point=49ml/min.

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Figure 4. Calibration plot of Nomogram based on the bootstrap method.

Supplementary Table 1. Variables identified according to the leave-one cross validation LASSO regression and stepwise multivariate logistics regression. The 1-SE criteria were chosen to build a concise model. LASSO: Least absolute shrinkage and selection operator regression; GFR: glomerular filtration rate; BMI: Body mass index.

Table 1 Baseline characteristics of the SF and NSF groups. BMI: Body mass index; ESWL: Extracorporeal shock wave lithotripsy; GFR: glomerular filtration rate. *: T-test and Mann–Whitney test was used for continuous variables with normally distributed and non-normally distributed, respectively. Categorical variables were tested by $\chi^2$ test or the Fisher's exact test if the requirements for the $\chi^2$ test were not satisfied.

| Variables | Total cohort, N(%), median(IQR) or mean±SD (n=576) | NSF group (n=172, 29.9%) | SF group (n=404, 70.1%) | P* |
|---|---|---|---|---|
| Gender (Female, n, %) | 186 (32.3) | 53 (30.8) | 133 (32.9) | 0.621 |
| Age (years) | 49 (40, 57) | 51 (42, 60) | 48 (39, 56) | **0.001** |
| BMI (kg/m2) | 23.92±3.31 | 24.59±3.77 | 23.64±3.07 | **0.001** |
| Heavy drinker (Yes, n, %) | 50 (8.7) | 18 (10.5) | 32 (7.9) | 0.322 |
| Diabetes (Yes, n, %) | 41 (7.1) | 15 (8.7) | 26 (6.4) | 0.331 |
| Hypertension (Yes, n, %) | 85 (14.8) | 30 (17.4) | 55 (13.6) | 0.237 |
| Smoker (Yes, n, %) | 188 (32.6) | 52 (30.2) | 136 (33.7) | 0.422 |
| Previous upper urinary stone history (Yes, n, %) | 71 (12.3) | 26 (15.1) | 45 (11.1) | 0.185 |
| Treated side (left, n, %) | 304 (52.8) | 96 (55.8) | 208 (51.5) | 0.341 |
| ESWL history within 12-month (Yes, n, %) | 11 (1.9) | 2 (1.2) | 9 (2.2) | 0.401 |
| GFR of treated kidney (ml/min) | 38 (31, 47) | 35 (28, 42) | 39.8 (32, 48.4) | **<0.001** |
| GFR of another kidney (ml/min) | 40.9 (32.7, 48.8) | 40 (30.7, 47.4) | 41.1 (33.3, 49.3) | 0.072 |

| | | | | |
|---|---|---|---|---|
| Ureteral Access Sheath (12/14F, n, %) | 19 (3.3) | 4 (2.4) | 15 (3.7) | 0.615 |
| Stone volume (cm³) | 0.73 (0.42, 1.23) | 0.99 (0.49, 1.57) | 0.67 (0.39, 1.16) | **<0.001** |
| Staghorn calculus (Yes, n, %) | 33 (5.7) | 17 (9.9) | 16 (4.0) | **0.007** |
| Largest stone diameter (cm) | 1.46 (1.05, 1.90) | 1.58 (1.20, 2.00) | 1.40 (1.00, 1.80) | **<0.001** |
| Stone number (n, %) | | | | 0.285 |
| One | 213 (37.0) | 60 (34.9) | 153 (37.4) | |
| Two | 159 (27.6) | 48 (27.9) | 111 (27.1) | |
| Three | 79 (13.7) | 18 (10.5) | 61 (15.1) | |
| Four | 40 (6.9) | 15 (8.7) | 25 (6.2) | |
| More or equal to five | 85 (14.8) | 31 (18.0) | 54 (13.4) | |
| Lower calyx stone (Yes, n, %) | 232 (40.3) | 83 (48.3) | 149 (36.9) | **0.011** |
| Multiple stone (Yes, n, %) | 288 (50) | 94 (54.7) | 194 (48.8) | 0.146 |
| Ipsilateral hydronephrosis (Yes, n, %) | 393 (68.2) | 118 (68.6) | 275 (68.1) | 0.900 |

| | Patient without stone-free status | | | |
|---|---|---|---|---|
| | **Univariate regression** | | **Multivariate regression** | |
| | Crude OR (95% CI) | ***P*-value** | Adjusted OR (95% CI) | ***P*-value** |
| Gender (Female) | 0.907 (0.618, 1.333) | 0.621 | / | 0.651 |
| Age (per year) | 1.030 (1.013, 1.046) | **<0.001** | 1.018 (1.001, 1.035) | **0.039** |
| BMI (per kg/m2) | 1.091 (1.033, 1.152) | **0.002** | 1.100 (1.037, 1.167) | **0.002** |
| Heavy drinker (Yes) | 1.359 (0.740, 2.494) | 0.322 | / | 0.346 |
| Diabetes (Yes) | 1.389 (0.716, 2.693) | 0.331 | / | 0.833 |
| Hypertension (Yes) | 1.341 (0.825, 2.179) | 0.237 | / | 0.979 |
| Smoker (Yes) | 0.854 (0.581, 1.255) | 0.422 | / | 0.591 |
| Previous upper urinary stone history (Yes) | 1.421 (0.845, 2.389) | 0.185 | / | 0.329 |
| Treated side (left) | 1.190 (0.832, 1.704) | 0.341 | / | 0.882 |
| ESWL history within 12-month (Yes) | 0.516 (0.110, 2.415) | 0.401 | / | 0.798 |
| GFR of treated kidney (per ml/min) | 0.955 (0.939, 0.971) | **<0.001** | 0.953 (0.936, 0.970) | **<0.001** |
| GFR of another kidney (per ml/min) | 0.990 (0.978, 1.002) | 0.093 | / | 0.927 |
| Ureteral Access Sheath (12/14F) | 0.901 (0.600, 1.352) | 0.615 | / | 0.433 |
| Stone volume (per cm3) | 1.414 (1.160, 1.722) | **0.001** | 1.458 (1.182, 1.799) | **<0.001** |
| Staghorn calculus (Yes) | 2.660 (1.311, 5.397) | **0.007** | / | 0.148 |
| Largest stone diameter (per cm) | 1.350 (1.054, 1.729) | **0.017** | / | 0.566 |
| Stone number | | 0.285 | / | 0.333 |
| One | Ref. | / | / | |
| Two | 1.103 (0.702, 1.732) | 0.161 | / | |
| Three | 0.752 (0.411, 1.377) | 0.318 | / | |
| Four | 1.530 (0.755, 3.101) | 0.057 | / | |
| More or equal to five | 1.464 (0.859, 2.495) | **0.911** | / | |

| | | | | |
|---|---|---|---|---|
| Lower calyx stone (Yes) | 1.596 (1.112, 2.290) | 0.011 | 1.802 (1.223, 2.654) | **0.003** |
| Multiple stones (Yes) | 1.305 (0.912, 1.866) | 0.146 | / | 0.548 |
| ipsilateral hydronephrosis (Yes) | 1.025 (0.698, 1.505) | 0.900 | / | 0.650 |

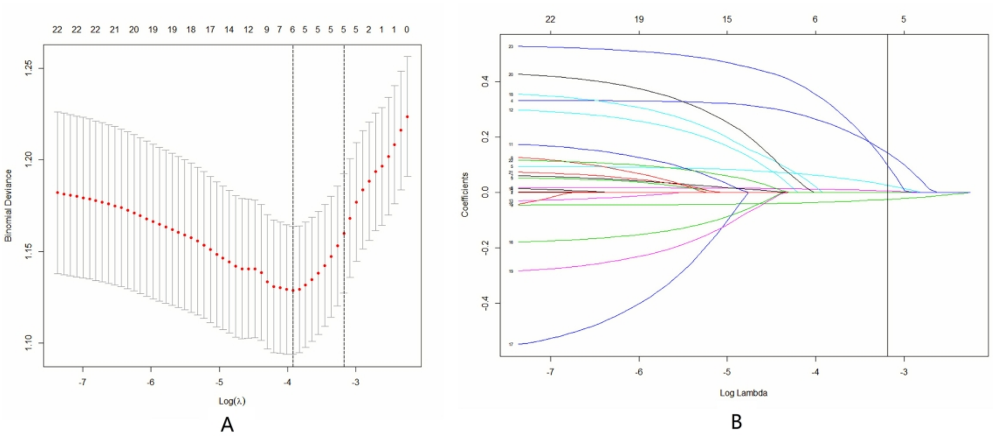


Figure 1. LASSO regression for candidate predictor selection. 1A. 10-fold cross-validation plot, dotted line means lambda values of best performance model and concise model. 1B. LASSO coefficient profile of included features, the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria).

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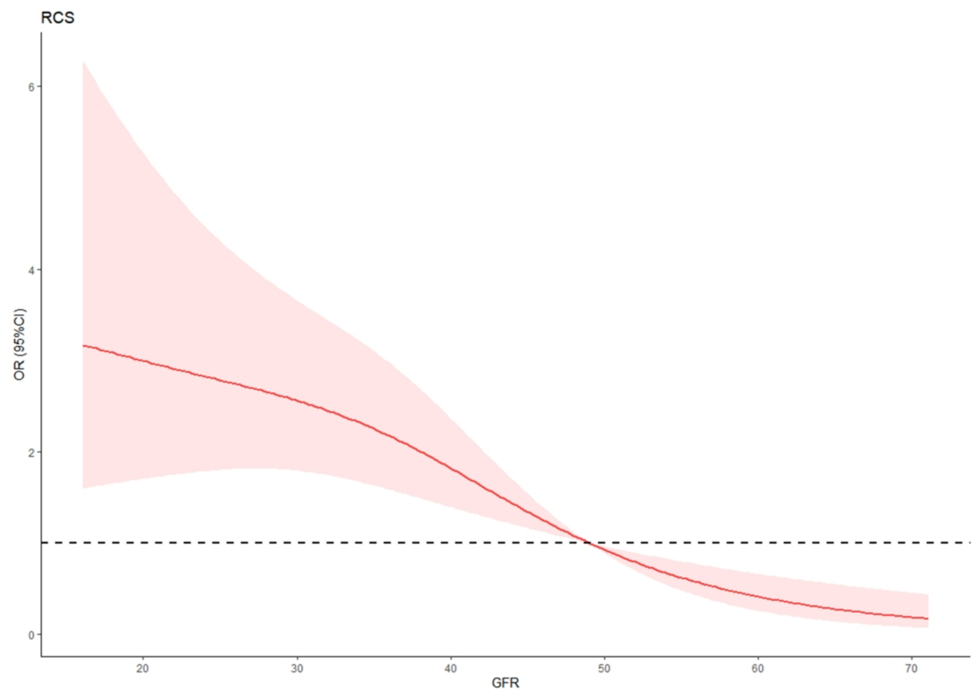


Figure 2. Restricted cubic spline plot between GFR and OR for stone removing failure. Reference point=49ml/min.

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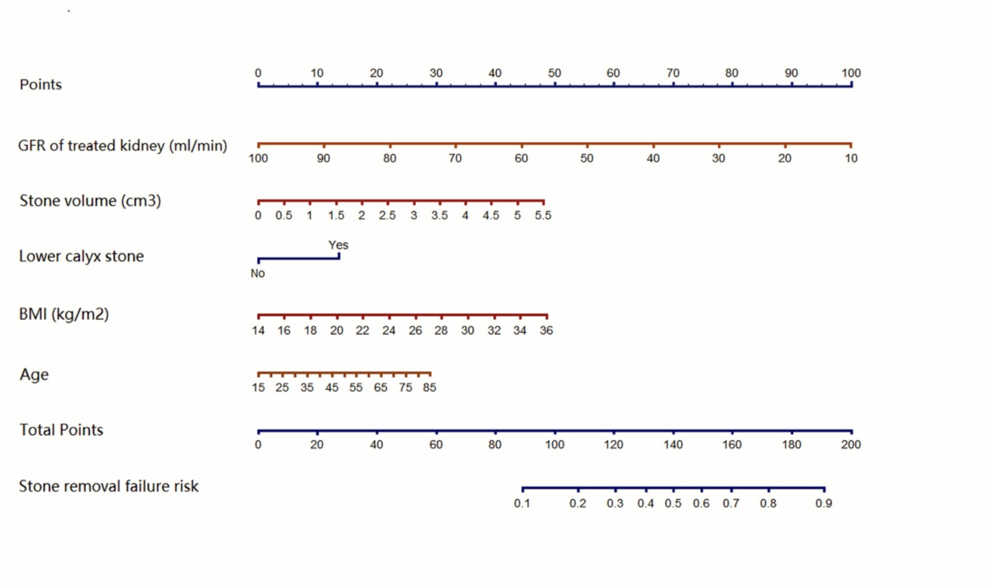


Figure 3. Nomogram based on the significant predictors selected by multivariate logistic regression model.

385x228mm (300 x 300 DPI)

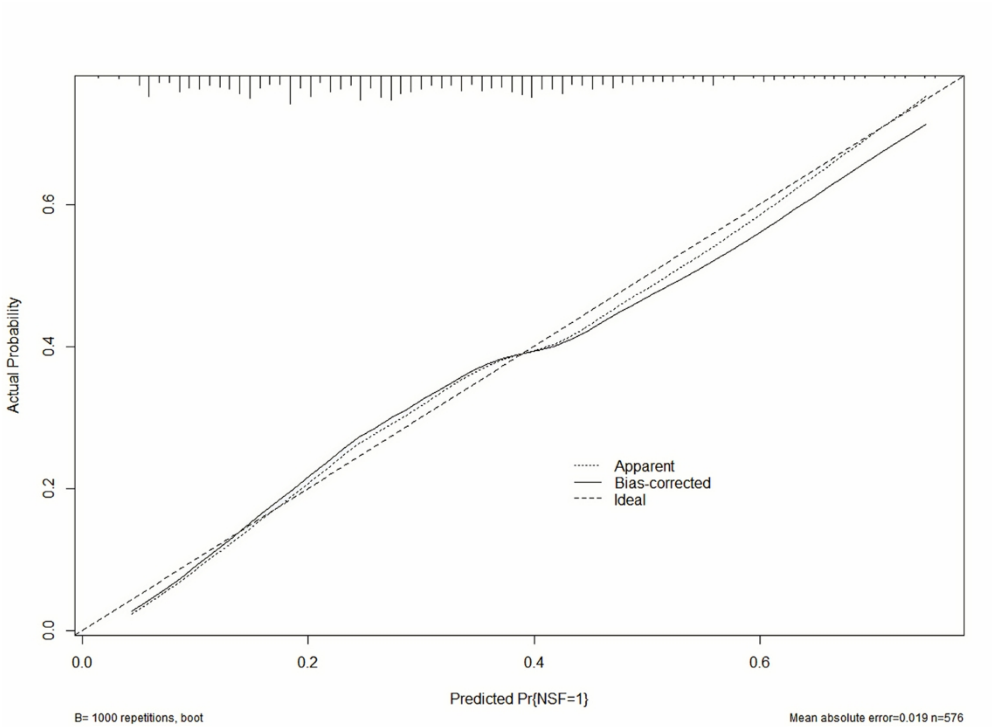


Figure 4. Calibration plot of Nomogram based on the bootstrap method.

315x228mm (300 x 300 DPI)

Supplementary Table 1. Variables identified according to the leave-one cross validation LASSO regression and stepwise multivariate logistics regression. The 1-SE criteria were chosen to build a concise model. LASSO: Least absolute shrinkage and selection operator regression; GFR: glomerular filtration rate; BMI: Body mass index.

| Variables identified by LASSO | Intercept | GFR of treated kidney (ml/min) | Stone volume (cm3) | BMI (kg/m2) | Age (years) | Lower calyx stone (Yes) |
|---|---|---|---|---|---|---|
| LASSO coefficients (λ=0.0416) | -0.887 | -0.025 | 0.141 | 0.025 | 0.005 | 0.095 |
| Logistics coefficients | -2.854 | -0.048 | 0.377 | 0.095 | 0.018 | 0.589 |

TRIPOD Checklist: Prediction Model Development

| Section/Topic | Item | Checklist Item | Page |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | 1 | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. | Page1, line1-3 |
| Abstract | 2 | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | Page2-3, line28-53 |
| **Introduction** | | | |
| Background and objectives | 3a | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | Page4-5,line89-93 |
| | 3b | Specify the objectives, including whether the study describes the development or validation of the model or both. | Page4-5,line89-93 |
| **Methods** | | | |
| Source of data | 4a | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | Page5, line95-102 |
| | 4b | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | Page5, line95-102 |
| Participants | 5a | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | Page5, line95-102 |
| | 5b | Describe eligibility criteria for participants. | Page5, line95-102 |
| | 5c | Give details of treatments received, if relevant. | Page5, line95-102 |
| Outcome | 6a | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | Page5, line105-110 |
| | 6b | Report any actions to blind assessment of the outcome to be predicted. | NA |
| Predictors | 7a | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. | Page5-6, line111-line120 |
| | 7b | Report any actions to blind assessment of predictors for the outcome and other predictors. | NA |
| Sample size | 8 | Explain how the study size was arrived at. | NA |
| Missing data | 9 | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | Page5, line95-102 |
| Statistical analysis methods | 10a | Describe how predictors were handled in the analyses. | Page5-6, line104-line120 |
| | 10b | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | Page7-8,line137-line163 |
| | 10d | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | Page7-8,line137-line163 |
| Risk groups | 11 | Provide details on how risk groups were created, if done. | NA |
| **Results** | | | |

# TRIPOD Checklist: Prediction Model Development

| | | | |
|---|---|---|---|
| Participants | 13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | Page 8, line166-linr172 |
| | 13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | Table 1 |
| Model development | 14a | Specify the number of participants and outcome events in each analysis. | Table 1 |
| | 14b | If done, report the unadjusted association between each candidate predictor and outcome. | Table 2 |
| Model specification | 15a | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | Table 2 |
| | 15b | Explain how to the use the prediction model. | NA |
| Model performance | 16 | Report performance measures (with CIs) for the prediction model. | Table 2 |
| **Discussion** | | | |
| Limitations | 18 | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | Page 13, line 269-283 |
| Interpretation | 19b | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence. | Page 10-12 |
| Implications | 20 | Discuss the potential clinical use of the model and implications for future research. | Page 10-12 |
| **Other information** | | | |
| Supplementary information | 21 | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | NA |
| Funding | 22 | Give the source of funding and the role of the funders for the present study. | Page 15, line314-316 |

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

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


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| | |
|---|---|
| <b>Primary Subject Heading</b>: | Urology |
| Secondary Subject Heading: | Urology, Surgery |
| Keywords: | Adult urology < UROLOGY, Urolithiasis < UROLOGY, Epidemiology < TROPICAL MEDICINE |


SCHOLARONE™ Manuscripts

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

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*: Yu-cheng Ma and Zhong-Yu Jian contributed equally to this work and should be considered as co-first authors.

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**Keywords:** Stone-free Status; Flexible Ureteroscopic lithotripsy; Risk Factors.

**Abstract word count:** 255

**Manuscript word count:** 2383

**Number of figures:** 4

**Number of tables:** 2


## 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 period 2001 to 2012 were collected from 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 1.18–1.80), lower calyx stones (OR 1.80; 95% CI 1.22–2.65), age (OR 1.02; 95% CI 1.00–1.04), body mass index (OR 1.10; 95% CI 1.04–1.17), and the estimated glomerular filtration rate of the affected kidney (OR 0.95; 95% CI 0.94–0.97) were identified as independent predictors of the 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 1,000 iterations and 10-fold validation, was 0.715 (95% CI 0.714–0.716). 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 the SFR that uses stone volume, lower calyx stones, age, body mass index, and the estimated glomerular filtration rate was developed, but remains to be externally validated.

## Strengths and limitations of this study

- This study investigated the association between ipsilateral renal function and the stone-free rate after flexible ureteroscopic lithotripsy.
- This study produced a potentially convenient prediction model for the success of stone removal after flexible ureteroscopic lithotripsy.
- The study was retrospective and data for certain variables were not available; additionally, all patients included were operated on by the same surgeon, which may have also introduced some bias.
- Because clinical data could not be obtained from other centres, no external validation was performed.

## Introduction

Kidney stone disease (KSD) is an increasingly prevalent and costly condition in the United States, affecting approximately 9% of the population[1, 2]. At present, extracorporeal shockwave lithotripsy, flexible ureteroscopy (fURS) lithotripsy, and percutaneous nephrolithotomy are widely available as surgical treatment options for KSD. In the United States, the use of ureteroscopy combined with laser lithotripsy has risen over time [3]. 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 [4].

Many factors have been reported to affect the stone-free rate (SFR) after fURS, including the size, number, and location of stones [5, 6]. Studies of factors affecting the 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 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 cleavage rate after fURS. Ipsilateral renal function can be accurately measured using nuclear medicine detection methods, such as renal imaging with single-photon emission computed tomography. In this study, we analyzed the effect of ipsilateral renal function on the stone clearance rate after fURS and constructed a clinical prediction model.

## Methods

### Study design and participants

This retrospective study was approved by the Ethics Committee of West China Hospital. Data from patients who underwent fURS for renal stones were obtained from the database of the Urology Department of West China Hospital, Sichuan University. Patients for whom information on the outcomes and predictors described below was not available were excluded from the study. Patients with anatomical deformities of the kidney, such as a sponge kidney or horseshoe kidney, were also excluded. Bilateral surgeries in 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 [4]. Research has shown that KUB is sufficient for evaluating SF status using a cut-off of residual components >2 mm[7]. All KUB images were evaluated by two authors (YM, ZJ) according to standard procedures.

Potential factors affecting the SFR were determined on the basis of a literature review and clinical experience. These factors were sex, age (years), body mass index (BMI; kg/m$^2$), 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 (cm$^3$), 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 [8]. The preoperative stone volume was calculated based on NCCT using the following formula:

$$\text{Volume}=\text{length}\times\text{width}\times\text{height}\times 1/6\pi \text{ [9]}$$

## Surgical techniques

The surgical techniques used in this study have been described in detail elsewhere [10, 11]. Briefly, the patients generally underwent double-J stent placement approximately 2 weeks before surgery because this is reportedly associated with a higher SFR [12]. As a result, for most of the patients, 14-/16-Fr ureteral access sheaths (UAS) could be used to reduce intrarenal pressure, which also aids in facilitating stone extraction without causing ureteral injury. fURS with holmium laser lithotripsy were performed with active basket retrieval of fragments, followed by the dusting technique. If the stone was located in the lower pole, basket displacement decreased the surgical difficulty, which is also associated with an increased SFR [4]. All patients were stented postoperatively for approximately 2 weeks. Tamsulosin was routinely used to reduce any related symptoms that occurred during this period.

## Statistical analysis

Based on the definition of SF above, patients were divided into SF and non-SF (NSF) groups.

The normality of data distribution was evaluated using the Kolmogorov–Smirnov test. Normally distributed continuous variables are presented as the mean±SD and were compared between groups using t-tests. Non-normally distributed data are presented as the median with interquartile range (IQR) and were compared between groups using the Mann–Whitney test. Categorical variables are presented as numbers and percentages, and were compared between groups using the chi-square or Fisher's exact test.

Given that there were 29 variables included in this analysis and only 172 positive-end cases (i.e., fragments >2 mm), the most useful predictive indicators were selected through least absolute shrinkage and selection operator (lasso) regression [13], which is suitable for the regression of high-dimensional data. As reported previously [14], the optimal λ for feature selection in lasso regression was identified by 10-fold cross-validation. Optimal λ was set via the minimum criteria and the minimum criteria–1SE ("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 method was used to further test the linear association between ipsilateral renal function and SFR. A restricted cubic spline 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, and significance was 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 2,432 patients who underwent fURS for kidney stones at West China Hospital between 2001 and 2012, 1,566 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, and 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 summarized in Table 1. The SFR in this study was 70.1%. Postoperative fever, which was defined as a temperature >38°C within the 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 1.18–1.80), lower calyx stones (OR 1.80; 95% CI 1.22–2.65), age (OR 1.02; 95% CI 1.00–1.04), BMI (OR 1.10; 95% CI 1.04–1.17), and the GFR of the treated kidney (OR 0.95; 95% CI 0.94–0.97) were identified as independent predictors of SF status.

Tuning parameter (λ) selection in the lasso model using 10-fold validation is shown in Figure 1A. A lasso coefficient profile of included features with the primary λ set to 100 is shown in Figure 1B; the vertical line indicates the optimal λ value (λ=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 (Supplementary 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 restricted cubic spline (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). 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 the 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: 0.714–0.716) based on 1,000 iterations and 10-fold validation. The Hodges–Lehmann test ($\chi^2$=8.73, d.f.=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 individualized 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. systematically reviewed studies that reported the SFR following fURS for KSD and found inter-study variation because of the different definitions and imaging methods used, as well as differences in time points[4]. 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 [4]. 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 [4, 15], 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 fiber used in fURS can result in a 10–15° loss of deflecting ability [16]. To decrease surgical difficulty and increase SFR[4], a basket displacement technique was routinely performed to remove lower-pole stones to other calyxes 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 [15, 17, 18]. A recent prospective study with computed tomography follow-up also reported that renal stone features are more critical than renal anatomy in predicting outcomes of shockwave lithotripsy [19].

Stone volume (length×width×height×1/6π [9]) based on NCCT was another independent predictor associated with SFR in our cohort. This finding is consistent with those of previous reports [4, 15, 20, 21]. 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 burdens. In the present study, a 14-/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-/16-Fr UAS also improved the efficacy of basketing fragments.

Age, BMI, and GFR were identified as new independent predictors of SFR status after fURS. KSD has been reported to be associated with an increased risk of loss of kidney function [22, 23]. 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 fURS to reach a daily urine volume of 2.5 L/day to achieve optimal stone clearance [24].

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, kidney stone patients with a deceased GFR may also have an extended history of KSD, have undergone repeated KSD surgery, and have a 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 computed tomography 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 fURS 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.

**Contributors**

Study concept and design: YM, ZJ, KW. 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, KW. Supervision: KW, HL.

**Competing interests**

The authors have no conflicts of interest to declare.

**Funding**

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**Ethics approval**

The study was approved by the West China Hospital of Sichuan University Medical Research Ethics Committee (20200508) and requirement for individual consent for this retrospective analysis was waived.

**Data availability statement**

Data are available upon reasonable request.

**Acknowledgments**

We sincerely thank engineer Ran Liu from Engineering Research Center of Medical Information Technology Ministry of Education for providing clinical data sorting support for this study.

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## Figure legends

**Figure 1. LASSO regression for candidate predictor selection**

1A. 10-fold cross-validation plot, dotted line means lambda values of best performance model and concise model. 1B. LASSO coefficient profile of included features, the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria).

**Figure 2. Restricted cubic spline plot between GFR and OR for stone removing failure**

Reference point=49ml/min.

**Figure 3. Nomogram based on the significant predictors selected by multivariate logistic regression model**

**Figure 4. Calibration plot of Nomogram based on the bootstrap method**

**Table 1. Baseline characteristics of the SF and NSF groups**

BMI: Body mass index; ESWL: Extracorporeal shock wave lithotripsy; GFR: glomerular filtration rate. *: T-test and Mann–Whitney test was used for continuous variables with normally distributed and non-normally distributed, respectively. Categorical variables were tested by $\chi^2$ test or the Fisher's exact test if the requirements for the $\chi^2$ test were not satisfied.

| Variables | Total cohort, N(%), median(IQR) or mean±SD (n=576) | NSF group (n=172, 29.9%) | SF group (n=404, 70.1%) | P* |
|---|---|---|---|---|
| Gender (Female, n, %) | 186 (32.3) | 53 (30.8) | 133 (32.9) | 0.621 |
| Age (years) | 49 (40, 57) | 51 (42, 60) | 48 (39, 56) | **0.001** |
| BMI (kg/m2) | 23.92±3.31 | 24.59±3.77 | 23.64±3.07 | **0.001** |
| Heavy drinker (Yes, n, %) | 50 (8.7) | 18 (10.5) | 32 (7.9) | 0.322 |
| Diabetes (Yes, n, %) | 41 (7.1) | 15 (8.7) | 26 (6.4) | 0.331 |
| Hypertension (Yes, n, %) | 85 (14.8) | 30 (17.4) | 55 (13.6) | 0.237 |
| Smoker (Yes, n, %) | 188 (32.6) | 52 (30.2) | 136 (33.7) | 0.422 |
| Previous upper urinary stone history (Yes, n, %) | 71 (12.3) | 26 (15.1) | 45 (11.1) | 0.185 |
| Treated side (left, n, %) | 304 (52.8) | 96 (55.8) | 208 (51.5) | 0.341 |
| ESWL history within 12-month (Yes, n, %) | 11 (1.9) | 2 (1.2) | 9 (2.2) | 0.401 |
| GFR of treated kidney (ml/min) | 38 (31, 47) | 35 (28, 42) | 39.8 (32, 49.4) | **<0.001** |

| | | | | |
|---|---|---|---|---|
| GFR of another kidney (ml/min) | 40.9 (32.7, 48.8) | 40 (30.7, 47.4) | 41.1 (33.3, 49.3) | 0.072 |
| Ureteral Access Sheath (12/14F, n, %) | 19 (3.3) | 4 (2.4) | 15 (3.7) | 0.615 |
| Stone volume (cm$^3$) | 0.73 (0.42, 1.23) | 0.99 (0.49, 1.57) | 0.67 (0.39, 1.16) | **<0.001** |
| Staghorn calculus (Yes, n, %) | 33 (5.7) | 17 (9.9) | 16 (4.0) | **0.007** |
| Largest stone diameter (cm) | 1.46 (1.05, 1.90) | 1.58 (1.20, 2.00) | 1.40 (1.00, 1.80) | **<0.001** |
| Stone number (n, %) | | | | 0.285 |
| One | 213 (37.0) | 60 (34.9) | 153 (37.9) | |
| Two | 159 (27.6) | 48 (27.9) | 111 (27.5) | |
| Three | 79 (13.7) | 18 (10.5) | 61 (15.1) | |
| Four | 40 (6.9) | 15 (8.7) | 25 (6.2) | |
| More or equal to five | 85 (14.8) | 31 (18.0) | 54 (13.4) | |
| Lower calyx stone (Yes, n, %) | 232 (40.3) | 83 (48.3) | 149 (36.9) | **0.011** |
| Multiple stone (Yes, n, %) | 288 (50) | 94 (54.7) | 194 (48.0) | 0.146 |
| Ipsilateral hydronephrosis (Yes, n, %) | 393 (68.2) | 118 (68.6) | 275 (68.1) | 0.900 |

**Table 2. Factors associated with stone-free status after RIRS by univariate and stepwise multivariate logistics regression**

BMI = Body mass index; ESWL= Extracorporeal shock wave lithotripsy; GFR = glomerular filtration rate; OR =Odds ratio.

| | **Patient without stone-free status** | | | |
|---|---|---|---|---|
| | **Univariate regression** | | **Multivariate regression** | |
| | Crude OR (95% CI) | ***P*-value** | Adjusted OR (95% CI) | ***P*-value** |
| Gender (Female) | 0.907 (0.618, 1.333) | 0.621 | / | 0.651 |
| Age (per year) | 1.030 (1.013, 1.046) | **<0.001** | 1.018 (1.001, 1.035) | **0.039** |
| BMI (per kg/m2) | 1.091 (1.033, 1.152) | **0.002** | 1.100 (1.037, 1.167) | **0.002** |
| Heavy drinker (Yes) | 1.359 (0.740, 2.494) | 0.322 | / | 0.346 |
| Diabetes (Yes) | 1.389 (0.716, 2.693) | 0.331 | / | 0.833 |
| Hypertension (Yes) | 1.341 (0.825, 2.179) | 0.237 | / | 0.979 |
| Smoker (Yes) | 0.854 (0.581, 1.255) | 0.422 | / | 0.591 |
| Previous upper urinary stone history (Yes) | 1.421 (0.845, 2.389) | 0.185 | / | 0.329 |
| Treated side (left) | 1.190 (0.832, 1.704) | 0.341 | / | 0.882 |
| ESWL history within 12-month (Yes) | 0.516 (0.110, 2.415) | 0.401 | / | 0.798 |
| GFR of treated kidney (per ml/min) | 0.955 (0.939, 0.971) | **<0.001** | 0.953 (0.936, 0.970) | **<0.001** |
| GFR of another kidney (per ml/min) | 0.990 (0.978, 1.002) | 0.093 | / | 0.927 |
| Ureteral Access Sheath (12/14F) | 0.901 (0.600, 1.352) | 0.615 | / | 0.433 |
| Stone volume (per cm3) | 1.414 (1.160, 1.722) | **0.001** | 1.458 (1.182, 1.799) | **<0.001** |
| Staghorn calculus (Yes) | 2.660 (1.311, 5.397) | **0.007** | / | 0.148 |
| Largest stone diameter (per cm) | 1.350 (1.054, 1.729) | **0.017** | / | 0.566 |
| Stone number | | 0.285 | / | 0.333 |
| One | Ref. | / | / | |

| | | | | |
|---|---|---|---|---|
| Two | 1.103 (0.702, 1.732) | 0.161 | / | |
| Three | 0.752 (0.411, 1.377) | 0.318 | / | |
| Four | 1.530 (0.755, 3.101) | 0.057 | / | |
| More or equal to five | 1.464 (0.859, 2.495) | **0.911** | / | |
| Lower calyx stone (Yes) | 1.596 (1.112, 2.290) | 0.011 | 1.802 (1.223, 2.654) | **0.003** |
| Multiple stones (Yes) | 1.305 (0.912, 1.866) | 0.146 | / | 0.548 |
| ipsilateral hydronephrosis (Yes) | 1.025 (0.698, 1.505) | 0.900 | / | 0.650 |

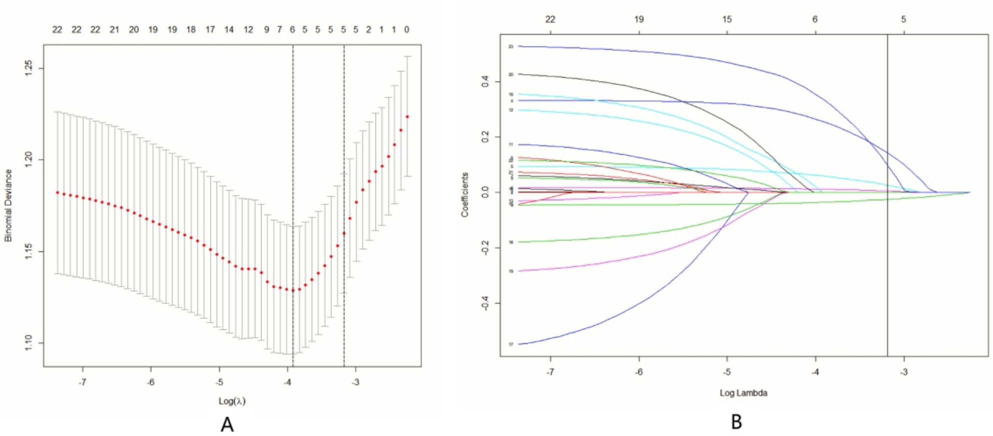


Figure 1. LASSO regression for candidate predictor selection. 1A. 10-fold cross-validation plot, dotted line means lambda values of best performance model and concise model. 1B. LASSO coefficient profile of included features, the vertical line was the optimal λ value (λ=0.0416, the 1-SE criteria).

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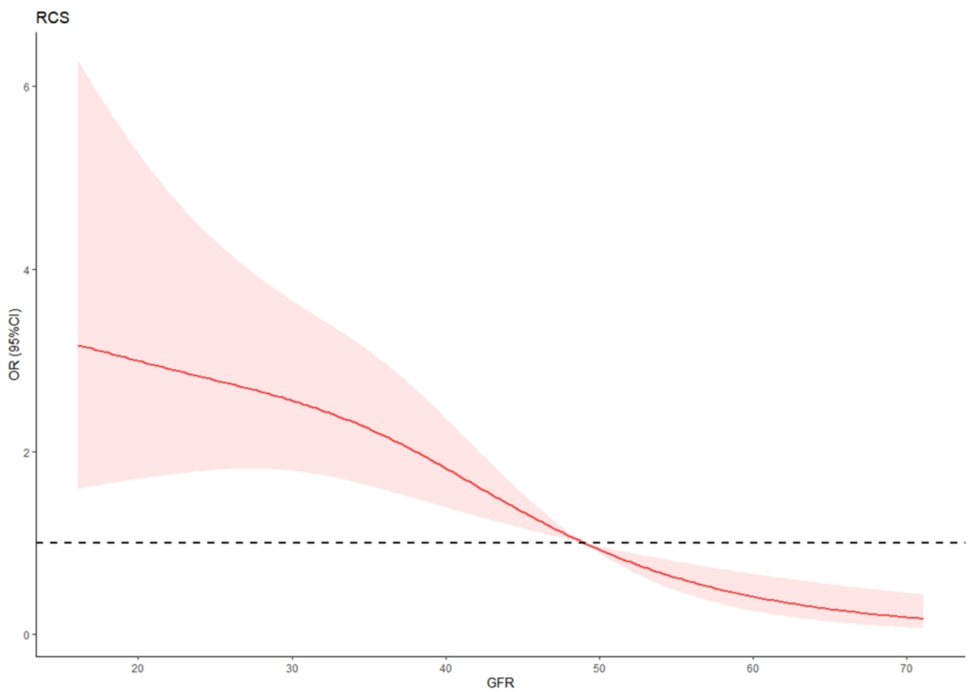


Figure 2. Restricted cubic spline plot between GFR and OR for stone removing failure. Reference point=49ml/min.

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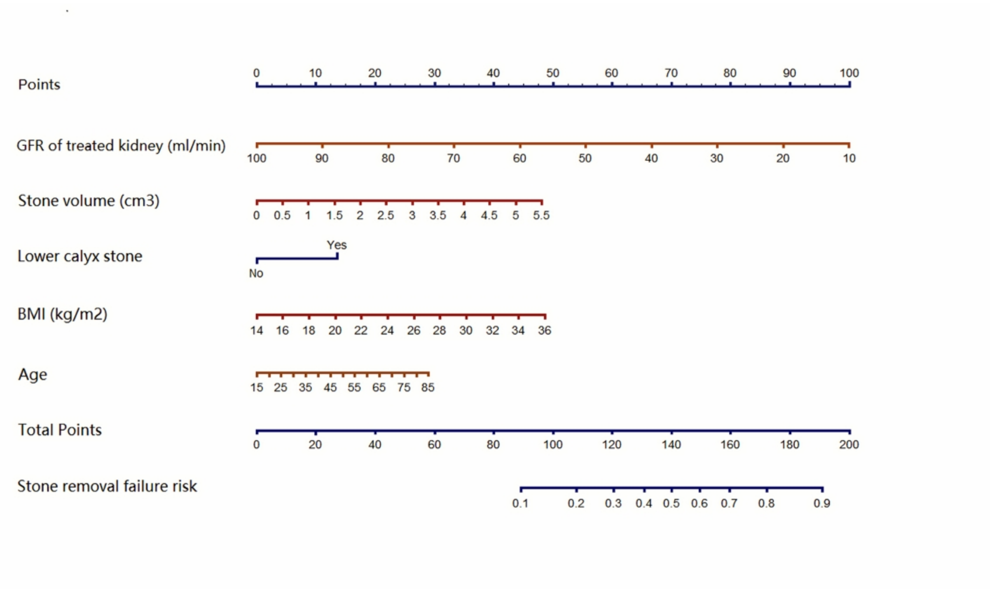


Figure 3. Nomogram based on the significant predictors selected by multivariate logistic regression model.

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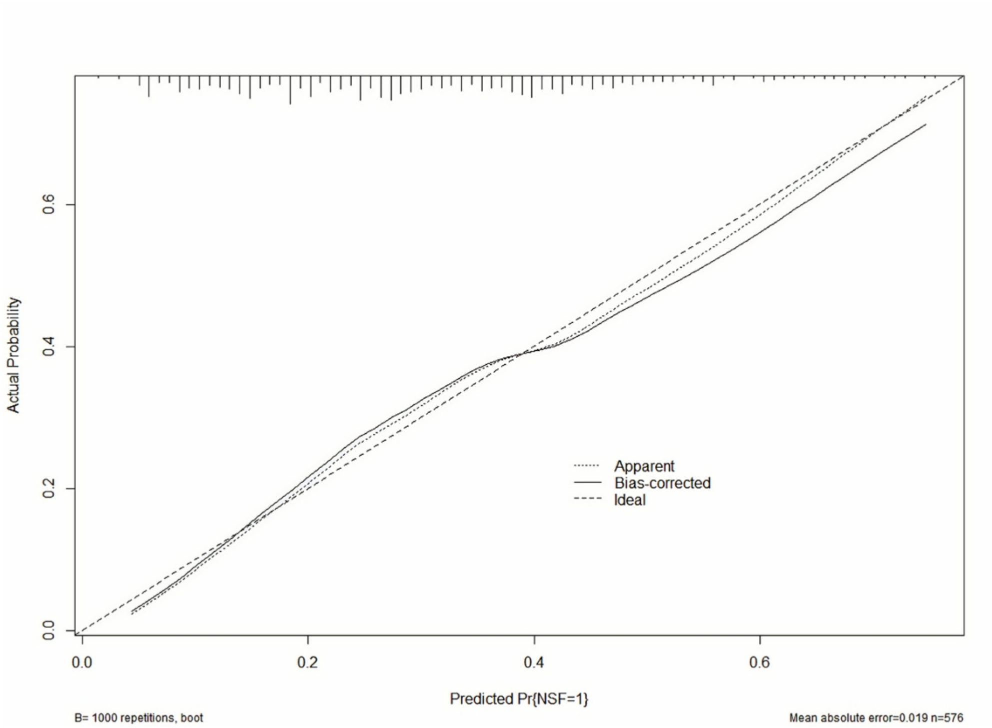


Figure 4. Calibration plot of Nomogram based on the bootstrap method.

315x228mm (300 x 300 DPI)

Supplementary Table 1. Variables identified according to the leave-one cross validation LASSO regression and stepwise multivariate logistics regression. The 1-SE criteria were chosen to build a concise model. LASSO: Least absolute shrinkage and selection operator regression; GFR: glomerular filtration rate; BMI: Body mass index.

| Variables identified by LASSO | Intercept | GFR of treated kidney (ml/min) | Stone volume (cm3) | BMI (kg/m2) | Age (years) | Lower calyx stone (Yes) |
|---|---|---|---|---|---|---|
| LASSO coefficients (λ=0.0416) | -0.887 | -0.025 | 0.141 | 0.025 | 0.005 | 0.095 |
| Logistics coefficients | -2.854 | -0.048 | 0.377 | 0.095 | 0.018 | 0.589 |

TRIPOD Checklist: Prediction Model Development

| Section/Topic | Item | Checklist Item | Page |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | 1 | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. | Page1, line1-3 |
| Abstract | 2 | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | Page2-3, line28-53 |
| **Introduction** | | | |
| Background and objectives | 3a | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | Page4-5,line89-93 |
| | 3b | Specify the objectives, including whether the study describes the development or validation of the model or both. | Page4-5,line89-93 |
| **Methods** | | | |
| Source of data | 4a | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | Page5, line95-102 |
| | 4b | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | Page5, line95-102 |
| Participants | 5a | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | Page5, line95-102 |
| | 5b | Describe eligibility criteria for participants. | Page5, line95-102 |
| | 5c | Give details of treatments received, if relevant. | Page5, line95-102 |
| Outcome | 6a | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | Page5, line105-110 |
| | 6b | Report any actions to blind assessment of the outcome to be predicted. | NA |
| Predictors | 7a | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. | Page5-6, line111-line120 |
| | 7b | Report any actions to blind assessment of predictors for the outcome and other predictors. | NA |
| Sample size | 8 | Explain how the study size was arrived at. | NA |
| Missing data | 9 | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | Page5, line95-102 |
| Statistical analysis methods | 10a | Describe how predictors were handled in the analyses. | Page5-6, line104-line120 |
| | 10b | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | Page7-8,line137-line163 |
| | 10d | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | Page7-8,line137-line163 |
| Risk groups | 11 | Provide details on how risk groups were created, if done. | NA |
| **Results** | | | |

TRIPOD Checklist: Prediction Model Development

| | | | |
|---|---|---|---|
| Participants | 13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | Page 8, line166-linr172 |
| | 13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | Table 1 |
| Model development | 14a | Specify the number of participants and outcome events in each analysis. | Table 1 |
| | 14b | If done, report the unadjusted association between each candidate predictor and outcome. | Table 2 |
| Model specification | 15a | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | Table 2 |
| | 15b | Explain how to the use the prediction model. | NA |
| Model performance | 16 | Report performance measures (with CIs) for the prediction model. | Table 2 |
| **Discussion** | | | |
| Limitations | 18 | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | Page 13, line 269-283 |
| Interpretation | 19b | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence. | Page 10-12 |
| Implications | 20 | Discuss the potential clinical use of the model and implications for future research. | Page 10-12 |
| **Other information** | | | |
| Supplementary information | 21 | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | NA |
| Funding | 22 | Give the source of funding and the role of the funders for the present study. | Page 15, line314-316 |

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.