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ORIGINAL ARTICLE

Risk factors for sepsis in patients with struvite stones following percutaneous nephrolithotomy

Xiaomin Gao[1] · Chaoyue Lu[1] · Fei Xie[1] · Ling Li[1] · Min Liu[1] · Ziyu Fang[1] · Zeyu Wang[1] · Shaoxiong Ming[1] · Hao Dong[1] · Rong Shen[1] · Yinghao Sun[1] · Yonghan Peng[1] · Xiaofeng Gao[1]

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Abstract

Purpose To describe the clinical characteristics of struvite stones and determine the preoperative predictors of sepsis in struvite patients undergoing percutaneous nephrolithotomy (PCNL).

Methods A retrospective study of patients who underwent PCNL between April 2011 and March 2018 was performed. The data of the struvite stones and non-struvite stones groups were compared following propensity score matching. Subsequently, the struvite stones group was sub-divided for further analysis according to the Sepsis-3 definition: non-sepsis and sepsis groups.

Results After matching based on age, gender, BMI, and number of access tracts, the comparative analysis showed that staghorn calculi and higher Guy's stone score were more frequently observed in non-struvite stone patients ($n=97$), while a history of urolithiasis surgery (56.70%), preoperative broad-spectrum antibiotic therapy (53.61%), positive preoperative urine culture (55.67%), and sepsis (35.05%) after surgery were more common in patients ($n=97$) with struvite stones (all P values <0.05). Eighteen (18.56%) patients presented with multidrug-resistant (MDR) bacteriuria. Multivariate analysis demonstrated that the preoperative presence of MDR bacteriuria (OR = 3.203; $P=0.043$) and increased serum creatinine (OR = 3.963; $P=0.010$) were independent risk predictors of sepsis. The two factors were used to construct a nomogram to predict the probability of sepsis. The nomogram was well calibrated and had moderate discriminative ability (concordance index: 0.711).

Conclusion Our study revealed that patients with struvite stones were associated with a significantly high risk of calculi recurrence and sepsis after surgery. The presence of MDR bacteriuria preoperatively was a reliable factor to predict sepsis.

Keywords Percutaneous nephrolithotomy · Struvite · Renal calculi · Multidrug resistant

Introduction

Struvite stones account for 10–15% of all urinary calculi and are generally considered to form in the presence of urease-producing bacteria. The mean endotoxin concentration in struvite stones is ≥ 35 times higher than that present in non-struvite stones [1, 2]. Furthermore, struvite stones account for 24% of staghorn calculi [3] and are one of the most common causes of staghorn calculi; they are also known to form rapidly (within 4–6 weeks) [1]. The presence of struvite stones is generally identified as an independent risk predictor of infection-related complications, including sepsis, in patients following percutaneous nephrolithotomy (PCNL) [4–6]. Therefore, the morbidity and mortality after surgery of patients with struvite stones are significantly higher than those of patients with stones comprising other components

Xiaomin Gao, Chaoyue Lu, and Fei Xie are contributed equally to this article.

Yinghao Sun
sunyhsmmu@126.com

Yonghan Peng
yonghanyhtl@163.com

Xiaofeng Gao
gxfdoc@hotmail.com

[1] Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, No.168, Changhai Rd, Shanghai 200433, China

[1, 7, 8]. The third international consensus definitions of sepsis and septic shock (Sepsis-3) updated the definition of sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection [9]. Sepsis-3 is based on the Sequential Organ Failure Assessment (SOFA) scoring system that evaluates changes in the functioning of six major organ systems in the body (respiratory, coagulation, hepatic, cardiovascular, neurological, and renal), and was recommended to replace previous definitions to recognize patients with sepsis or at risk of developing sepsis early [9]. Since the time of Sepsis-3 report being published, it has been cited 3174 times (as of July 26, 2018), indicating its immense value in clinical practice. However, to our knowledge, evaluation of risk factors for sepsis based on Sepsis-3 in patients undergoing PCNL for calculi has rarely been reported. Therefore, the principal aim of this study was to describe the clinical characteristics of struvite stones compared with non-struvite stones and apply Sepsis-3 criteria to identify preoperative predictors of sepsis in struvite patients undergoing PCNL.

Methods

Study design and data collection

After obtaining institutional review board approval, we retrospectively reviewed all consecutive patients who underwent PCNL at the Changhai Hospital from April 2011 to March 2018. All operations were performed by a single experienced urologist (X.F.G) following the standard procedure. Detailed clinical records and laboratory investigations were obtained for all enrolled patients (Table 1). We routinely provided antimicrobial prophylaxis (second-generation cephalosporin) for all patients. Appropriate antibiotics would be administered as empirical therapy when patients had any focus of infection. In addition, a positive urine culture report preoperatively guided the use of sensitive antibiotics. MDR bacteriuria was defined as bacteriuria with the organisms resistant to at least one agent in three or more antimicrobial categories [10].

PCNL technique

A ureteral catheter was placed after induction of general anesthesia in the lithotomy position. Under ultrasonographic guidance, percutaneous access was obtained. Next, a guidewire and the Amplatz dilators were inserted in the tract to place the 22F–24F Amplatz working sheaths. 17F nephroscopy and 1000 μm holmium laser fiber or 22F nephroscopy and ultrasonic endoscopic lithotripter were performed to maximize the dusting effect. The stone fragments were flushed out by irrigation, grasper or forceps. At the end of the procedure, a 6F–7F double-J stent was usually placed for 2–4 weeks and an 18F–20F nephrostomy tube for 2–4 days for drainage.

Perioperative outcome assessment

Data regarding surgery time, access number, transfusion, residual stones, type of surgery, perioperative outcomes, and complications were obtained postoperatively. According to definitions for Sepsis-3, sepsis was defined by a SOFA (Table 2) Score of 2 or more consequent to confirmed or suspected infection. Septic shock was defined as a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mmHg and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation [9]. Complications were graded according to the modified Clavien system. Residual stones were defined as residual fragments of diameter more than 2 mm detected by CT. Struvite stones are known to form in the presence of urease-producing bacteria [1]. Therefore, patients with struvite stones were typically thought to have an infection.

Statistical analysis

We performed propensity score matching to control for imbalances in confounding factors in the cohort. The propensity score was estimated for all patients using multivariate logistic regression based on the following covariates: age, gender, BMI, and number of access tracts. As a result, struvite stone patients were matched 1:1 with non-struvite stone patients based on the propensity score. Comparisons of normally distributed continuous variables were performed using Student's *t* test, and the Mann–Whitney *U* test was used for non-normally distributed data. Chi square or Fisher's exact test was used for comparisons of categorical variables. Multivariable forward stepwise logistic regression analysis was performed subsequently. Two-tailed *p* values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

Nomograms for sepsis were established based on the results of multivariate analysis by R software (Version 3.4.1; Institute for Statistics and Mathematics, Vienna, VIC, Austria) with the package rms. The performance of the nomogram was assessed by a calibration plot for internal calibration and the discriminative ability of the nomogram was measured by the concordance index (c-index) [11]. The larger the c-index, the more accurate was the prognostic ability of the nomogram (low discriminative ability: 0.50–0.70; moderate discriminative ability: 0.71–0.90; high discriminative ability: 0.90–1) [12].

Table 1 Demographic and clinical data of all population

Parameter	Total $N=194$	Struvite $N=97$	Non-struvite $N=97$	P
Age, years	49.01 (13.19)	48.69 (12.90)	49.33 (13.52)	0.737
BMI, kg/m^2	23.76 (3.43)	23.65 (3.53)	23.87 (3.35)	0.650
Gender, male	95 (48.97%)	42 (43.30%)	53 (54.64%)	0.114
Diabetes mellitus	16 (8.25%)	9 (9.28%)	7 (7.22%)	0.602
CSD, mm	39.38 (26.29)	43.03 (28.41)	35.72 (23.57)	0.053
Staghorn calculi	82 (42.27%)	29 (29.90%)	53 (54.64%)	< 0.001*
Guy's stone score				0.001*
Grade 1	24 (12.37%)	15 (15.46%)	9 (9.28%)	
Grade 2	86 (44.33%)	52 (53.61%)	34 (35.05%)	
Grade 3	61 (31.44%)	18 (18.56%)	43 (44.33%)	
Grade 4	23 (11.86%)	12 (12.37%)	11 (11.34%)	
Main stone composition				
COM	119 (61.34%)	36 (37.11%)	83 (85.57%)	< 0.001*
COD	117 (60.31%)	61 (62.89%)	56 (57.73%)	0.456
Struvite	97 (50.00%)	97 (100.00%)	0	
Brushite	2 (1.03%)	0	2 (2.06%)	
Carbapatite	153 (78.87%)	83 (85.57%)	70 (72.16%)	0.020*
Uric acid	11 (5.7%)	1 (1.03%)	10 (10.31%)	0.005*
Cystine	1 (0.52%)	0	1 (1.03%)	
History of urolithiasis surgery				
PCNL	35 (18.04%)	25 (25.77%)	10 (10.31%)	< 0.001*
RIRS	28 (14.43%)	17 (17.53%)	11 (11.34%)	0.220
ESWL	23 (11.86%)	6 (6.19%)	17 (17.53%)	0.015*
Open surgery	7 (3.61%)	7 (7.22%)	0 (0)	
All	93 (47.94%)	55 (56.70%)	38 (39.18%)	< 0.001*
Type of preoperative decompression				
Indwelling of ureteral stent	18 (9.28%)	9 (11.22%)	9 (10.94%)	1.000
Percutaneous nephrostomy	5 (2.58%)	3 (5.10%)	2 (3.13%)	1.000
Both	8 (25.81%)	2 (2.04%)	6 (6.19%)	0.279
Day of antibiotic use before surgery	3.93 (3.08)	3.57 (2.30)	4.30 (3.67)	0.098
Preoperative broad-spectrum antibiotic therapy	61 (31.44%)	52 (53.61%)	9 (9.28%)	< 0.001*
Preoperative Cr, mg/dl	0.99 (0.46)	1.01 (0.55)	0.97 (0.37)	0.527
Positive preoperative urine culture	82 (42.27%)	54 (55.67%)	28 (28.87%)	< 0.001*
Positive preoperative MDR urine culture	34 (17.53%)	18 (18.56%)	16 (16.49%)	0.706
Blood bilirubin, μmol/L	11.54 (5.78)	10.58 (5.24)	12.51 (6.15)	0.020*
Blood WBC, 10^9/L	6.37 (1.80)	6.18 (1.61)	6.56 (1.96)	0.141
NLR	2.23 (1.72)	2.37 (2.24)	2.09 (0.94)	0.261
Type of surgery				< 0.001*
Holmium laser lithotripsy	145 (74.74%)	51 (52.58%)	94 (96.91%)	
Ultrasonic endoscopic lithotripsy	49 (25.26%)	46 (47.42%)	3 (3.09%)	
Surgery time, m	104.10 (42.82)	101.96 (44.09)	106.25 (41.64)	0.487
Multiple access tracts	16 (8.25%)	10 (10.31%)	6 (6.19%)	0.296
Residual stone	73 (37.63%)	31 (31.96%)	42 (43.30%)	0.103
Complications				
Fever	26 (13.40%)	14 (14.43%)	12 (12.37%)	0.673
Bleeding	16 (8.25%)	11 (11.34%)	5 (5.15%)	0.117
Transfusion	5 (2.58%)	5 (5.15%)	0 (0)	
Sepsis	43 (22.16%)	34 (35.05%)	9 (9.28%)	< 0.001*
Septic shock	6 (4.48%)	5 (5.15%)	1 (1.03%)	0.213

CSM cumulative stone diameter, *NLR* neutrophil–lymphocyte ratio, *MLR* monocyte–lymphocyte ratio *COM* calcium oxalate monohydrate *COD* calcium oxalate dihydrate *PCNL* percutaneous nephrolithotomy, *RIRS* retrograde intrarenal surgery, *ESWL* extracorporeal shock wave lithotripsy, *MDR* multidrug resistant

*Statistically significant

Table 2 Components of SOFA Score

	$N=97$
SOFA Score	
0	46 (47.42%)
1	17 (17.53%)
2	17 (17.53%)
3	6 (6.19%)
4	8 (8.25%)
≥ 5	3 (3.10%)
Respiration, PaO_2/FIO_2, mmHg	
0 (≥ 400)	77 (79.38%)
1 (< 400)	9 (9.28%)
2 (< 300)	10 (10.31%)
3 (< 200 with respiratory support)	1 (1.03%)
4 (< 100 with respiratory support)	0
Coagulation, platelets, $\times 10^3$/μL	
0 (≥ 150)	83 (85.57%)
1 (< 150)	10 (10.31%)
2 (< 100)	3 (3.09%)
3 (< 50)	1 (1.03%)
4 (< 20)	0
Liver, bilirubin, mg/dL	
0 (1.2)	87 (89.69%)
1 (1.2–1.9)	8 (8.25%)
2 (2.0–5.9)	2 (2.06%)
3 (6.0–11.9)	0
4 (> 12.0)	0
Cardiovascular	
0 (MAP ≥ 70 mmHg)	77 (79.38%)
1 (MAP < 70 mmHg)	10 (10.31%)
2 (Dopamine < 5 or dobutamine (any dose))[a]	6 (6.19%)
3 (Dopamine 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1)[a]	4 (4.12%)
4 (Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1)[a]	0
Glasgow Coma Scale Score[b]	
0 (15)	97 (100%)
1 (13–14)	0
2 (10–12)	0
3 (6–9)	0
4 (< 6)	0
Renal, creatinine, mg/dL (urine output, ml/d)	
0 (< 1.2)	80 (82.47%)
1 (1.2–1.9)	11 (11.34%)
2 (2.0–3.4)	5 (5.15%)
3 (3.5–4.9) (< 500)	1 (1.03%)
4 (> 5) (< 200)	0

FIO_2 fraction of inspired oxygen, *MAP* mean arterial pressure, PaO_2 partial pressure of oxygen

[a]Catecholamine doses are given as μg/kg/min for at least 1 h

[b]Glasgow Coma Scale Scores range from 3 to 15; higher score indicates better neurological function

Results

A total of 1145 patients with struvite stones or non-struvite stones (98 vs. 1047) were included in this study. 97 patients with struvite stones were matched to 97 patients with non-struvite stones. Detailed demographic and clinical data of the propensity score-matched cohort are shown in Table 1. Although staghorn calculi and higher Guy's stone score were frequently observed in non-struvite stone patients, history of urolithiasis surgery, preoperative broad-spectrum antibiotic therapy, positive preoperative urine culture, higher blood bilirubin, ultrasonic endoscopic lithotripsy, and sepsis after surgery were more common in patients with struvite stones (all P values < 0.05). Moreover, the main stone composition consisting of calcium oxalate monohydrate (COM), brushite, carbapatite, uric acid, and cysteine was more frequently observed in non-struvite stone patients (all P values < 0.05). There were no significant differences in the remaining factors between the two groups.

We then analyzed the detailed demographic and clinical data of patients with struvite stones (Table 3). There were 42 (43.30%) men and 55 (56.70%) women, with a mean age of 48.69 (12.90) years. The ASA score of all patients was grade 1 or 2. Other detailed information is presented in Table 3. Longer CSD, higher preoperative Cr, positive MDR urine culture preoperatively, and the presence of classically described urease-producing bacteria were more frequently observed in patients who experienced sepsis or septic shock compared to those in patients who never suffered from sepsis or shock after surgery (All $P < 0.05$).

Positive urine culture was present in 54 (55.67%) patients preoperatively, including 18 (18.56%) patients with MDR bacteriuria. As shown in Fig. 1, 59 organisms were isolated from the urine culture, with *E. coli* (18.64%, 11/59 isolates) and *Proteus mirabilis* (18.64%, 11/59 isolates) being the most common. As shown in Fig. 2, a total of 20 isolates were identified as MDR, with *E. coli* (40%, 8/20 isolates), *Proteus mirabilis* (20%, 4/20 isolates), and *Staphylococcus species* (15%, 3/20 isolates) being the top three most prevalent MDR organisms. In total, 11 (61.11%) of 18 patients with MDR organisms developed postoperative sepsis compared to 23 (29.11%) of 79 patients without MDR organisms ($P = 0.010$). In addition, patients with positive MDR urine culture preoperatively had a higher risk of developing fever ($P = 0.031$), bleeding ($P < 0.001$), SIRS/sepsis requiring additional antibiotics ($P = 0.001$), and septic shock ($P = 0.002$) compared to patients who had a negative MDR urine culture preoperatively (Table 4). However, the two groups were comparable with regard to transfusion ($P = 0.499$) rates.

Based on the Sepsis-3 definition, 34 (35.05%) patients developed sepsis following surgery, of whom 5 (5.10%) experienced septic shock. Those with postoperative sepsis were more likely to have had higher preoperative serum creatinine levels (Cr) and positive MDR urine culture preoperatively (Table 5). There were no significant differences between those with and without sepsis with regard to remaining factors. In univariate analysis, increased preoperative Cr and positive preoperative MDR urine culture were associated with a higher probability of sepsis (Table 5). In multivariate analysis, increased preoperative Cr (OR = 3.880; $P = 0.011$) and positive preoperative MDR urine culture (OR = 3.164; $P = 0.045$) were identified as independent risk factors of postoperative sepsis.

The nomogram was depicted by two independent predictors described in multivariate analysis (Fig. 3). To use the nomogram, an individual patient's value was located on the variable axis, and each subtype was assigned a score according to the point scale. The sum of points was calculated as total points, which implied the probability of sepsis (the bottom scale). The nomogram was internally validated by computing the bootstrap-corrected Harrell index and by the calibration plot. The c-index was 0.711, indicating a moderate discriminative ability of the model; and as illustrated in Fig. 4, the nomogram was well calibrated.

Discussion

In the present study, we compared the detailed demographic and clinical data of patients with struvite stones ($n = 97$) and those with non-struvite stones ($n = 97$) by performing propensity score matching. Our results demonstrated that a history of urolithiasis surgery, preoperative broad-spectrum antibiotic therapy, positive preoperative urine culture, higher blood bilirubin, ultrasonic endoscopic lithotripsy, and sepsis after surgery were more common in patients with struvite stones (all P values < 0.05), while staghorn calculi and higher Guy's stone score were more frequently observed in non-struvite stone patients. In subgroup analysis, longer CSD, higher preoperative Cr, presence of MDR urine culture preoperatively, and the presence of classically described urease-producing bacteria were more commonly observed in patients who experienced sepsis or septic shock compared to patients who never suffered from sepsis or shock after surgery (All $P < 0.05$). Moreover, preoperative positive MDR bacteriuria (odds ratio [OR] = 3.203; $P = 0.043$) and increased serum creatinine (OR = 3.963; $P = 0.010$) were identified as independent risk predictors of sepsis according to multivariate analysis. A nomogram was established based on these two factors to predict the probability of sepsis. It was well calibrated and had a moderate discriminative ability (concordance index: 0.711). In conclusion, patients with struvite stones were more likely to experience stone recurrence compared to patients with non-struvite stones (history

Table 3 Demographic and clinical data of struvite patients

Parameter	Total N=97	Sepsis (+) N=34	Sepsis (−) N=63	P
Age	48.69 (12.90)	51.38 (11.78)	47.24 (13.33)	0.132
BMI	23.65 (3.53)	23.30 (2.49)	23.84 (3.98)	0.473
Gender, male	42 (43.30%)	12 (35.29%)	30 (47.62%)	0.242
Diabetes mellitus	9 (9.28%)	3 (8.82%)	6 (9.38%)	1.000
CSD	43.03 (28.41)	51.54 (30.69)	38.44 (26.21)	0.030*
Staghorn calculi	29 (29.90%)	14 (41.18%)	15 (23.81%)	0.075
Guy's stone score				0.294
Grade 1	15 (15.46%)	4 (11.76%)	11 (17.46%)	
Grade 2	52 (53.61%)	16 (47.06%)	36 (57.14%)	
Grade 3	18 (18.56%)	7 (20.59%)	11 (17.46%)	
Grade 4	12 (12.37%)	7 (20.59%)	5 (7.94%)	
History of urolithiasis surgery				
PCNL	25 (25.77%)	10 (29.41%)	15 (23.81%)	0.547
RIRS	17 (17.53%)	6 (17.65%)	11 (17.46%)	0.982
ESWL	6 (6.19%)	2 (5.88%)	4 (6.35%)	0.726
Open surgery	7 (7.22%)	4 (4.12%)	3 (4.76%)	0.389
All	55 (56.70%)	22 (64.71%)	33 (52.38%)	0.242
Type of preoperative decompression				
Indwelling of ureteral stent	9 (9.28%)	2 (5.88%)	7 (11.11%)	0.339
Percutaneous nephrostomy	3 (3.09%)	1 (2.94%)	2 (3.17%)	0.581
Both	2 (2.06%)	2 (5.88%)	0	
Day of antibiotic use before surgery	3.54 (2.31)	3.79 (2.37)	3.44 (2.28)	0.479
Preoperative broad-spectrum antibiotic therapy	52 (53.61%)	22 (64.71%)	30 (46.88%)	0.107
Preoperative Cr, mg/dl	0.99 (0.46)	1.01 (0.55)	0.97 (0.37)	0.001*
Positive preoperative urine culture	54 (55.67%)	23 (67.65%)	31 (49.21%)	0.081
Positive preoperative MDR urine culture	18 (18.56%)	11 (32.35%)	7 (11.11%)	0.010*
Type of bacteria				
Classically described urease-producing bacteria[a]	11 (11.34%)	8 (23.53%)	3 (4.76%)	0.014*
Other bacteria[b]	43 (44.33%)	15 (44.12%)	28 (44.44%)	0.975
Blood bilirubin, μmol/L	10.58 (5.24)	10.62 (6.91)	10.56 (4.13)	0.961
Blood WBC, 10^9/L	6.18 (1.61)	6.32 (1.86)	6.10 (1.47)	0.520
NLR	2.37 (2.24)	2.90 (3.52)	2.08 (0.95)	0.082
Type of surgery				0.365
Holmium laser lithotripsy	51 (52.58%)	20 (58.82%)	31 (49.21%)	
Ultrasonic endoscopic lithotripsy	46 (47.42%)	14 (41.18%)	32 (50.79%)	
Surgery time	101.96 (44.09)	103.29 (47.42)	101.24 (42.56)	0.828
Multiple access tracts	10 (10.31%)	4 (11.76%)	6 (9.52%)	1.000
Residual stone	31 (31.96%)	15 (44.12%)	16 (25.40%)	0.059
Blood transfusion	5 (5.15%)	4 (11.76%)	1 (1.59%)	0.093

CSM cumulative stone diameter, *NLR* neutrophil–lymphocyte ratio, *MLR* monocyte–lymphocyte ratio, *PCNL* percutaneous nephrolithotomy, *RIRS* retrograde intrarenal surgery, *ESWL* extracorporeal shock wave lithotripsy, *MDR* multidrug resistant

[a]Classically described urease-producing bacteria: *Proteus* species, *Providencia* species, and *Morganella morganii*

[b]Other bacteria *Staphylococcus* species, *Streptococcus* species, *Enterococcus faecalis*, *Candida albicans*, *E. coli*, *Klebsiella* species, *Candida* species, mixed organisms, *baumanii*, and *Pseudomonas aeruginosa*

*Statistically significant

of urolithiasis surgery: 56.70% vs. 39.18%; $P < 0.001$). Struvite stone patients were also associated with a significantly high possibility of developing sepsis (35.05% vs. 9.28%; $P < 0.001$), although approximately half of them received broad-spectrum antibiotic therapy preoperatively (53.61% vs. 9.28%; $P < 0.001$) and the rate of residual stones was

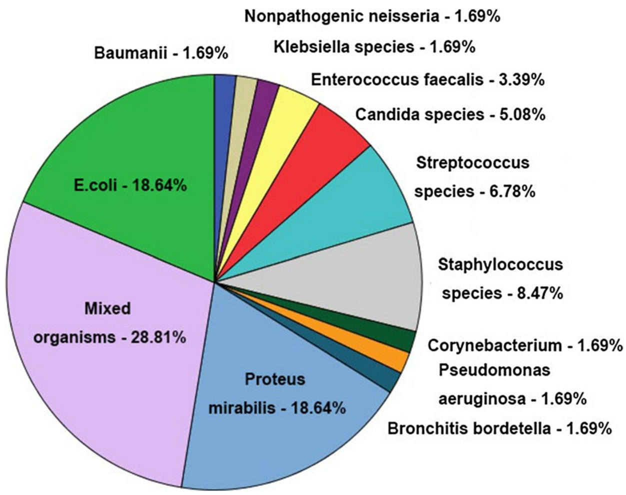

Fig. 1 Isolated pathogens from preoperative urine culture

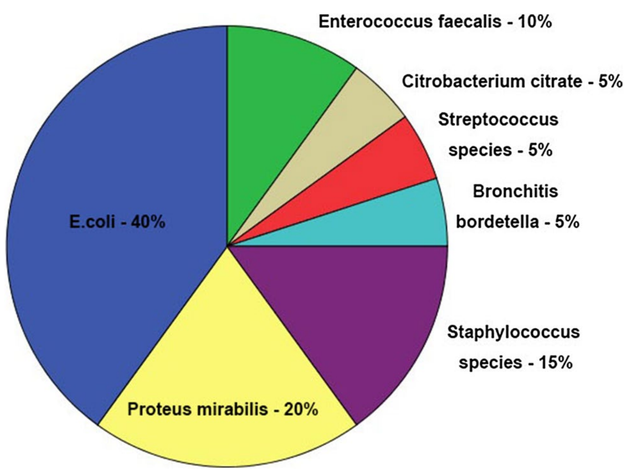

Fig. 2 Isolated multidrug-resistant (MDR) bacteria from preoperative urine culture

low (31.96% vs. 43.30%; $P=0.103$). However, our findings revealed that preoperative positive MDR bacteriuria was a favorable factor to predict sepsis and the nomogram was a reliable tool for urologists to make clinical decisions preoperatively.

Sepsis is a common and serious complication in patients with struvite stones following PCNL [7, 8]. Stone-colonizing bacteria and bacterial endotoxins are released during PCNL, which then translocate to systemic circulation, contributing to the occurrence of postoperative infections and even sepsis [2, 13]. As mentioned above, large endotoxin concentrations can be identified in struvite stones. It has been previously reported that massive endotoxins are released during manipulation of struvite stones and the subsequent increased serum endotoxin concentrations are similar to those seen in Gram-negative sepsis [2]. Early and rapid diagnosis and treatment of these sepsis patients is important to prevent the development of multiple organ dysfunctions. In 2016, the Third International Consensus taskforce framed the definition of sepsis as “life-threatening organ dysfunction due to a dysregulated host response to infection” [14]. In contrast to Sepsis-1, the term “systemic inflammatory response” was replaced by “dysregulated host response” and “SIRS” was replaced by “SOFA” in Sepsis-3. This modification was based on the improved understanding of sepsis pathobiology (pathogen factors) and significant biological and clinical heterogeneity was noted in affected individuals (host factors) [9, 15]. The use of SIRS criteria to identify sepsis is now believed to be unhelpful because it included a small portion of inpatients who were sepsis negative (poor discriminant validity) [16] and excluded some who were sepsis positive (poor concurrent validity) [17]. Therefore, the newly published Sepsis-3 definition has been unanimously identified as having higher sensitivity and specificity compared to previous definitions [18, 19]. We therefore used the Sepsis-3 criteria to diagnose sepsis in patients following PCNL and to group them for further analysis. In the present study, 34 (35.05%) patients developed sepsis following surgery, of whom 5 (5.15%) experienced septic shock according to the Sepsis-3 definition.

The formation of struvite stones is always associated with bacteria that produce the enzyme urease, including *Proteus species, Providencia species, and Morganella*

Table 4 Details of postoperative complications according to the Clavien–Dindo classification

	Total	Preoperative MDR urine culture (+) ($n=18$)	Preoperative MDR urine culture (−) ($n=79$)	P
Complication classification				
Fever (grade 1)	14	6 (33.33%)	8 (10.13%)	0.031*
Bleeding (grade 1)	11	8 (44.44%)	3 (3.80%)	< 0.001*
SIRS/sepsis requiring additional antibiotics (grade 2)	27	11 (61.11%)	16 (20.25%)	0.001*
Transfusion (grade 2)	5	2 (11.11%)	3 (3.80%)	0.499
Septic shock (grade 4)	5	4 (22.22%)	1 (1.27%)	0.002*

*Statistically significant

Table 5 Univariate and multivariate logistic regression analysis of factors associated with sepsis

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.026 (0.992–1.062)	0.134		
BMI	0.956 (0.847–1.080)	0.469		
Gender (male/female)	0.600 (0.254–1.418)	0.244		
Diabetes mellitus (yes/no)	0.919 (0.215–3.932)	0.910		
CSD	1.017 (1.001–1.032)	0.033*		
Staghorn calculi (yes/no)	2.240 (0.914–5.487)	0.078		
Guy grade (≥ 3/< 3)	2.056 (0.846–4.997)	0.112		
History of urolithiasis surgery (yes/no)	1.406 (0.609–3.247)	0.425		
Preoperative decompression (yes/no)	1.034 (0.317–3.376)	0.955		
Day of antibiotic use before surgery	1.068 (0.892–1.280)	0.475		
Preoperative broad-spectrum antibiotic therapy (yes/no)	2.017 (0.854–4.765)	0.110		
Preoperative Cr	4.268 (1.525–11.944)	0.006*	3.880 (1.364–11.032)	0.011*
Positive preoperative urine culture (yes/no)	2.158 (0.903–5.162)	0.084		
Positive preoperative MDR urine culture (yes/no)	3.826 (1.319–11.096)	0.014*	3.164 (1.027–9.746)	0.045*
Blood bilirubin	1.002 (0.925–1.085)	0.961		
Blood WBC	1.089 (0.841–1.411)	0.516		
NLR	1.291 (0.886–1.882)	0.184		
ultrasonic endoscopic lithotripsy (yes/no)	0.678 (0.292–1.575)	0.366		
Surgery time	1.001 (0.992–1.011)	0.826		
Multiple access tracts (yes/no)	1.267 (0.332–4.838)	0.730		
Residual stone (yes/no)	2.319 (0.959–5.609)	0.062		
Blood transfusion (yes/no)	8.267 (0.885–77.206)	0.064		

*Statistically significant

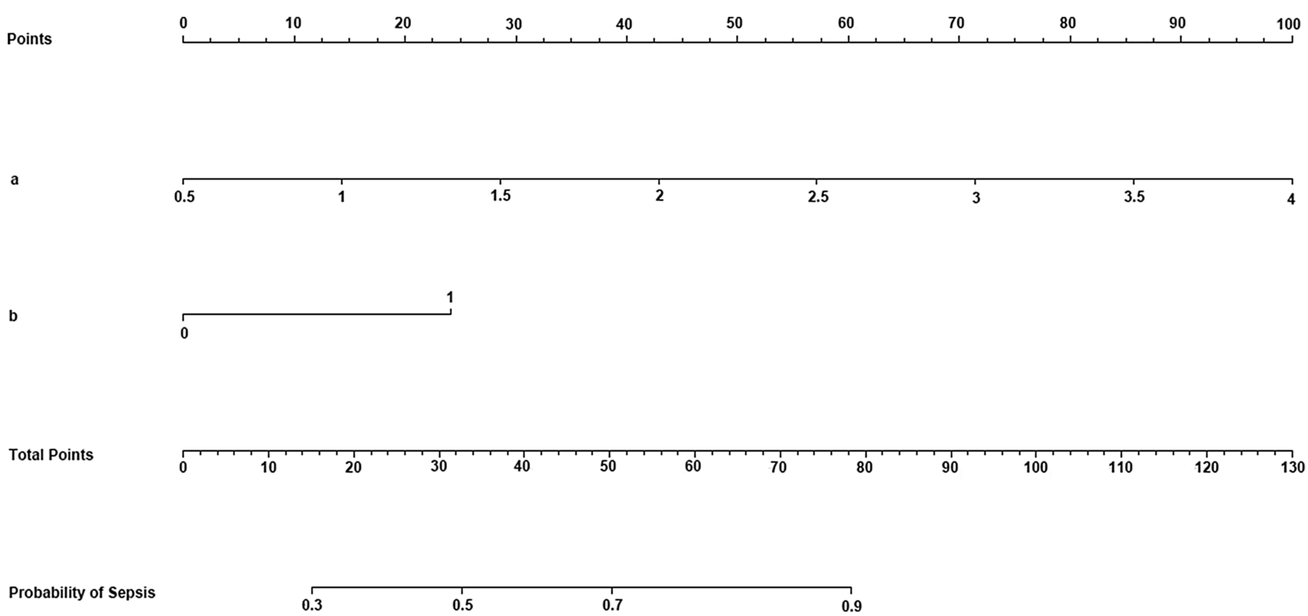

Fig. 3 Nomogram with preoperative serum creatinine values (**a**) and preoperative MDR bacteriuria (**b**) predicts the probability of sepsis

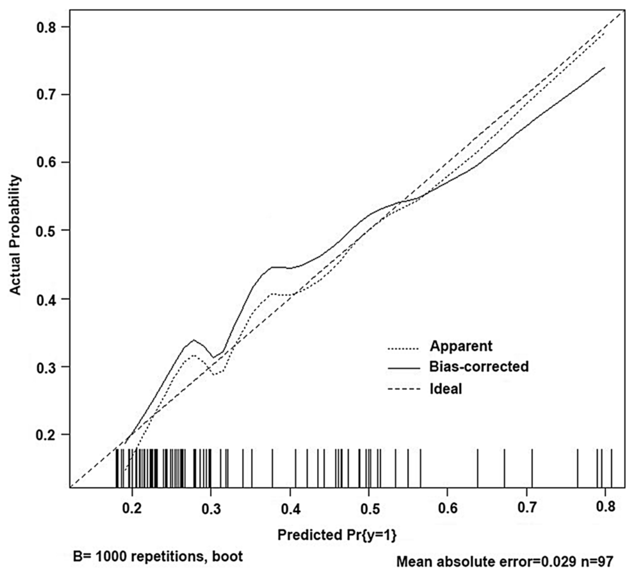

Fig. 4 Calibration plot of the nomogram for the probability of sepsis

morganii, etc. Moreover, these stones can also harbor Gram-negative bacteria that contain endotoxins [20]. In the present study, *E. coli* (18.64%, 11/59 isolates) and *proteus mirabilis* (18.64%, 11/59 isolates) were the most common organisms isolated from urine culture, which indicated that the large number of *E. coli* bacteria and their endotoxins might greatly contribute to the occurrence of postoperative sepsis. Although the positive preoperative urine culture was not identified as an independent risk factor of sepsis in multivariate analysis, the presence of MDR bacteria significantly increased the risk of sepsis by more than threefold (OR = 3.203; $P = 0.043$). This finding is of concern because the emergence of MDR organisms has now become a significant public health threat with fewer or even no effective antibiotics available to treat infections caused by these. The increasing number of infections caused by MDR bacteria in recent years has become a worldwide problem [21]. In the USA, at least 2 million patients develop antibiotic resistance-related infections each year and more than 23,000 patients died due to these infections [22]. A meta-analysis revealed that the presence of MDR Gram-negative bacteria increased the risk of mortality by 50% compared to the risk posed by the presence of non-MDR Gram-negative bacteria among inpatients [23]. Patel et al. reported a relatively high prevalence of MDR bacteriuria (24/81, 30%) in patients following PCNL and found that the presence of MDR bacteria significantly increased the risk of postoperative infectious complications by nearly fivefold (OR = 4.89; $P = 0.016$) [24]. Therefore, the emergence and growth of MDR is a substantial clinical and economic burden, associated with increased mortality, greater hospital and antibiotic costs, and longer stays in hospitals and intensive care units [25]. Moreover, patients with MDR bacteria were more likely to experience fever, bleeding, SIRS/sepsis requiring additional antibiotics, and septic shock. Therefore, this finding is of high clinical importance, and extra caution needs to be exercised in the management of patients with struvite stones undergoing PCNL.

Our results also demonstrated that increased preoperative serum creatinine levels independently predicted postoperative sepsis (OR = 3.963; $P = 0.010$). Patients with staghorn calculi or longer CSD are generally accompanied by weakened renal function. Staghorn calculi or CSD has been identified as a risk predictor for postoperative sepsis in previous studies among patients with renal stones without considering stone composition [4]. However, in multivariate analysis, staghorn calculi or CSD was excluded for showing no significance. This suggests that high preoperative serum creatinine level has a stronger predictive ability for sepsis than staghorn calculi or CSD in patients with struvite stones. Chen et al. recently retrospectively investigated 802 complex kidney stone patients who underwent PCNL and identified 19 (2.4%) patients with sepsis [26]. Their results demonstrated that a urine test with concurrent positive WBCs and urine nitrites (WBC + NIT +) was an independent risk factor of sepsis (OR: 3.9; $P = 0.021$); while our study did not find statistically significant association between preoperative urine WBC + NIT + ($P = 0.405$) and sepsis. Due to differences in criteria for sepsis and heterogeneity of the study population, it is difficult to generalize the conclusion of this study. Previous studies have demonstrated that NLR can predict the prognosis of patients with inflammatory and malignant diseases well. Reports from several researches also recommend NLR as an infection marker in sepsis patients [27, 28]. Sen et al. reported that the incidence of sepsis was significantly higher following PCNL in patients with high NLR values than in patients with low NLR [27] ($P = 0.006$). In the present study, we evaluated the role of NLR in predicting the occurrence of sepsis in patients with struvite stones. Our results revealed that high NLR was not statistically associated with sepsis in univariate analysis ($P = 0.184$).

Our study has several strengths. First, we performed propensity score matching for comparing patients with struvite and non-struvite stones to control for the imbalances in confounding factors. Second, it is the first study to investigate the predictors of sepsis among patients with struvite stones. Because struvite recurrence rate is relatively high [1], patients with recurrent struvite stones can be counseled appropriately about these risk factors and nomograms be constructed for predicting the inevitable second surgery. Third, even though there is no gold standard method to determine struvite stones preoperatively, they can be identified in the clinic based on the presence of urease-producing bacteria, formation of staghorn calculi in a short time, and decreased CT value (666 ± 87 HU at 120 kV) [29]. Therefore, our findings are also clinically meaningful for suspected struvite stone patients who undergo surgery.

There are some limitations of this study, including its retrospective nature, representing the database of a single institution, and the small sample size. Intraoperative stone analysis and renal pelvic culture were not performed in all patients, which limits our interpretation. We now routinely collect intraoperative samples for stone analysis and renal pelvic culture for deciding postoperative antibiotic strategies. We were also unable to evaluate the baseline value of SOFA. Because the baseline SOFA Scores of patients with nephrolithiasis in outpatient clinics are generally assumed to be 0, even patients with preexisting organ dysfunction cannot be detected. In addition, our study conclusions might not be generalizable to a "Western" population as the mean BMI in this study was rather low (mean BMI 23.76 ± 3.43 kg/m^2) and the rate of *E. coli* bacteriuria was < 20%, while it can be much higher in Western countries.

Conclusion

Our study demonstrated that staghorn calculi and higher Guy's stone score were more frequently observed in non-struvite stone patients, while a history of urolithiasis surgery, preoperative broad-spectrum antibiotic therapy, positive preoperative urine culture, and sepsis after surgery were more common in patients with struvite stones. The presence of preoperative MDR bacteriuria could strongly predict postoperative sepsis. Furthermore, the nomogram established in this study is a moderately accurate tool that can predict the probability of sepsis.

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Author contributions GXM: manuscript writing, manuscript editing. LC and XF: data collection. LL, LM, FZ, and WZ: data collection and statistical analysis. MS, DH, and SR: manuscript editing. SY, PY, and GXF: project development, manuscript editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the local research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent For this retrospective study formal consent was not required.

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