The Validity of Neutrophil/lymphocyte Ratio as A Predictive Factor for Systemic Inflammatory Response Syndrome after Flexible Ureteroscopy Lithotripsy

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Purpose: To explore the risk factors and predictive factors of systemic inflammatory response syndrome (SIRS) after flexible ureteroscopy (fURS) for upper urinary tract stones.

Materials and Methods: Patients who underwent fURS from January 2014 to September 2019 were retrospectively analyzed, which were divided into the SIRS group and non-SIRS group. Clinical data of all patients, including gender, age, American society of anesthesia score, diabetes, etc., were collected. Univariate and multivariate logistic regression was used to determine the independent risk factors for SIRS after fURS, and the receiver operating characteristic (ROC) curve was drawn to verify the validity of the results. In addition, patients from October 2019 to January 2020 were prospectively collected to verify the results.

Results: A total of 369 patients were retrospectively included. Univariate analysis showed significant differences in postoperative stone residuals ($P = 0.039$), preoperative neutrophil/ lymphocyte ratio (NLR) ($P < 0.001$), and lymphocyte/monocyte ratio (LMR) ($P = 0.001$) between two groups. Further, preoperative NLR and postoperative stone residuals were independent according to multivariate logistic regression analysis. The optimal cut-off value of preoperative NLR by ROC curve was 2.61, and the area under ROC curve was 77.9%. Prospective analysis based on 53 patients showed that the incidence of SIRS in patients with NLR > 2.61 was significantly higher than that in other patients. (RR = 4.932, $P = 0.040$).

Conclusion: Preoperative NLR can be used as a predictive factor for SIRS in patients with fURS according to our study. It may provide an evidence for clinicians to make preoperative decisions or medical plans.

Keywords: fURS; SIRS; neutrophil/lymphocyte ratio; inflammation

INTRODUCTION

The application of flexible ureteroscope had a history of more than 50 years since it was firstly used in 1964[(1)]. With the rapid improvement of endoscopies in recent years, flexible ureteroscope was widely used in the diagnosis and treatment of urinary diseases[(2)]. Though flexible ureteroscopy (fURS) had gradually become one of the main choice for upper urinary tract stones because of its safety and effectiveness[(3)], complications were also reported.

A retrospective study showed that the incidence of infectious complications after fURS ranged from 1.7% to 18.8%, including fever, septicemia and septic shock[(4)]. Without timely treatment, patients might rapidly deteriorate to serious complications, such as urogenic sepsis, septic shock, or even multiple organ dysfunction syndrome. It was estimated that the mortality was reported to be 10-20% in simple sepsis, 20-50% in severe sepsis, and 40-80% in septic shock[(5)]. Therefore, it was very important to predict the infectious complications after an operation on upper urinary tract stones. Previous studies had reported that the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) could predict the infection and prognosis for tumor patients[(6,7)]. However, it was still obscure whether they could predict the occurrence of systemic inflammatory response syndrome (SIRS) after fURS. Therefore, we aimed to explore the risk factors of SIRS after fURS and the clinical significance of NLR, PLR and LMR in predicting SIRS after fURS.

MATERIALS AND METHODS

General information

A total of 369 patients with upper urinary stones who underwent fURS in the Second Affiliated Hospital of Chongqing Medical University from January 2014 to September 2019 were retrospectively included. According to whether these patients were diagnosed with SIRS after operation, they were divided into the SIRS group and non- SIRS group. In total, there were 29 males and 14 females with an average age of 54.9 ± 11.3 years were included in the SIRS group, and 223 males and 103 females with an average age of 51.1 ± 12.7 years were included in non-SIRS group. Further, the data of 53 patients from October 2019 to January 2020 were prospectively collected to verify the results.

Inclusion and exclusion criteria

Inclusion criteria: all patients with upper urinary tract

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Table 1. The demographic characteristics and surgery-related data of included patients.

	Overall	Non-SIRS group	SIRS group	*P*	95% CI
Number of patients (N)	369	326	43		
Age (years old, Mean ± SD)	51.6 ± 12.6	51.1±12.7	54.9 ± 11.3	0.063	-7.782-0.207
Gender ((N, %)				0.898	0.530-2.062
-Male	252 (68.3%)	223 (68.4%)	29 (67.4%)		
-Female	117 (31.7%)	103 (31.6%)	14 (32.6%)		
Stone surgery history (N, %)	110 (29.8%)	95 (29.1%)	15 (34.9%)	0.439	0.666-2.548
-PCNL	17 (4.6%)	15 (4.6%)	2 (4.7%)		
-ESWL	41 (11.1%)	38 (11.7%)	3 (7.0%)		
-URS/fURS	43 (11.7%)	34 (10.4%)	9 (20.9%)		
-Open surgery	9 (2.4%)	8 (2.5%)	1 (2.3%)		
Diabetes (N,%)	55 (14.9%)	52 (16.0%)	3 (7.0%)	0.120	0.118-1.325
ASA score(Mean±SD)	2.1 ± 0.4	2.1 ± 0.4	2.1 ± 0.4	0.772	-0.104-0.140
Stone burden(cm^2, Mean±SD)	1.04 ± 0.90	1.04 ± 0.88	1.06 ± 1.05	0.931	-0.301-0.275
Operation time(min, Mean±SD)	69.4±36.6	69.6 ± 37.1	67.8 ± 33.3	0.766	-9.928-13.456
Preoperative serum reatinine(N,%)				0.872	0.261-3.127
-normal	341 (92.4%)	301 (92.3%)	40 (93.0%)		
-Elevated	28 (7.5%)	25 (7.7%)	3 (7.0%)		
Postoperative stone residuals (N, %)		0.039	1.026-4.256		
-No	300 (81.3%)	270 (82.8%)	30 (69.8%)		
-Yes	69 (18.7%)	56 (17.2%)	13 (30.2%)		
Preoperative NLR(Mean±SD)	2.75 ± 1.47	2.60 ± 1.26	3.90 ± 2.28	< 0.001	-1.749-0.847
Preoperative PLR(Mean±SD)	130.15 ± 51.55	128.70 ± 50.04	141.16 ± 62.40	0.136	-28.885-3.957
Preoperative LMR(Mean±SD)	4.96 ± 2.36	5.12 ± 2.40	3.82 ± 1.66	0.001	0.556-2.038
Unilateral or bilateral (N,%)				0.498	0.564-3.237
-Unilateral	321 (87.0%)	285(87.4%)	36 (83.7%)		
-Bilateral	48 (13.0%)	41(12.6%)	7 (16.3%)		
Preoperative D-J stent(N,%)		0.151	0.034-1.911		
-No	340 (92.1%)	298 (91.4%)	42 (97.7%)		
-Yes	29 (7.9%)	28 (8.6%)	1 (2.3%)		

Abbreviations: PCNL: percutaneous nephrolithotripsy; ESWL: extracorporeal shock wave lithotripsy; URS: ureteroscopy lithotripsy; fURS: flexible ureteroscopy; ASA: American Society of Anesthesiologists score; NLR: Neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; CI: confidence interval; SIRS: systemic inflammatory response syndrome.

stones treated by fURS.

Exclusion criteria: (1) patients who met at least one of SIRS diagnostic criterions before operation(10).[2] Patients with tumors, hematological diseases or other diseases.[3] Patients with abnormal urinary system anatomy, such as horseshoe kidney, polycystic kidney, ureteropelvic junction obstruction, etc.(4) Patients needing simultaneous operations; (5) Pregnant women or children.

All patients underwent routine urine examination and culture to determine whether patients were suffered from urinary tract infection. If infection existed, sensitive antibiotics would be intravenously used. Following, the operation could be performed after the infection was controlled and urine culture was negative. Antibiotics were routinely used for no more than 48 hours after operation, which would be prolonged if infections could not be controlled[8].

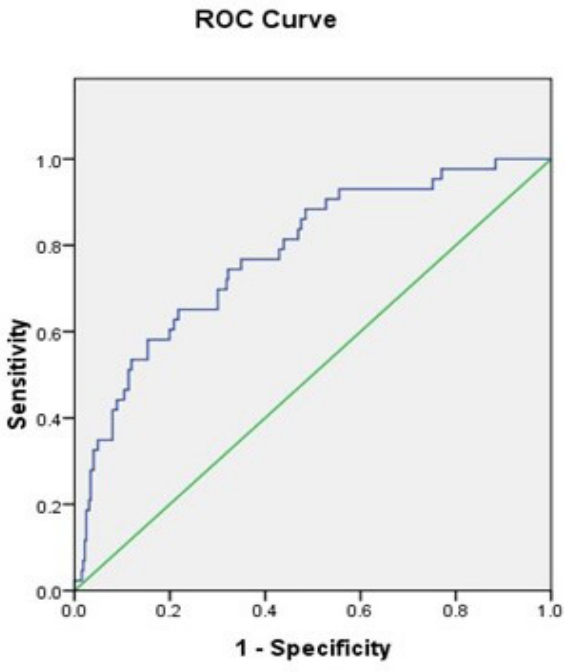

Figure 1. the ROC of preoperative NLR.

Surgical procedures

The operation was performed by a senior doctor (Q. Jiang). After general anesthesia, a lithotomy position was adopted. The first-stage double-J stent in a part of patients would be taken out. Following, the ureter would be examined by ureteroscope (9.5F STORZ), and a guide wire would be placed before the flexible ureteroscope sheath (14F COOK) inserted. Further, the flexible ureteroscope (7.5F STORZ) accompanying by a holmium laser (200um) was used for lithotripsy with energy of 1J and a frequency of 20HZ. After the stones were crushed, they would be removed using a basket as much as possible. Finally, a 5F double-J stent and catheter would be inserted. For some patients with bilateral operation, the contralateral would be treated by the same method. Importantly, the blood routine for the diagnosis of SIRS was immediately tested after surgery to avoid possible bias.

Research indicators

Gender, age, American society of anesthesia (ASA) score, diabetes, previously urinary system surgery on the affected side, stone burden, unilateral or bilateral surgery, preoperative double-J stent indwelling, oper-

Table 2. Multivariate logistic regression results.

	P	OR	95% CI
Age	0.078	1.030	0.997-1.065
Gender	0.928	1.037	0.471-2.282
Stone surgery history	0.305	1.494	0.693-3.219
Diabetes	0.154	0.389	0.106-1.424
ASA score	0.242	0.521	0.174-1.554
Stone burden	0.986	1.004	0.635-1.588
Operation time	0.413	0.995	0.984-1.007
Preoperative serum reatinine	0.295	0.457	0.106-1.977
Postoperative stone residuals	0.031	2.592	1.092-6.153
Preoperative NLR	0.002	1.497	1.156-1.938
Preoperative PLR	0.252	0.995	0.988-1.003
Preoperative LMR	0.205	0.868	0.698-1.080
Unilateral or bilateral	0.738	1.198	0.417-3.443
Preoperative D-J stent	0.216	0.268	0.033-2.157

Abbreviations: OR: odds ratio; CI: confidence interval; ASA score: American Society of Anesthesiologists score; NLR: Neutrophil/lymphocyte ratio; PLR: platelet / lymphocyte ratio; LMR: lymphocyte / monocyte ratio.

ation time, postoperative stone residuals, preoperative serum creatinine, and NLR, PLR, and LMR from preoperative blood routine within 3 days were collected. In addition, postoperative KUB without stones or residuals smaller than 3mm was defined as no stone residual[11]. More, the stone burden was calculated by multiplying the longest diameter of the perpendicular diameter of the stone. In patients with multiple stones, the total stone burden was calculated as the sum of the burden of each stone. (cm^2)[9]. The collection and evaluation of all data was carried out by one researcher (R. Bai).

SIRS standard

Postoperative patients who met two or more items of the following criteria could be diagnosed as SIRS[10] (including 1) white blood cell count < 4×10^9 or > 12×10^9, or immature cell > 10%; 2) body temperature T > 38℃ or < 36℃; 3) heart rates > 90 bpm; 4) respiratory rates > 20/min, or PaCO2 < 32 mmHg.

Statistical methods

The data were processed by SPSS17.0 software. The continuous data were shown as mean ± standard deviation (SD), and the counting data were shown as number and rate. Moreover, t-test and chi-square tests were respectively used to compare these data between groups. A logistic regression analysis was used to determine possible risk factors, and the receiver operating characteristic (ROC) curve was used to calculate the maximum sum of sensitivity and specificity to be the optimal cut-off point of independent risk factors. $P < 0.05$ was regarded to be statistically significant.

RESULTS

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (Approval number: 2020519). In retrospective analysis, the average age of all patients was 51.6 ± 12.6 years. Postoperative stone residuals were significantly more in SIRS group (30.2% vs 17.2%, $P = 0.039$). A total of 110 (29.8%) patients had experienced at least one treatment because of upper urinary tract stones before, including shock wave lithotripsy (SWL), ureteroscopy lithotripsy (URS), fURS, percutaneous nephrolithotripsy (PCNL), or open surgery.

In addition, compared to the patients in non-SIRS group, the preoperative NLR was significantly higher (3.90 ± 2.28 vs 2.60 ± 1.26, $P < 0.001$) and the preoperative LMR was significantly lower (3.82 ± 1.66 vs 5.12 ± 2.40, $P = 0.001$) for patients in SIRS group.

However, no significant differences between the two groups could be found in age ($P = 0.063$), ASA score ($P = 0.772$), stone burden ($P = 0.931$), operation time ($P = 0.766$), preoperative serum creatinine ($P = 0.872$), diabetes ($P = 0.120$), unilateral or bilateral surgery ($P = 0.498$), preoperative double-J stent indwelling ($P = 0.151$), and PLR value ($P = 0.136$), respectively. No patient dead from SIRS and other complications. The detailed demographic characteristics and clinical data of all patients had been shown in **Table 1**.

Multivariate logistic regression analysis showed that preoperative NLR (OR = 1.497, 95% CI 1.156 - 1.938, $P = 0.002$) and postoperative stone residuals (OR = 2.592, 95% CI 1.092 - 6.153, $P = 0.031$) were independent risk factors which could lead to SIRS after fURS. However, the effect of preoperative LMR became insignificant ($P = 0.205$). (**Table 2**)

ROC curve showed that the best cut-off value of preoperative NLR was 2.61, with a sensitivity of 67.4% (95% CI 0.513 - 0.805), specificity of 61.0% (95% CI 0.555 - 0.663), positive predictive value of 18.7% (95% CI 0.130 - 0.258), and negative predictive value of 93.5% (95% CI 0.890 - 0.962). The area under ROC curve could be calculated to be 77.9% ($P < 0.001$, 95% CI 0.706 - 0.852) (**Figure 1**).

Further, to verify the results, 53 patients who received fURS treatment from October 2019 to January 2020 were prospectively analyzed. All patients met the inclusion criteria. According to whether the preoperative NLR value was less than 2.61, the patients were divided into two groups (**Table 3**). The incidence of SIRS between two groups showed a significant difference (RR = 4.932, $P = 0.040$).

DISCUSSION

The feasibility, safety and effectiveness of fURS for upper ureteral stones had been verified for a long time[12]. However, complications were also reported, such as renal colic, urinary tract infection, stone street formation, ureteral stent-related symptoms and ureteral stricture, etc[13].

Infection was one of the most common complications. If untreated, it could rapidly develop into SIRS, bacteremia and even sepsis. Up to now, many studies had been carried out to explore the risk factors of infection after fURS. In Fan's study[4], preoperative pyuria, infectious stone and operation time was found to be closely related to infection after fURS. While Senocak et al. believed that positive urine culture before surgery would an important factor[15]. Further, Ozgor et al. found that risk factors of operation time longer than 60 min, renal function and age might be independent for fURS related infection[16]. However, there was no consensus on this issue.

In our study, we found that patients with stone residuals after fURS had a higher risk to SIRS, which was similar to a retrospective study for patients after PCNL[17]. The reason for stone residuals leading to fever or infection

Table 3. Verification results of preoperative NLR in predicting the occurrence of SIRS.

	NLR ≥ 2.61	NLR < 2.61	*P*	95% CI
Number of patients (N)	22	31		
SIRS (N, %)	7 (31.8%)	2 (6.5%)	0.040	1.130-21.523
Age(Mean ± SD)	49.41 ± 14.47	46.52 ± 14.78		
Gender (N, %)				
-Male	16 (72.7%)	22 (71.0%)		
-Female	6 (27.3%)	9 (29.0%)		
Stone surgery history (N, %)	6 (27.3%)	4 (12.9%)		
Diabetes (N, %)	1 (4.5%)	4 (12.9%)		
Stone burden(cm2, Mean±SD)	0.86 ± 0.72	0.77 ± 0.38		
Preoperative serum reatinine (N, %)	5 (22.7%)	6 (19.4%)		
Postoperative stone residuals (N, %)	1 (4.5%)	1 (3.2%)		
Unilateral or bilateral (N, %)				
-Unilateral	19 (86.4%)	30 (96.8%)		
-Bilateral	3 (13.6%)	1 (3.2%)		
Preoperative D-J stent (N, %)	1 (4.5%)	6 (19.4%)		

Abbreviations: NLR: Neutrophil/lymphocyte ratio; CI: confidence interval; SIRS: systemic inflammatory response syndrome.

might be that the fragments of residuals contained bacteria or endotoxins[18]. In another study, Degirmenci et al. obtained a similar result[19]. They believed that the infectious complications caused by residual fragments would be due to microorganisms, which might easily enter vessels through the damaged endothelium, thus leading to systemic complications, including SIRS.

Another reason might be that the residual fragments or powder blocked the double-J stent, resulting in evidently increased pressure in renal pelvis. It would be more helpful to bacteria migration and endotoxins absorption. However, some researchers argued that there was insignificant relationship between residuals and postoperative infectious complications[10,20]. Therefore, this result needed to be further verified.

The concept of NLR was first put forward by Goodman et al[21]. In 1995, they found that NLR was more sensitive than white blood cell count in the diagnosis of appendicitis. Subsequently, more and more studies proved that NLR was related to the severity of sepsis[22]. In addition, several studies had reported that preoperative NLR and PLR could be used as predictors for SIRS or sepsis after PCNL[8,9,14]. However, their role in fURS was still obscure.

The results from ROC curve and prospective analysis in our study showed that when the NLR value was higher than 2.61, SIRS would be easier to occur after operation. But, the best cutoff point in Sen's study was reported to be 2.50[8]. Gurol et al. proposed that the best NLR cutoff point for predicting bacteremia and septicemia was 5.0[23]. This difference might be caused by different ethnic groups[24].

Further studies had shown that the increase of NLR would related to the levels of plasma pro-inflammatory cytokines, such as IL-1, IL-6, IL-7, IL-8, IL-12, etc[25]. Accumulation of these cytokines in the tissue microenvironment could lead to excessive inflammation. More, Hwang et al.[26] believed that neutrophils responded rapidly to infection, resulting in a sharp increase in affected areas. On the other hand, the release of various anti-inflammatory cytokines could induce immunosuppression and evident lymphocyte apoptosis. Another study demonstrated that neutrophil apoptosis could be delayed in patients with severe sepsis[27]. Summarizing, preoperative NLR might be useful as a predictor for SIRS after fURS[28].

Some study proved that PLR and LMR was also related to infection. A meta-analysis mentioned that PLR was associated with Helicobacter pylori infection[29], while others confirmed that LMR was associated with viral infection[30]. However, insignificancies were found for these two parameters in our study.

Finally, several limitations in this study should be considered. At first, this study was a single-center retrospective study, a selection bias could not be avoided though a prospective analysis was also carried out. Secondly, there was no bacterial culture of urine and stones during/after the operation, some parameters could not be included for analysis, such as pyuria, infectious stones, etc. Therefore, the results of this study needed to be further verified.

CONCLUSIONS

According to our results, preoperative NLR might be a simple and noninvasive method for predicting the occurrence of postoperative SIRS. Those patients with preoperative NLR greater than 2.61 and postoperative stone residuals should be more concerned.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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