Establishment of Predictive Model for Related Factors of Systemic Inflammatory Response Syndrome (SIRS) After Percutaneous Nephrolithotomy (PCNL)

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Research article

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Abstract

**Background:** The percutaneous nephrolithotomy (PCNL) is a primary method of stone treatment, but the infection is a very common postoperative complication. The systemic inflammatory response syndrome (SIRS) is a stage of the infection process and a very important early clinical manifestation of sepsis, so identifying the risk factors associated with SIRS after PCNL plays an important role in ensuring patients’ safety and preventing sepsis.

**Methods:** Between September 2016 and September 2017, there were total 352 patients who were diagnosed as renal stone and were treated with PCNL, and included in this study at last. Patients were divided into two groups according to whether SIRS occurred or not. The univariate analysis was performed on the related risk factors such as patients’ age, gender, number of stone, diabetes et al. Then logistic regression was used for multivariate analysis and established a prediction model.

**Results:** There are 352 renal stone patients were treated with PCNL, and 106 patients (30.1%) suffered SIRS after operation. It was found that the operative time, preoperative fever and diabetes could be deemed as risk factors, and the logistic regression results indicated that diabetes (OR=2.049, 95%CI 1.008-4.166) and operative time (OR=1.011, 95%CI 1.003-1.019) entered the regression equation.

**Conclusion:** Diabetes and operative time are independent risk factors for SIRS after PCNL, so the probability of SIRS after PCNL can be determined in accordance with these two indicators.

**Background**

Renal stone is one of the most common diseases in urology, and it has a high incidence in the world. A cross-sectional survey of the prevalence of urinary calculi in China showed that the prevalence rate was 6.50% (1). Percutaneous nephrolithotomy (PCNL) has been widely used in the treatment of renal stone (2), and PCNL also becomes the standard of care for large (> 2 cm) renal stone (3). However, PCNL is a high-risk operation, as the operative time is long and the stone itself is concurrent infection, so postoperative infection is the main complication, and the failure in treating in time will threaten the lives of patients.

Systemic inflammatory response syndrome (SIRS) refers to the systemic non-specific inflammatory response caused by the stimulation of infectious and non-infectious factors such as various severe infections, trauma, hemorrhagic shock, burns, tissue ischemia and hypoxia and reperfusion injury, which eventually leads to the body's uncontrolled response to inflammation. Infection is a continuous clinical process, and SIRS is one of the stages, and it is also a very important early clinical manifestation of sepsis. The broken stones in percutaneous nephrolithotomy reversely flow into the blood under the action of trauma and hyperbaric perfusion, which is likely to cause SIRS. After PCNL 10–35% of patients mount a SIRS with a small percent progressing to sepsis (4). Therefore, controlling SIRS is very significantly important to prevent the occurrence of sepsis after PCNL and ensure perioperative safety of patients.
At present, there are many papers discussing the risk factors of systemic inflammatory response syndrome after percutaneous nephrolithotomy, and the factors such as stone size, operative time, number of channels, positive results of urine culture, renal pelvicyurine, stone cultures etc. are risk factors for SIRS after percutaneous nephrolithotomy. (5, 6) It is necessary to establish a nomogram predictive model to predict the postoperative severe infection risk. The prediction of the SIRS risk after PCNL by scientific methods is helpful for clinical staff to early assess the SIRS risk of patients during the perioperative period and then to implement early interventions, which can ensure patient safety and promote early rehabilitation (5, 7, 8).

**Methods**

**Study design and study setting**

This retrospective study was approved by the hospital ethics committee (2018-237-2, No. 1 Hospital of China Medical University), so the case data of qualified patients were surveyed in the medical record room. Between September 2016 and September 2017, there were total 352 cases in the Urology Department of No. 1 Hospital of China Medical University. 352 cases were all included for statistical analysis. Inclusion criteria for patients: Patients were diagnosed as renal stone based on imaging and were treated with PCNL. The patient was over 18 years old. Exclusion criteria for patients: Patients with open surgery for renal calculi, complicated with sepsis, and American Society of Anaesthesiologist(ASA) 3 and 4 were excluded. All operations were evaluated with routine blood examination, hemoglobin, urine routine and culture, blood glucose, kidney function tests, stone clearance rate, Guy’s degree et al, intravenous pyelogram and contrast enhanced computed tomography if necessary to diagnose.

All operations were performed by doctors who has experienced in PCNL surgery with above qualifications as associate professors. Patients with positive urine culture before surgery were treated with sensitive antibiotics until urine routine was normal and urine culture was negative. The operative method was to take lithotomy position after the general anesthesia for the patient. The 5F-7F ureteral catheter was retrogradely inserted under direct cystoscopy, and the isotonic solution was injected to form “artificial hydronephrosis” to indwell the catheter. In the prone position, the pillow was placed under the abdomen to form a low arc in the waist back. Under the guidance of B-ultrasound, the puncture was performed from the posterior axillary line under 12 or between 11 ribs to the dorsal calyces of the affected kidney, and the number of puncture points and channels were determined according to the position, size and number of the patient's stone. After the puncture was successful, the metal guide wire was placed. After withdrawing the needle sheath, the channel was expanded to 24F, and the expansion sheath was indwelled. The position of the stone was checked. The stone could be taken out directly, and the larger stones were crushed by Swiss LithoClastMaster (EMS, Nyon, Switzerland) first, and then were sucked out or pinched out. Finally, the residual stones in each renal pelvis were checked, and the postoperative 14F-16F renal fistula and 5F-7F double J tube were indwelled.
SIRS was diagnosed in patients who met two or more criteria: fever, > 38°C or < 36°C; heart rate, > 90 beats/min; respiratory rate, > 20 breaths/min or; leukocyte count, < 4 × 10^9/L or > 12 × 10^9/L, or immature granulocytes > 10%. (9)

Statistical
Statistical analyses were performed using the Statistical Package for SPSS 20.0 (ChineseIBM, China). Statistical significance was set at a \( p \) value < 0.05, all \( p \) values were single tailed. The measurement data was represented by \( \pm \) SD, and the count data was expressed by the number of cases (percentage). Continuous variables were compared with the independent sample t test, and the count data univariate analysis with the chi-square test, rank sum test was used for rank data. In order to define potential risk factors for SIRS, we performed multivariate logistic regression analysis, and established a predictive model. The beta (ß) regression coefficient, and the odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Using SPSS 20.0 and Empower Stats (http://www.empowerstats.com/cn/) to do further analysis. Missing data would be managed by 5 replications and a chained equation approach method in the SPSS (10). A nomogram was formulated to provide visualized probability prediction (11). We assessed predictive performance of the models by discrimination and calibration using C-statistic and Hosmer-Lemeshow chi-square statistic. Discrimination was conducted to calculate the area under AUC curve by ROC analysis. An AUC of 0.5 indicates no discrimination whereas AUC of 1.0 shows perfect discrimination (12). An internal validation study was conducted using 1000 bootstrap re-samples to determine final variables for SIRS. Calibration was performed by a calibration plot, which assessed whether the predicted and observed probabilities were in concordance (13).

Results

(1) General information of the patients: See Table 1 for details.
Table 1
General information of the patients and univariate analysis results for SIRS after PCNL

| Variable               | SIRS(+)       | SIRS(-)       | total          | P-value |
|------------------------|---------------|---------------|----------------|---------|
| Number of cases        | 106(30.11%)   | 246(69.89%)   | 352(100%)      |         |
| Gender                 |               |               |                |         |
| male                   | 60(56.60%)    | 150(61.00%)   | 210(59.7%)     | 0.443   |
| female                 | 46(43.40%)    | 96(39.00%)    | 142(40.3%)     |         |
| Age                    |               |               |                |         |
| Male                   | 53.53 ± 11.40 | 53.99 ± 9.37  | 55.20 ± 10.69  | 0.983   |
| Female                 | 54.63 ± 11.91 | 55.48 ± 10.10 | 54.4 ± 10.27   | 0.659   |
| average                | 54.01 ± 11.58 | 54.57 ± 9.67  | 53.86 ± 9.97   | 0.661   |
| Body Mass Index        | 24.95 ± 4.16  | 25.35 ± 4.98  | 25.22 ± 4.73   | 0.477   |
| Urine culture          |               |               |                |         |
| positive               | 1(0.90%)      | 8(3.25%)      | 9(2.6%)        | 0.373   |
| negative               | 105(99.10%)   | 238(96.75%)   | 343(97.4%)     |         |
| Rental stones          |               |               |                |         |
| single                 | 54(50.94%)    | 129(52.44%)   | 183(52.0%)     | 0.797   |
| multiple               | 52(49.06%)    | 117(47.56%)   | 169(48.0%)     |         |
| Hemoglobin             | 128.61 ± 20.34| 19.40 ± 18.36 | 129.16 ± 18.97 | 0.722   |
| Blood pressure         |               |               |                |         |
| Systolic pressure      | 140.22 ± 19.41| 140.45 ± 19.34| 140.38 ± 19.36| 0.155   |
| Diastolic pressure     | 84.03 ± 10.00 | 83.26 ± 11.54 | 83.49 ± 11.08  | 0.552   |
| Diabetes               |               |               |                |         |
| Yes                    | 11(10.38%)    | 48(1.68%)     | 59(16.8%)      | 0.035*  |
| no                     | 95(89.62)     | 198(98.32%)   | 293(83.2%)     |         |
| Blood glucose          | 5.83 ± 1.62   | 5.85 ± 1.71   | 5.84 ± 1.68    | 0.927   |
| Hydronephrosis         |               |               |                |         |
| Yes                    | 78(73.58%)    | 172(69.92%)   | 270(76.7%)     | 0.363   |
| no                     | 28(26.42%)    | 74(30.08%)    | 82(23.3%)      |         |
| Variable                        | SIRS(+) | SIRS(-) | total | P-value |
|--------------------------------|---------|---------|-------|---------|
| Renal failure                  |         |         |       |         |
| Yes                            | 2(1.90%)| 3(1.2%) | 5(1.4%)| 1.000   |
| no                             | 104(98.11%)| 243(30.08%)| 347(98.6%)|         |
| Fever before operation         |         |         |       |         |
| Yes                            | 9(8.49%)| 15(6.10%)| 24(6.8%)| 0.002*  |
| no                             | 97(91.51%)| 231(93.90%)| 328(93.2%)|         |
| Operative time                 | 61.87 ± 34.65 | 51.84 ± 24.78 | 54.86 ± 28.45 | 0.008* |
| Cast stone or staghorn stone   |         |         |       |         |
| Yes                            | 11(10.38%)| 14(5.69%) | 25(7.1%)| 0.458   |
| no                             | 95(89.62%)| 232(94.31%)| 327(92.9%)|         |
| History of stone surgery       |         |         |       |         |
| Yes                            | 45(42.45%)| 115(46.75%)| 160(45.5%)| 0.001** |
| no                             | 61(57.55%)| 131(53.25%)| 192(54.5%)|         |
| Stone clearance rate           |         |         |       |         |
| Stone removal                  | 105(99.06%)| 241(97.97%)| 346(98.30%)| 0.783   |
| residual stone                 | 1(0.94%)| 5(2.03%) | 6(1.70%)|         |
| hospital stays                 | 14(13,18) | 14(12,16) |         |         |
| Guy's degree                   |         |         |       |         |
| 1                              | 4(3.77%)| 6(2.44%) | 10(2.84%)| 0.019*  |
| 2                              | 74(69.81%)| 206(83.74%)| 280(79.55%)|         |
| 3                              | 17(16.04%)| 20(8.13%) | 37(10.51%)|         |
| 4                              | 11(10.38%)| 14(5.69%) | 25(7.10%)|         |

A total of 352 patients who underwent PCNL for renal stones were included in the present study. Among them, 210 were males (59.7%) and 142 were females (40.3%). Their average age was 53.86 ± 9.97 years, average body mass index was 25.22 ± 4.73 and average operative time was 54.86 ± 28.45. 9 cases (2.6%) were positive for preoperative urine culture, 169 cases (48%) were multiple renal stones, 25 cases (7.1%) were cast stones or staghorn stones, and 59 cases (16.8%) were concurrent diabetes. Their average preoperative blood glucose was 5.84 ± 1.68mm/L. There were 270 cases (76.7%) with concurrent hydronephrosis, 5 cases (1.4%) with concurrent renal insufficiency, 24 cases (6.8%) with preoperative fever, 160 cases (45.5%) with a preoperative history, 106 cases (30.1%) with SIRS, and there was no
patients with sepsis. There was no difference between the groups of SIRS and non-SIRS in age, gender, BMI.

(2) Univariate analysis results for SIRS after percutaneous nephrolithotomy: it was found in the univariate analysis that the difference of operative time, preoperative fever, diabetes and previous stone operative history was statistically significant, p < 0.05, as shown in Table 2.

| Variable          | OR    | 95% confidence interval | P-value |
|-------------------|-------|-------------------------|---------|
| Diabetes          | 2.038 | 1.006–4.130             | 0.048   |
| Operative time    | 1.012 | 1.004–1.020             | 0.004   |

(3) Multivariate logistic regression analysis results for SIRS after PCNL: Variables with p < 0.2 in univariate analysis were selected for Logist regression, including gender, systolic pressure, diabetes, fever before operation, operative time, history of stone surgery. It was found in the multivariate analysis that diabetes and operative time were risk factors, as shown in Table 2, as a result, the regression predictive model \( P = \frac{1}{1 + e^{-(−2.097+0.712 \text{ diabetes} + 0.012 \text{ operative time})}} \) was determined. For example, non-diabetic patients, 60 minutes of operation, p = 0.21; non-diabetic, 120 minutes of operation, p = 0.34; diabetic patients, 60 minutes of operation, p = 0.35, diabetic patients, 120 minutes of operation, p = 0.51. The risk probability could be obtained according to the risk factors, so that the medical staff can perform targeted observation on the SIRS of the postoperative patients.

(4) Nomogram was established incorporating two predictive factors (diabetes and operative time) (Fig. 1). Operative time shared the largest contribution to SIRS, following by diabetes. Each clinicopathological factor corresponds to a specific point by drawing a line straight upward to the point axis. After sum of the points is located on the total points axis, the sum represents the probability of SIRS by drawing survival by drawing straight down to SIRS axis. For example, it spends sixty minutes (28 points) on diabetic patients during PCNL. The total point was 56 and suspected SIRS was approximately 35%. This predictive value could be used to make decision for clinical treatment and patient counseling.

The C-index for the predictive model was 0.608 [95% confidence interval (CI): 0.504–0.748], which showed discrimination ability. The ROC curve was presented in Fig. 2. The H-L chi-square statistic was 12.834, which indicated good statistical performance upon internal validation between the nomogram prediction and actual observation for the probability of SIRS (\( P = 0.196 \)). The calibration plot was showed in Fig. 3.

The red solid line is a smoothed curve that represents an estimate of the relation between the predicted and the observed probability of SIRS. Ideally this line fits the black solid line that represents perfect calibration.
Discussion

In this study, there were slightly more males than females, but there was no significant difference between SIRS and non-SIRS. A total of 30.1% of patients suffered SIRS, and no patients suffered sepsis. Current studies have shown that the incidence of SIRS after PCNL is between 10% and 30% (6, 14). The result is similar to the literature research results (15, 16), but higher than the study of Wang A]QL (12.5%) and Singh P(17.5%)(3, 9).

The patients with preoperative stone operation history accounted for 45.5%, indicating that the recurrence rate of renal stones was high, and the treatment was complicated. There were 9 patients with positive urine culture, and 24 patients with preoperative fever and concurrent infection. Although preoperative fever was a risk factor in univariate analysis, it did not enter the regression equation after multivariate analysis. The reasons were analyzed to find that, first, preoperative fever patients strictly underwent the anti-infective treatment, second, the patients who were found bacterial infection in urine routine and positive urine culture were also treated effectively, third, they did not undergo the operation until their test results were normal, so the preoperative fever failed to become a risk factor and no patients suffered sepsis.

The results of the study showed that there were two risk factors finally entering into the equation for SIRS after PCNL, one was diabetes and the other was operative time. Diabetes was a risk factor for SIRS after PCNL (17, 18). Zhu Zhenjie(18) believe that the incidence of SIRS after PCNL in patients with blood glucose above 7.1 mmol/L was more than twice that of patients with normal preoperative blood glucose, but the blood glucose value of patients with preoperative concurrent diabetes was controlled in the normal range, indicating that diabetes itself would bring certain risk of SIRS after PCNL, so even if the preoperative blood glucose was controlled in normal range, it still should be taken seriously as a postoperative risk factor. And the result of OR was similar with Zhu Zhenjie(17).

Operation time is a very important risk factor consistent with other studies (8). The prolongation of operation time, with the increase of the absorption of lavage fluid and toxin into blood, increases the chance of infection. A large amount of absorption of lavage fluid can make patients in a state of hypothermia, coagulation dysfunction, even increase the patient's circulatory load and disturb the balance of water and electrolyte. SIRS is more likely to occur after operation. Shortening the operation time is an important measure to prevent SIRS. Current Clinicians with the continuous improvement of endoscopy technology, the operation time is also decreasing. But in Chen L's research the operation time did not enter the regression Eq. (6).

7.1% of the patients suffered cast stones or staghorn stones. These stones were difficult to handle and prone to cause complications, so the rich clinical experience was required for surgeons. In addition, their operative time was relatively long, but they finally did not enter the regression equation.

With the doctor's attention to SIRS after percutaneous nephrolithotomy for patients with stones, the continuous enhancement of operative skills and the improvement of preoperative preparation, although
nearly one-third of patients suffered SIRS after percutaneous nephrolithotomy, the sepsis case was zero, indicating that PCNL operation is getting more mature and safe. The early symptomatic treatment for SIRS can prevent patients’ conditions from further development, so it is necessary to use predictive models to assess the patients, and then early observation and early treatment are performed to ensure patient safety after PCNL.

There were several limitations in our study. First, this is a retrospective study from single institute, which might lead to selection bias. Secondly, patient’s data are not perfect, such as calculus load and stone composition analysis can’t be calculated, which affects the analysis of risk factors, so we could not provide a more comprehensive analysis. Finally, sample size is small and lacks representativeness. We needed to do large-scale prospective studies.

**Conclusion**

Diabetes and operative time are independent risk factors for SIRS after PCNL, so the probability of SIRS after PCNL in patients with stones can be defined according to these two indicators, which can help clinical staff assess the change of patient’s condition, and then give early interventions to provide a reliable basis for the prevention of postoperative sepsis.

**Declarations**

**Ethics approval and consent to participate**

This retrospective study was approved by the hospital ethics committee (2018-237-2, No. 1 Hospital of China Medical University). Patients voluntarily consented to participate in the study.

The authors declare that consent for publication and insure Availability of data and material.

**Competing interests:**

The authors declare that they have no conflict of interest.

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Authors' contributions:

Jin Zheng: study design, data collection, data interpretation, literature search and manuscript draft; Min Ju: literature search, data collection, statistical analysis, data interpretation; Linlin Gao: literature search, data collection; Yingli Pan: study design, literature search, statistical analysis.

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References

1. Zeng GH, Mai ZL, Xia SJ. A cross-sectional survey of urolithiasis prevalence in China Z. China J Urol. 2015;36:528–31.
2. Wang SG, Yu H. Percutaneous Nephrolithotomy—New Exploration for Day Operation. Journal Of Peking University. 2017;49:753–6.
3. Singh P, Yadav S, Singh A, Saini AK, Kumar R, Seth A, et al. Systemic Inflammatory Response Syndrome Following Percutaneous Nephrolithotomy: Assessment of Risk Factors and Their Impact on Patient Outcomes. Urol Int. 2016;96:207–11.
4. Ruslan K, Joseph AG, Max K, Adam CM. MantuG., Post-Percutaneous. Nephrolithotomy Systemic Inflammation Response: A Prospective Analysis of Preoperative Urine, Renal Pelvic Urine and Stone Cultures. J Urol. 2011;186:189–2903.
5. Chen L, Xu QQ, Wang XF. Analysis of risk factors of systemic inflammatory response syndrome after percutaneous nephrolithotomy. Chin J Urol. 2008;29:173–6.
6. Omar M, Noble M, Sivalingam S, El Mahdy A, Gamal A, Farag M, et al. Systemic Inflammatory Response Syndrome after Percutaneous Nephrolithotomy: A Randomized Single-Blind Clinical Trial Evaluating the Impact of Irrigation Pressure. J Urol. 2016;196:109–14.
7. Zhou SL, Deng YQ, Tan F. Retrospective Analysis for the Risk Factors of Systemic Inflammatory Response Syndrome(SIRS)after Percutaneous Nephrostofithotomy(PCNL). Journal of SunYat-Sen University(Medical Science). 2016;37:295–9.
8. Wang QL, Liao WB, Yang SX. Retrospectively analysis of risk factors for systemic inflammatory response syndrome following retrograde intrarenal stone surgery. Int J ClinExp Med. 2016;9:8327–33.
9. 11
96
Medical R. 2005; 11: 96.
10. Royston P. Multiple imputation of missing values. The Stata Journal. 2004;4:227–41.
11. Kattan MW, Karpeh MS, Mazumdar M, Brennan MF. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. J Clin Oncol. 2003;21:3647–50.

12. Hosmer DW. Assessing the fit of the model. Applied logistic regression,. 2000: 143–202.

13. Austin PC, Steyerberg EW. Graphical assessment of internal and external calibration of logistic regression models by using loess smoothers. Stat Med. 2014;33:517–35.

14. Sen V, Bozkurt IH, Aydogdu O, Yonguc T, Yarimoglu S, Sen P, et al. Significance of preoperative neutrophil-lymphocyte count ratio on predicting postoperative sepsis after percutaneous nephrolithotomy. Kaohsiung J Med Sci. 2016;32:507–13.

15. Koras O, Bozkurt IH, Yonguc T, Degirmenci T, Arslan B, Gunlusoy B, et al. Risk factors for postoperative infectious complications following percutaneous nephrolithotomy: a prospective clinical study. Urolithiasis. 2015;43:55–60.

16. Yang T, Liu S, Hu J, Wang L, Jiang H. The Evaluation of Risk Factors for Postoperative Infectious Complications after Percutaneous Nephrolithotomy. Biomed Res Int. 2017; 2017: 4832051.

17. Zhu ZJ, Xu QQ, Huang XB, Hong Y, Yang QY, Wang S, et al. [Risk factor analysis of systemic inflammatory response syndrome in type 2 diabetics after percutaneous nephrolithotomy]. Beijing Da Xue Xue Bao Yi Xue Ban. 2016;48:643–9.

18. Wei W, Leng J, Shao H, Wang W. Diabetes, a risk factor for both infectious and major complications after percutaneous nephrolithotomy. Int J Clin Exp Med. 2015;8:16620–6.

Figures
Figure 1

Nomogram to predict SIRS after PCNL. (X1=Diabetes; X2=Operative time)
Figure 2

ROC curves for validating the discrimination power of the nomogram

Full
AUC=0.608
Figure 3

Calibration plots of the nomogram for the probability of SIRS after PCNL.