

The value of postoperative HLA-DR expression and high mobility group box 1 level in predictive diagnosis of sepsis in percutaneous nephrolithotomy surgery

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ABSTRACT

Objective: To analyze the value of postoperative human leukocyte antigen-DR (HLA-DR) expression and high mobility group box 1 (HMGB1) level in predictive diagnosis of postoperative sepsis for patients with percutaneous nephrolithotomy (PCNL) surgery.

Methods: The present prospective observational study included 387 patients with renal calculus who received PCNL surgery from January 2017 to October 2020 in our hospital. After exclusion criteria, 33 patients with sepsis and 78 patients with no sepsis remained. All patients received PCNL surgery. Sepsis definition is according to the third international consensus definitions for sepsis and septic shock (Sepsis-3). The data of the HMGB1, c-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT) and HLA-DR expression were collected within admission and 24 h and 72 h after surgery. Postoperative HMGB1 levels and HLA-DR expression at 24 h and 72 h were respectively compared between the two groups using *t* test. ROC curve was used to analyze the value of postoperative HLA-DR expression and HMGB1 level in predictive diagnosis of sepsis.

Results: The positive rate of urine culture and the time of hospitalization time in patients with sepsis were significantly higher than those in patients with no sepsis. Sepsis group had higher levels of HMGB1 at post-24 h (93.07 ± 11.37) ng/mL vs (75.41 ± 4.85) ng/mL, $p < 0.05$ and 72 h (96.58 ± 12.12) ng/mL vs (81.16 ± 8.86) ng/mL, $p < 0.05$ than non-sepsis group. Meanwhile, sepsis group had lower expression of HLA-DR at post-24 h (50.01 ± 7.42) % vs (69.32 ± 10.58) %, $p < 0.05$ and 72 h (54.85 ± 9.45) % vs (69.98 ± 11.00) %, $p < 0.05$ than non-sepsis group. ROC analysis showed that the HLA-DR expression at postoperative 24 h had highest predictive value in the diagnosis of sepsis, the AUC of HLA-DR was 0.934, cutoff value 56.19%, with sensitivity 89.7%, specificity 81.8%.

Conclusion: Postoperative HLA-DR and HMGB1 can both be used as a predictive diagnosis of sepsis for patients with renal calculus received PCNL surgery.

HIGHLIGHTS

- Sepsis group had higher levels of high mobility group box 1 at post-24 h and 72 h than non-sepsis group.
- Sepsis group had lower expression of HLA-DR at post-24 h and 72 h than non-sepsis group.
- Postoperative HLA-DR and HMGB1 can both be used as a predictive diagnosis of sepsis for patients with renal calculus received PCNL surgery.

Abbreviations: PCNL: Percutaneous nephrolithotomy; ROC: Receiver operating characteristic; SD: Standard deviation; HMGB1: High-mobility group box 1 protein; HLA-DR: human leukocyte antigen-DR; PE: Phycoerythrin; FITC: Fluorescein isothiocyanate; UTI: Urinary tract infection; WBC: White blood cell

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Introduction

In recent years, due to irregular work and rest, disordered diet and other reasons, the number of kidney stone patients has risen year after year in China. At

present, percutaneous nephrolithotomy (PCNL) with high stone clearance rate and wide application range is one of the main surgical methods for renal calculi [1]. However, the patients are prone to complications such

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as fever, respiratory aggravation, etc. In severe cases, it can progress to urinary sepsis with high mortality. It has been reported that the incidence of PCNL related urinary sepsis is 0.9–4.7% [2], and the mortality rate is as high as 30–40% [3].

Inflammatory mediators play an important role in the occurrence and development of sepsis. The level of tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1) are considered as important pro-inflammatory mediators in the pathogenesis of sepsis. However, in the past 10 years, TNF- α and IL-1 antagonists had not achieved obvious effect in clinical application. The important reason is that most of the experiments were targeted inflammatory mediators, which are the inflammatory mediators in the early stage of sepsis. Therefore, it is very important to explore the late inflammatory mediators. Recent studies had confirmed that extracellular high mobility group box 1 (HMGB1), was an important inflammatory mediator and pro-inflammatory cytokine. It is the central molecule to initiate and maintain the inflammatory response, which is closely related to the pathogenesis of sepsis. HMGB1 appears 16–24 h after endotoxin stimulation, significantly later than that of other early inflammatory factors, and lasts longer. Previous studies have shown that the level of serum HMGB1 in sepsis patients is increased, and the degree of increase is related to the severity of infection. The higher HMGB1 level in patients, the greater the possibility of death [4,5]. Among the cellular biomarkers studied in relation to sepsis-induced immunosuppression, monocyte protein surface expression of human leukocyte antigen DR (HLA-DR) has emerged as a reliable parameter representing innate immune function in both experimental and clinical contexts [6]. In sepsis, the rapid decrease of HLA-DR expression on circulating monocytes correlated well with severity and outcome [7]. In some studies, HLA-DR expression rate \leq 30% was used as an indicator of severe sepsis. The expression rate of HLA-DR decreased, and it was in immunosuppressive state for several days, which led to the aggravation of infection [8].

Objectives

Therefore, this paper attempts to analyze whether the HMGB1 level and HLA-DR expression can predict the occurrence of urinary sepsis in patients with renal calculi after PCNL, so as to provide reference for the diagnosis and treatment of such patients.

Materials and methods

Subjects

This prospective observational study enrolled 387 patients with renal calculus who received percutaneous nephrolithotomy (PCNL) surgery from January 2017 to October 2020 in our hospital, and 167 patients agreed to participate in the clinical study and signed the informed consent form. Inclusive criteria: Patients with renal calculi confirmed by clinical B-ultrasound or CT examination; patients with complete case and postoperative data. Exclusion criteria: (1) patients with sepsis before operation; (2) patients with a history of acute or chronic infection within the last 14 days; (3) patients with autoimmune diseases or using immunosuppressive drugs; (4) patients with previous urological surgery; (5) patients with severe liver, renal, malignancy, cardiovascular dysfunctions (6) patients with mental disorders or unable to cooperate with treatment. After exclusion criteria, 33 patients with sepsis and 78 patients with no sepsis remained. All experiments using human samples in this study was approved by the Medical Ethics Committee of the Chongqing Jiangjin District Central Hospital (No. CQDH-20170009) and conducted according to the Declaration of Helsinki principles. In addition, the study was in accordance with the medical ethics standards, and all the examinations were informed by the family members of the patients.

PCNL surgery

All patients were examined for urine bacterial culture in the middle segment one week before operation. If the urine culture was positive, the patients were treated adequately with antimicrobials three days before operation. In addition, all patients received auxiliary examination before operation to regulate and control their blood glucose, blood pressure and cardiopulmonary function. Future, the patients were administered preventive intravenous injection antibiotics 30 min before operation. After anesthesia, routine disinfection and sterile towel laying. PCNL surgery was performed as described elsewhere [9,10]. All patient's nephrostomy tract puncture under local anesthesia was conducted to indwell a guide wire by a preoperative cooperative procedure with the department of radiology, and PCNL were conducted with the patient under general anesthesia. Blood was routinely prepared during the operation, and patients with large intraoperative bleeding were given blood transfusion treatment. A JJ stent/ureteric catheter/nephrostomy tube was placed in most of the cases. After surgery, we decided to use or change

anti-infective drugs according to the patient's condition and observed the drainage of thin renal tube and urine color were observed. For moderate and severe postoperative bleeding, blood transfusion and promoting coagulation were given. For refractory bleeding, intervention or open surgery were given.

Diagnostic criteria for urinary sepsis

Sepsis definition is according to the third international consensus definitions for sepsis and septic shock (Sepsis-3) [11]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Patients with Sequential Organ Failure Assessment (SOFA) score ≥ 2 points from the baseline (the baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction) or positive quick SOFA (qSOFA) score (positive qSOFA score is defined as 2 or more qSOFA signs near the onset of infection, including systolic blood pressure ≤ 100 mmHg, respiratory rate ≥ 22 /min, altered mentation) were diagnosed with sepsis. All patients assessed SOFA score every day within 1 month after operation and urine culture every 3 days to diagnose sepsis. Patients who met the diagnostic criteria of Sepsis-3 and had a positive urine culture were diagnosed with sepsis.

Data measurement

The serum HMGB1, c-reactive protein (CRP) and interleukin-6 (IL-6) levels were measured by enzyme-linked immunosorbent assay (ELISA) method. Briefly, fasting cubital venous blood (5 mL) of all patients were collected within admission and 24 h and 72 h after surgery. The blood samples were collected and were centrifuged at 2000 g for 15 min. After centrifugation, the levels of HMGB1, CRP and IL-6 were tested using commercially available ELISA kits: HMGB1 (MBS024146 MyBioSource, detection Range: 6.25 ng/mL–200 ng/mL), CRP (MBS8807458 MyBioSource, detection Range: 1.57 ng/mL–100 ng/mL), IL-6 (MBS825090 MyBioSource, detection Range: 4.69 pg/mL–300 pg/mL). The serum procalcitonin (PCT) levels of all patients were detected by Electrochemiluminescence Method (Cobas E602, Roche, sensitivity < 0.02 ng/mL, detection Range: 0.02 ng/mL–100 ng/mL).

HLA-DR expression on monocyte using flow cytometry

The level of HLA-DR expression on monocyte was detected by Flow cytometry, using PE-conjugated

monoclonal antibodies to CD14 (Beckman Coulter) and FITC-conjugated monoclonal antibodies to HLA-DR (Beckman Coulter). Isotype-matched mouse monoclonal antibody was used as negative controls. HLA-DR cell surface density was expressed as the ratio of mean fluorescence intensity evaluated on CD14⁺ cells. The measurement was conducted on a FACS Calibur flow cytometry analyzer (BD Biosciences).

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL). Data were expressed by mean \pm SD or median (range) according to distribution, which was confirmed by Kolmogorov-Smirnov analysis. Mann-Whitney test or Student's *t*-test was used for comparison between two groups. Chi square test was used for rates. ROC curve was used for analysis of the predictive power of HLA-DR and HMGB1 in sepsis. A value of $p < 0.05$ was considered to be statistically significant.

Results

General information and propensity score matching results of patients

From January 2017 to October 2020, a total of 387 patients with renal calculi who met the inclusion and exclusion criteria underwent PCNL surgery in our hospital, including 33 patients with sepsis and 78 patients with no sepsis after PCNL surgery. As show in Table 1, compared the demographic and clinical data, the positive rate of urine culture and the time of hospitalization time in patients with sepsis were significantly higher than those in patients with no sepsis ($p < 0.05$). No other significantly difference was found between two groups. All patients with sepsis were examined for urine bacterial culture in the middle segment. The results showed that 21 patients with sepsis urine culture positive, and the proportion of Escherichia coli positive was the highest (Table 2).

Comparison of HMGB1 level and HLA-DR expression between the two groups

In two groups, the levels of HMGB1 at postoperative 72 h were remarkably higher than that at postoperative 24 h. The level of HMGB1 in sepsis group was higher than that in no sepsis group at postoperative 24 h and 72 h ($p < 0.05$). The HLA-DR expression in sepsis group was lower than that in no sepsis group at postoperative 24 h and 72 h ($p < 0.05$) (Table 3). Besides, the serum

Table 1. Comparison of demographic and clinical data concentration of patients with and without urinary sepsis after PCNL operation.

Variable	Urinary sepsis (n = 33)	Non urinary sepsis (n = 78)	p*
Age	53.33 ± 8.18	51.53 ± 7.20	0.249
Female, n (%)	15 (40.54)	45 (57.70)	0.089
BMI	25.25 ± 2.18	25.26 ± 2.27	0.978
Preoperative urine culture positive, n (%)	22 (66.67)	40 (51.28)	0.031
Stone size(cm)	2.10 ± 0.25	2.04 ± 0.33	0.345
Preoperative antibiotics			
Broad spectrum antibiotics, n (%)	12 (36.36)	19 (24.36)	0.089
Sensitive antibiotics, n (%)	21 (63.64)	59 (75.64)	
Preoperative antibiotic use time (h)	24 (0.5–72)	0.5 (0.5–72)	0.232
Operation time (min)	91.36 ± 20.13	94.41 ± 19.90	0.464
Hospitalization time (d)	41.69 ± 4.25	32.72 ± 1.64	<0.001
Mortality, n (%)	5 (15)		
WBC (*10 ⁹ /L)	5.87 ± 1.93	5.60 ± 1.49	0.429
HMGB1 (ng/mL)	37.28 ± 5.83	37.20 ± 5.61	0.945
HLA-DR (%)	68.45 ± 7.60	68.39 ± 6.75	0.966

*p value was calculated by Student *t* test or Mann-Whitney *U* test for comparison for continuous data and rates were compared by Chi square test. BMI: body mass index.

Table 2. Urine culture results.

Bacterial species	Number of cases	Proportion (%)
<i>Escherichia coli</i>	11	52.38
<i>Klebsiella pneumoniae</i>	4	19.05
<i>Staphylococcus aureus</i>	2	9.52
<i>Enterococcus faecalis</i>	2	9.52
<i>Enterobacter cloacae</i>	2	9.52
<i>Proteus mirabilis</i>	1	4.76

CRP, IL-6 and PCT levels of the patients were significantly higher than that in the patients with no sepsis at postoperative 24 h and 72 h ($p < 0.05$).

Predictive diagnostic value of HMGB1 and HLA-DR in sepsis

Finally, we draw ROC curves to evaluate the diagnostic value of all biomarkers for patients. We found that HMGB1 and HLA-DR could be potential diagnostic biomarkers of patients with sepsis (Figure 1). The results showed that the HMGB1 expression at postoperative 24 h had a higher predictive value in the diagnosis of sepsis, the AUC of HLA-DR was 0.913, cutoff value 81.44 ng/mL, with sensitivity 81.8%, specificity 87.2%. The HLA-DR expression at postoperative 24 h had highest predictive value in the diagnosis of sepsis, the AUC of HLA-DR was 0.934, cutoff value 56.19%, with sensitivity 89.7%, specificity 81.8%.

Discussion

This study included a total of 33 patients with sepsis and 78 patients with no sepsis after PCNL surgery. Previous studies have shown that age, gender, preoperative urinary tract infection and stone size are the prognostic factors for the occurrence of urogenic sepsis after PCNL [8,12]. In our present study, no significantly

difference was found between two groups in age, sex, BMI, stone size, preoperative antibiotic use time, operation time, etc. The positive rate of urine culture and the time of hospitalization time in patients with sepsis were significantly higher than those in patients with no sepsis.

HMGB1 has been identified as a cytokine mediator of lethal systemic inflammation (such as sepsis), arthritis and local inflammation [13,14]. Under the stimulation of exogenous bacterial endotoxins (LPS) or endogenous proinflammatory cytokines (TNF- α and IL-1 β), HMGB1 is actively released from macrophages, monocytes and pituitary cell cultures in a time and dose-dependent manner. At the same time, HMGB1 can be passively released not only from activated innate immune cells, but also by necrotic or damaged cells. HMGB1 released by necrotic cells can induce inflammatory response, thus transmitting 'injury' signals to the neighboring immune cells. In a mouse model of sepsis, serum HMGB1 levels began to increase significantly at 18 h after peritonitis induction. Serum HMGB1 increased significantly for at least 72 h, which was similar to the delayed kinetic process of endotoxemia [15]. The late appearance of HMGB1 is similar to the onset of animal endotoxemia or sepsis mortality and distinguishes it from TNF- α and other previously described early mediators of systemic inflammatory response [16]. Karakike et al. confirmed that late HMGB1 peak was associated with worse prognosis, especially in patients with underlying chronic inflammatory conditions [17]. Several clinical studies had also observed a significant increase serum HMGB1 level in sepsis patients [4]. Here, we found that the levels of HMGB1 in patients with urogenic sepsis were higher than those in patients without urogenic sepsis at 24 h and 72 h after operation, and the expression of HLA-DR was lower than that in

Table 3. Comparison of serum biomarkers concentration of expression in renal calculi patients with and without urogenic sepsis after PCNL operation.

Variable	Urinary sepsis (n = 33)	Non urinary sepsis (n = 78)	p*
Post-24h			
CRP (ng/mL)	12.23 ± 2.13	11.36 ± 1.41	0.012
PCT (ng/mL)	15.61 ± 2.15	12.87 ± 2.05	<0.001
IL-6 (pg/mL)	26.87 ± 2.06	23.08 ± 2.37	<0.001
HMGB1 (ng/mL)	93.07 ± 11.37	75.41 ± 4.85	<0.001
HLA-DR (%)	50.01 ± 7.42	69.32 ± 10.58	<0.001
Post-72h			
CRP (ng/mL)	15.47 ± 2.53	11.62 ± 1.56	<0.001
PCT (ng/mL)	16.17 ± 2.72	12.48 ± 2.31	<0.001
IL-6 (pg/mL)	27.22 ± 3.02	23.00 ± 2.14	<0.001
HMGB1 (ng/mL)	96.58 ± 12.12	81.16 ± 8.86	<0.001
HLA-DR (%)	54.85 ± 9.45	69.98 ± 11.00	<0.001

*p comparison between urinary sepsis and non urinary sepsis groups using Student *t* test for continuous data.

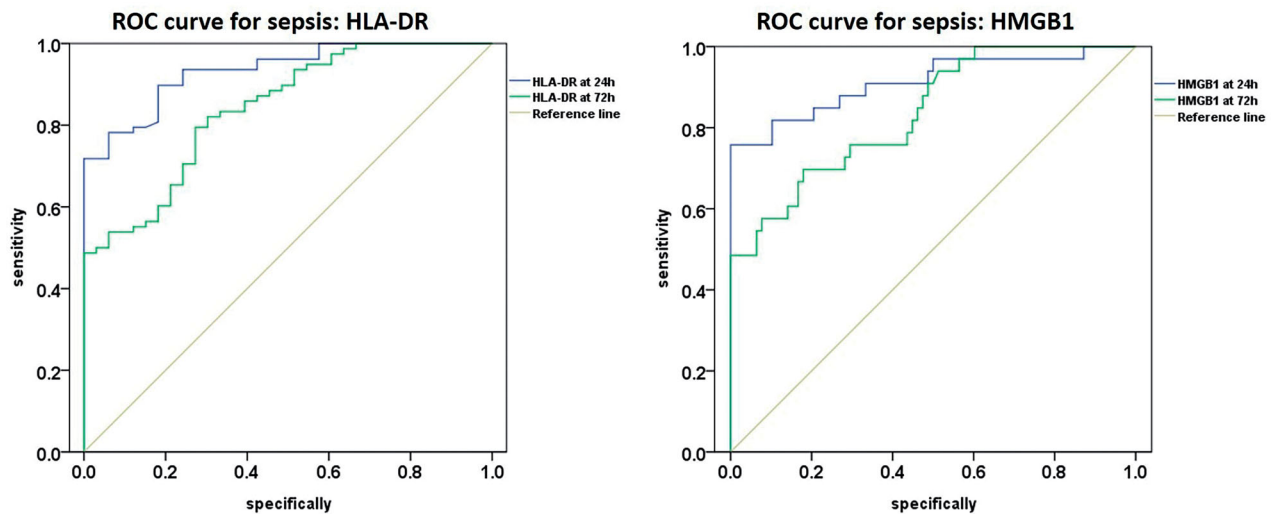


Figure 1. The predictive value of HLA-DR expression and HMGB1 level in patients with renal calculi after PCNL surgery in predicting the diagnostic value of sepsis complications.

patients without urogenic sepsis, suggesting that HMGB1 may be potential indicators for the diagnosis of urogenic sepsis.

HLA-DR is a class II antigen, which is a glycosylated transmembrane protein expressed on antigen presenting cells. HLA-DR is also constitutively expressed on monocytes such as macrophages, dendritic cells and B cells. The expression of HLA-DR on monocytes is essential for presenting the ingested microbial peptides to CD4 or CD8 positive T cells, thus initiating specific immune responses to eliminate potential pathogens. Now, the decreased expression of monocyte HLA-DR (mHLA-DR) is considered as a reliable marker of immunosuppression and/or septic complications in critically ill patients [18]. The expression of HLA-DR can be evaluated by standardized tests in clinical practice [19]. Importantly, low levels of mHLA-DR were observed in patients with subsequent nosocomial infections [20]. On the contrary, the level of mHLA-DR returned to normal rapidly (generally within less than 1 week) in the injured patients who recovered smoothly. Reduced

mHLA-DR has thus been shown to predict adverse outcomes in various groups of critically ill patients [21]. Compared with the normal level, patients with mHLA-DR expression less than 30% had lower survival rate and a 30-fold increased risk of death [22].

A large number of studies have shown that the expression of HLA-DR is decreased in patients with sepsis. Loss of mHLA-DR expression is an early event of sepsis. The persistence of this change is associated with severity score, nosocomial infection and death [23]. The down regulation of HLA DR expression on monocytes detected by flow cytometry is considered to be a general biomarker of sepsis induced immunosuppression and an independent predictor of nosocomial infection [17]. Polk et al. [24] have revealed the relationship between sepsis and low mHLA-DR expression in 1986. Subsequently, the expression of mHLA-DR was identified as an effective prognostic marker for sepsis. Jonathan et al. found that significantly reduced numbers of HLA-DR cells typified sepsis splenic tissue [25]. Lukaszewicz et al.'s study supported that monitoring

immune functions through mHLA-DR in intensive care unit patients therefore could be useful to identify high risk of secondary infection [7]. The number of HLA-DR expressed by monocytes and the density of HLA-DR expressed have been proved to have prognostic value. Previous studies have reported the use of low HLA-DR expression to accurately predict patients most likely to die of sepsis [26]. Here, we found that the expression of HLA-DR was lower than that in patients without urogenic sepsis, suggesting that HLA-DR may be potential indicators for the diagnosis of urogenic sepsis.

The ROC Curves provides the ability to identify optimal cutoff points, evaluate performance comparison across multiple diagnostic tests and evaluate performance of a diagnostic test across multiple population samples. Calculations of Area Under Curve (AUC) and measures of accuracy determines the differentiating power of the test. Thus, we used the ROC curve to analyze the value of HMGB1 and HLA-DR in predicting the diagnosis of urinary sepsis at postoperative 24 h and 72 h. The result suggested that the detection of HLA-DR expression at postoperative 24 h has a higher predictive value in the diagnosis of sepsis.

Limitations

Although our studies have shown that postoperative HMGB1 level and HLA-DR expression are associated with the occurrence of urinary sepsis after PCNL, some potential limitations should be considered. In fact, we did not measure the expression of HMGB1 and HLA-DR at more time points and did not exclude all the risk factors for the occurrence of urinary sepsis after PCNL, such as operation time, intraoperative infusion of normal saline, morphology and distribution of renal stones, single or multiple cases. However, the number of patients with urinary sepsis in the sample is relatively small, and more rigorous prospective study design is needed to comprehensively analyze the indicators and time points that may have predictive diagnostic value for postoperative urinary sepsis and endure large sample size to verify the results we have achieved.

Conclusion

Postoperative HLA-DR and HMGB1 can both be used as a predictive diagnosis of sepsis for patients with renal calculus received PCNL surgery.

Ethics approval

The present study was approved by the ethic committee of Chongqin Jiangjin District Central Hospital.

Informed consent

All authors agreed the submission and the policy of the journal and copyright.

Author contributions

HFH conducted most of the experiments and wrote the manuscript; YL, XYZ and ZHH conducted the experiments and analyzed the data, TMC designed the study and revised the manuscript. All authors have read and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data in this study can be obtained by proper request from the authors.

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