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Risk Factors of Sepsis and Factors Influencing the Decision to Perform Emergency Drainage in Obstructive Acute Pyelonephritis Secondary to Urinary Calculi

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Purpose: To investigate the risk factors for sepsis and analyze the criteria for emergency drainage in patients with obstructive acute pyelonephritis (APN) secondary to urinary calculi.

Materials and Methods: We included 64 patients with obstructive APN secondary to urinary calculi. Patients were divided into two groups: the sepsis and non-sepsis groups. Independent risk factors for sepsis were also identified. Forty-three patients in the sepsis group were further divided into two subgroups: those who underwent emergency drainage and those who did not. A retrospective analysis was performed.

Results: Of the 64 patients, 43 showed signs of sepsis. There was a lower lymphocyte count and lymphocyte percentage, as well as a higher C-reactive protein level and neutrophil-to-lymphocyte ratio (NLR) in the sepsis group compared with the non-sepsis group. Increased sepsis showed a statistically significant association with increased Charlson comorbidity index (CCI). Four out of 21 patients in the non-sepsis group underwent emergency drainage compared with 26 out of 43 patients in the sepsis group. Independent variables for sepsis in a multivariate logistic regression analysis showed positive blood culture, high NLR, and increased CCI score. Among sepsis patients, the likelihood of performing emergency drainage increased with higher creatinine, positive urine culture, and higher CCI score.

Conclusions: In patients with obstructive APN secondary to urinary calculi, a high CCI score were associated with a higher probability of progression to sepsis. In patients with higher creatinine and higher CCI scores, proactive treatment is usually necessary.

Keywords: Pyelonephritis; Sepsis; Urinary calculi; Nephrostomy, percutaneous; Ureteroscopy

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INTRODUCTION

Obstructive acute pyelonephritis (APN) secondary to urinary calculi is not a common disease, but it can lead to severe events, such as sepsis, septic shock, and disseminated intravascular coagulopathy. APN is divided into three classifications: uncomplicated infections that do not require hospitalization, uncomplicated infections with a

normal urinary tract that require inpatient parenteral therapy, and complicated or obstructive infections that require hospitalization for emergency drainage or urologic surgery. Urosepsis and septic shock, in association with obstructive uropathy, usually requires active treatment, such as drainage. It has a mortality rate of approximately 2% even with intensive treatment and emergency drainage (defined as drainage performed within 24 hours of admission) [1].

Determining the prognostic factors for progression to sepsis or septic shock in obstructive APN would help with the establishment of treatment options. We examined the risk factors for sepsis in patients with obstructive APN secondary to urinary calculi. Moreover, because the judgment of physicians is a major factor in deciding the course of treatment, we analyzed the differences between patients who underwent emergency drainage and those who did not in the sepsis group, as well as the criteria for treatment with emergency drainage. We also explored appropriate treatment approaches for obstructive APN secondary to urinary calculi.

MATERIALS AND METHODS

We performed a retrospective analysis of patients admitted to the Department of Urology at Samsung Changwon Hospital for treatment of obstructive APN secondary to urinary calculi between January 2004 and December 2013. The study was reviewed and approved by the Institutional Review Board of Samsung Changwon Hospital (approval number: SCMC 2017-09-003).

Among patients with urinary calculi admitted at the outpatient department or emergency center, we selected those showing signs of APN; we excluded patients with an infection outside the urinary tract.

APN is defined as at least five white blood cells (WBCs) per high-power field in a centrifuged urinary specimen, at least 10^4 colony-forming units per milliliter of urine specimen, a fever of at least 38°C, and flank pain or similar symptoms [2]. Sepsis is defined as a systemic inflammatory response syndrome satisfying at least 2 of the following criteria: body temperature >38 or <36; heart rate >90 beats/minute; respiratory rate >20 breaths per minute or arterial CO_2 pressure <32 mmHg; WBC count >12,000/mm^3 or <4,000/mm^3, or immature neutrophils >10%; grossly identifiable infection focus; or culture or body fluid positive

for pathogenic microorganisms [2-5].

Drug sensitivity was tested via blood culture tests and urine culture tests using voided midstream urine. If the drug sensitivity results showed a resistance to early empiric antibiotics, treatment was changed to a drug showing sensitivity.

Patients with obstructive APN secondary to urinary calculi were divided into two groups: the sepsis group and the non-sepsis group. The following information was compared between the two groups: patient demographics; age; gender; performance status; presence of diabetes mellitus (DM); presence of hypertension (HTN)/cardiovascular disease (CVD)/neurologic disease; WBC count ($\times 10^3$/μl); percentage (%) and count of lymphocytes; percentage (%) and count ($\times 10^3$/μl) of neutrophil; platelet (PLT) count ($\times 10^3$/μl); prothrombin time (seconds)-international normalized ratio (PT-INR); C-reactive protein (CRP, mg/dl); albumin (g/dl); creatinine (mg/dl); total bilirubin (mg/dl); result of urine culture and blood culture; degree of hydronephrosis; laterality; stone position; stone size; method of emergency drainage; neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR).

Patients in the sepsis group were further divided into two groups and were compared: those who underwent emergency drainage and those who did not. Two methods of emergency drainage (ureterorenoscopy [URS] and percutaneous nephrostomy [PCN]) were used. In URS, following general or spinal anesthesia, a semi-rigid Wolf ureteroscope and Holmium laser were used to remove the ureteral stone, and 6 Fr polyurethane JJ ureteral stents were placed. In PCN, by referral to the Radiology Department, patients were put under local anesthesia before placing a 7 Fr pigtail catheter by ultrasound guidance. The severity of comorbid disease was quantified using the Charlson comorbidity index (CCI), with CCI scores classified into three bands: mild, for CCI scores of 1-2; moderate, for CCI scores of 3-4; and severe, for CCI scores ≥5.

Variables were compared between the groups using an independent sample t-test or chi-square test, and multivariate logistic regression analysis was used to determine independent risk factors. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA).

Table 1. Univariable analysis of variables for sepsis between non-sepsis group and sepsis group

Variable	Non-sepsis group (n=21)	Sepsis group (n=43)	p-value
Age (y)	65.43±16.20	61.74±14.67	0.37
Gender			0.51
Male	5	7	
Female	16	36	
Performance status			0.98
0-1	17	36	
2-4	4	1	
Hospital stay (d)	9.71±8.40	12.53±9.82	0.26
Diabetes mellitus			0.59
No	12	28	
Yes	9	15	
HTN/CVD/neurologic disease			0.87
No	10	25	
Yes	13	30	
WBC count ($\times10^3/\mu l$)	12.78±7.02	15.05±6.33	0.2
Lymphocyte (%)	11.20±9.44	6.70±4.42	0.011
Lymphocyte count ($\times10^3/\mu l$)	1.18±0.68	0.84±0.40	0.013
Neutrophil (%)	81.43±11.33	88.17±5.38	0.002
Neutrophil count ($\times10^3/\mu l$)	10.69±6.43	13.44±6.01	0.098
PLT count ($\times10^3/\mu l$)	177.19±80.03	184.65±96.16	0.76
PT-INR	1.08±0.20	1.15±0.21	0.16
CRP (mg/L)	106.69±76	207.06±111.66	0.001
Albumin (g/dl)	3.11±0.73	3.00±0.61	0.51
Creatinine (mg/dl)	1.63±1.33	1.96±1.28	0.35
Total bilirubin (mg/dl)	0.87±0.59	1.04±0.38	0.18
Urine culture			0.6
Negative	11	19	
Positive	10	24	
Blood culture			0.003
Negative	18	20	
Positive	3	23	
Hydronephrosis			0.25
Grade 1	12	19	
Grade 2	8	18	
Grade 3	1	6	
Laterality			0.14
Right	7	26	
Left	11	16	
Bilateral	3	1	
Stone position			0.76
Upper	14	29	
Middle	1	5	
Lower	6	9	
Stone size (mm)	7.52±4.72	8.19±3.85	0.55
NLR	10.90±8.68	18.67±12.68	0.014
PLR	199.10±139.26	307.47±345.81	0.17
CCI			0.02
1-2	15	6	
3-4	4	11	
≥5	2	26	
Observation (n=34)	17 (50.0)	17 (50.0)	0.003
Intervention (n=30)	4 (13.3)	26 (86.7)	0.96
URS (n=5)	0 (0)	5 (100.0)	
PCN (n=25)	4 (16.0)	21 (84.0)	

Values are presented as mean±standard deviation, number only, or number (%).
HTN: hypertension, CVD: cardiovascular disease, WBC: white blood cell, PLT: platelet, PT-INR: prothrombin time (seconds)–international normalized ratio, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, CCI: Charlson comorbidity index, URS: ureterorenoscopy, PCN: percutaneous nephrostomy.

Table 2. Multivariate analysis of independent variables for sepsis (all patients)

Variable	OR	95% CI	p-value
Blood culture	8.415	1.660-242.665	0.01
NLR	1.092	1.006-1.142	0.03
CCI score			0.04
1-2	1	1	
3-4	1.52	0.678-3.46	
≥5	3.70	0.45-30.37	

OR: odds ratio, 95% CI: 95% confidence interval, NLR: neutrophil-to-lymphocyte ratio, CCI: Charlson comorbidity index.

RESULTS

Patient's characteristics, initial laboratory findings, culture result, and radiologic findings between the non-sepsis group and sepsis group were analyzed. Out of the 64 total patients, 43 (67.2%) developed sepsis; eight patients (12.5%) developed septic shock, but no patients died due to any related causes. The mean age was 65.43 and 61.74 years in the non-sepsis group and sepsis group, respectively; the sex ratio (male/female) was 0.31 and 0.21, respectively. These differences were not significant (p=0.37, 0.51). There was no difference between the two groups in performance status (p=0.98). Hospital stay was longer in the sepsis group (9.71 days vs. 12.53 days), but this was not statistically significant (p=0.26). There were no significant differences between the two groups in DM or HTN/CVD/neurologic disease (p=0.59, 0.87).

WBC count, neutrophil count, PLT count, PT-INR, albumin, creatinine, total bilirubin, urine culture results, degree of hydronephrosis, laterality, stone position, stone size, and PLR also showed no significant differences between the two groups. In the sepsis group, there was a slower lymphocyte counter and lymphocyte percentage (p=0.011, 0.013), and a higher CRP and NLR (p=0.001, 0.014) than in the non-sepsis group. The risk of sepsis increased with higher CCI. In the non-sepsis group, four out of 21 patients underwent emergency drainage (URS or PCN), compared with 26 out of 43 patients in the sepsis group. The method of emergency drainage was not related to the progression of sepsis (p=0.96) (Table 1).

Independent variables for sepsis in the multivariate logistic regression analysis were positive blood culture (odds ratio [OR], 8.415; p=0.01), high NLR (OR, 1.092; p=0.03), and increased CCI score (OR, 1.52, 3.70; p=0.04) (Table 2).

Within the sepsis group, patients who did and did not undergo emergency drainage were compared. The emergency drainage group, when compared with the non-drainage group, showed a longer mean hospital stay at 14.70 days (p=0.05), a lower PLT count at 163.96, and significantly higher creatinine at 2.93. Positive urine and blood cultures were significantly higher in the emergency drainage group, at 69.2% (vs. 35.3%) and 69.2% (vs. 29.4%), respectively. There was a significant correlation between the CCI score and emergency drainage (p<0.001) (Table 3). In the emergency drainage group, there was no statistical difference between the PCN and URS groups with regard to all laboratory and radiologic findings.

Variables for emergency drainage in the multivariate logistic regression analysis were creatinine (OR, 5.03; p=0.04), positive urine culture (OR, 1.09; p=0.01), and increased CCI score (p=0.05) (Table 4).

DISCUSSION

Urosepsis, accounting for 20-30% of all sepsis patients, is commonly caused by urinary stones, tumors, or stenosis, resulting in the obstruction of the urinary tract [6]. The severity of urosepsis depends on local factors and a response of the host. Such a response is affected by age, HTN, diabetes, performance status, and immune suppression, such as acquired immunodeficiency syndrome, transplant recipients, and long-term steroid use.

Local factors include neurogenic bladder, urinary calculi, congenital abnormalities of the ureter, and iatrogenic factors, such as endoscopic surgery [7].

Although urinary calculi are the most common disease of the urogenital system, when infection accompanies obstructive uropathy, it can progress to bacteremia and sepsis, which can be fatal [8].

Lim et al. [7] reported that old age, a decrease in serum albumin level, and high NLR are independent risk factors for the development of urosepsis. In our study, comorbid conditions expressed in terms of the CCI score was found to be risk factors for urosepsis, while old age did not show any statistical significance (p=0.37).

One aspect of the physiological immune response to stress is an increase in the number of neutrophils and a decrease in the number of lymphocytes [7]. Zahorec [9] proposed the use of NLR as an additional indicator of infection in focused clinical treatment. NLR is an easy way

Table 3. Univariate analysis of variables between the non-emergency drainage group and emergency drainage group within the sepsis group

Variable	Non-emergency drainage group (n=17)	Emergency drainage group (n=26)	p-value
Age (y)	58.00±16.13	64.20±13.39	0.18
Gender			0.9
Male	3	4	
Female	14	22	
Performance status			0.69
0-1	15	21	
2-4	2	5	
Hospital stay	9.24±10.10	14.70±9.20	0.05
Diabetes mellitus			0.21
No	13	15	
Yes	4	11	
HTN/CVD/neurologic disease			0.66
No	8	0	
Yes	9	12	
WBC count (×10^3/μl)	15.41±4.63	14.82±7.32	0.77
Lymphocyte (%)	6.41±2.67	6.88±5.28	0.74
Lymphocyte count (×10^3/μl)	0.92±0.31	0.79±0.44	0.29
Neutrophil (%)	87.86±3.62	88.37±6.33	0.77
Neutrophil count (×10^3/μl)	13.58±4.26	13.34±7.01	0.9
PLT count (×10^3/μl)	216.29±100.20	163.96±89.34	0.05
PT-INR	1.13±0.24	1.17±0.18	0.54
CRP (mg/L)	210.26±115.04	204.97±111.64	0.88
Albumin (g/dL)	3.09±0.67	2.93±0.57	0.42
Creatinine (mg/dL)	1.43±0.72	2.30±1.45	0.02
Total bilirubin (mg/dL)	1.01±0.37	1.06±0.39	0.67
Urine culture			0.03
Negative	11	8	
Positive	6	18	
Blood culture			0.01
Negative	12	8	
Positive	5	18	
Hydronephrosis			0.15
Grade 1	10	9	
Grade 2	4	14	
Grade 3	3	3	
Laterality			0.41
Right	9	17	
Left	7	9	
Bilateral	1	0	
Stone position			0.99
Upper	12	17	
Middle	2	3	
Lower	3	6	
Stone size (mm)	8.76±5.43	7.81±2.38	0.43
NLR	16.24±8.65	20.27±14.70	0.31
PLR	278.59±223.01	326.35±410.04	0.66
Septic shock			0.45
No	15	20	
Yes	12	6	
CCI			<0.001
1-2	5	0	
3-4	9	6	
≥5	3	20	

Values are presented as mean±standard deviation or number only.
HTN: hypertension, CVD: cardiovascular disease, WBC: white blood cell, PLT: platelet, PT-INR: prothrombin time (seconds)–international normalized ratio, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, CCI: Charlson comorbidity index.

Table 4. Multivariable analysis of independent variables in sepsis group patients

Variable	OR	95% CI	p-value
Creatinine (mg/dl)	5.03	0.82-31.02	0.04
Urine culture	1.092	1.78-350.02	0.01
CCI score			0.05
1-2	1	1	
3-4	1.52	1.75-5.609	
≥5	3.7	0.169-17.568	

OR: odds ratio, 95% CI: 95% confidence interval, CCI: Charlson comorbidity index.

to quantify the severity of stress and systemic inflammation in clinically ill patients, which has been shown to be correlated with various forms of cancer, including ovarian, colorectal, gastric, and hepatocellular carcinoma [10-13]. Other studies also reported that age, sex, and performance may be risk factors. Yamamoto et al. [14] reported that old age and paralysis were risk factors for sepsis in patients who underwent emergency drainage for APN accompanied by upper urinary calculi. Bossink et al. [15] reported, in a univariate analysis, that decreased albumin could predict sepsis in patients with infection. Moreover, Tambo et al. [5] reported that reduced PLT count and decreased albumin may be risk factors for sepsis in obstructive APN patients. In a study of obstructive APN, Kamei et al. [16] stated that thrombocytopenia and a positive blood culture were independent risk factors. Another study reported that old age and poor performance status are likely significant risk factors for septic shock and suggested that this might be due to delayed diagnosis of APN from vague symptom reporting [14]. In our study, we found that albumin was lower in the sepsis group (3.11 g/dl vs. 3.00 g/dl), but this difference was not statistically significant (p=0.51). We also found that PLT was higher in the sepsis group, but without significance (p=0.76).

Several studies have reported that poor performance, as a result of spinal cord injury, may be a risk factor for sepsis and septic shock [17,18]; however, we were unable to verify this because there were only two patients with spinal cord injury in our study.

Wagenlehner et al. [19] reported immune impairment, such as in old age, DM, transplant, use of anticancer agents or corticosteroids, and acquired immunodeficiency syndrome, as a risk factor for sepsis. In our study, the rate of DM was higher in the non-sepsis group (42.9%) than in the sepsis group (34.9%), while the CCI score,

which reflects general comorbidity rather than a single disease, was shown to correlate with sepsis (OR, 1.52, 3.70; p=0.04).

In the non-sepsis group, four out of 21 patients underwent emergency drainage (URS or PCN), compared with 26 out of 43 patients who underwent emergency drainage in the sepsis group (p=0.03) (Table 1).

Our study found high creatinine and increased CCI score to be risk factors for emergency drainage. Yoshimura et al. reported old age, poor performance status, and sex as potential risk factors [20]. Other studies mention that high CRP level and old age are independent predictors of urinary diversion, and CRP is described as an objective and useful parameter for emergency drainage in patients with renal colic [18].

This study has some limitations. We were unable to compare the emergency drainage methods of URS and PCN, and because this was a retrospective analysis of a single center, the results may lack obejectivity and generalizability. In the future, multicenter studies will need to be performed in collaboration with various hospitals.

CONCLUSIONS

In patients with obstructive APN secondary to urinary calculi, high CCI score and high NLR were associated with increased risk of sepsis. Such patients will require even closer monitoring and careful treatment than other patients.

Among patients who developed sepsis, those with higher creatinine and higher CCI score were more likely to require active treatment, such as emergency drainage.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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