

Clinical significance of urinary obstruction in critically ill patients with urinary tract infections

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Abstract

Urinary obstruction may be a complicating factor in critically ill patients with urinary tract infections (UTIs) and requires efforts for identifying and controlling the infection source. However, its significance in clinical practice is uncertain. This retrospective study investigated the overall hospital courses of patients in the intensive care unit (ICU) with UTIs from the emergency department.

Baseline severity was assessed by the sequential organ failure assessment (SOFA) score; outcomes included probability and inotropic-, ventilator-, renal replacement therapy (RRT)-, and ICU-free days and 28-day mortality.

Of 122 patients with UTIs, 99 had abdominal computed tomography scans. Patients without computed tomography scans more frequently had quadriplegia and a urinary catheter than those without scans (P=.001 and .01). Urinary obstruction was identified in 40 patients who had higher SOFA scores and lactate levels (P=.01 and P<.001). The use and free days of inotropic drugs and ventilator did not differ between the groups. However, patients with obstruction were more likely to require RRT and had shorter durations of RRT-free days (odds ratio 3.8; P=.06 and estimate -3.0; P=.04). Durations of ICU-free days were shorter, but it disappeared after adjustment for initial SOFA scores (estimate -2.3; P=.15). Impact of the timing of urinary drainage on outcomes was evaluated, demonstrating that an intervention within 72 hours lengthened the duration of RRT-free days compared with that after 72 hours (estimate -6.0 days; P=.03). On the other hand, the study did not find the association between other outcomes including 28-day mortality and the timing of urinary drainage.

Urinary obstruction can be a complicating factor, resulting in a higher probability of RRT implementation and shorter durations of RRT- and ICU-free days in critically ill patients with UTIs. Furthermore, delayed intervention for urinary drainage may result in longer durations of RRT. Efforts should be warranted to find the presence of urinary obstruction and to control infection source in critically ill patients with UTIs.

Abbreviations: CI = confidence interval, CT = computed tomography, ICU = intensive care unit, OR = odds ratio, RRT = renal replacement therapy, SOFA = sequential organ failure assessment, UTI = urinary tract infection.

Keywords: obstruction, renal replacement therapy, source control, urinary tract infection

1. Introduction

The urinary tract is a common site of infection in critically ill patients with sepsis.^[1–3] Although its prognosis is relatively favorable compared with that of infections from other origins, a considerable proportion of patients have died from urinary sepsis.^[4,5] Therefore, intensive management over the hospital

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course is essential in this disease population. The Surviving Sepsis Campaign Guideline, regarded as the international standard for the treatment of sepsis, recommends evidence-based strategies to improve outcomes of sepsis including that originating from the urinary tract.^[6] Strategies are composed of early recognition, aggressive fluid resuscitation, hemodynamic support, appropriate antibiotics, and infection source control.

Sometimes urinary tract infections (UTIs) are complicated due to urinary obstruction, which is caused by stricture, stones, or malignancy. In stable cases, management for relieving obstruction may be delayed; however, emergency drainage is required in critically ill patients in order to control the infection source.^[6,7] In other words, the presence of a urinary obstruction can be a complicating factor needing additional tests and interventions. However, several issues remain unsolved in the management of patients with urinary sepsis, as follows: those who need imaging studies for urinary obstruction, when urinary drainage is performed, and whether the presence of urinary obstruction and the timing of urinary drainage affect hospital courses and clinical outcomes. Although a recent review article described that imaging for obstruction can be conducted in those who have risk factors,^[8] these have been few studies regarding this proposal. Moreover, the clinical significance of urinary obstruction remains uncertain in critically ill patients with urinary sepsis.

This study retrospectively investigated overall hospital courses in critically ill patients who were admitted the intensive care unit (ICU) from the emergency department due to UTIs. We evaluated the clinical pattern of critically ill patients with UTIs via computed tomography (CT) and sought to identify factors related to urinary obstruction. Thereafter, we explored the impacts of urinary obstruction and the timing of urinary drainage on outcomes.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the medical records of patients admitted to the ICU via the emergency department at a tertiary teaching hospital in Seoul, Korea, from January 2011 to May 2016. Our institution has an open ICU system,^[9,10] but all patients requiring ICU admission should be referred to an attending intensivist. The necessity of admission to the ICU is categorized by the priority model, which is based on the guideline published by the Korean Society of Critical Care Medicine and prepared based on the guideline of the Society of Critical Care.^[11] Most patients are treated by specialists, and as part of a tertiary teaching hospital, physicians try to provide evidence-based management to ICU patients based on the current guidelines including Survival Sepsis Campaign Guidelines.^[6] A total of 202 patients older than 18 years who were diagnosed with UTIs were eligible. UTI was defined if those suspected of infection had pyuria (>5 white blood cells per high-power field) when urinalysis was performed or had a culture-confirmed uropathogen. Of these, 80 patients who had combined infections of other origins or who had end-stage renal disease needing dialysis were excluded. Ultimately, the study included 122 ICU patients with UTIs (Fig. 1).

The included patients were divided into 2 groups based on whether they had abdominal CT scans upon admission. Then, the CT images were evaluated for the presence of urinary obstruction. Urinary obstruction was defined based on the presence of structural obstruction with hydronephrosis by CT imaging. Subjects were eventually classified into 3 groups: those without CT scans; those without obstruction; and those with obstruction (Fig. 1). We also reviewed the causes of the urinary obstruction in patients with urinary obstruction.

This study was approved by the institutional review board of the Chung-Ang University Hospital (IRB No. 1804–001–16160). As this study was a retrospective study, the IRB waived the requirements for written informed consents.

2.2. Data collection

Patients' demographics and clinical data, including age, sex, comorbidities, history of urinary stone, and use of indwelling urinary catheter, were collected from electronic medical records. Baseline disease severity was assessed using the sequential organ failure assessment (SOFA) score. To calculate the SOFA score, related parameters were obtained at ICU admission.^[12] In addition, we evaluated initial body temperatures, pathogens identified from blood or urine cultures; white blood cell count; lactate and C-reactive protein levels; and urine pH. Serum creatinine levels of the previous 5 years to 7 days before admission were obtained if available, and the causes of urinary obstruction.

2.3. Outcomes

First, we evaluated the differences according to the CT images to explore the physicians' clinical patterns when they managed the severely ill patients who had suspected UTIs in the emergency department. Next, the differences of baseline characteristics and clinical outcomes between patients with and without urinary obstruction were evaluated. Clinical outcomes over 28 days

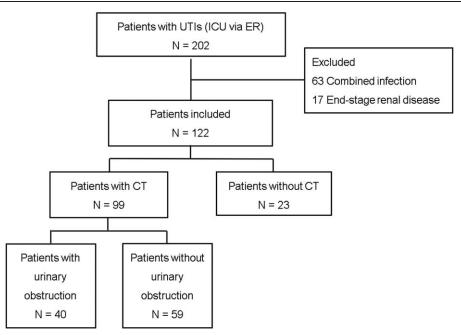


Figure 1. Enrollment flow chart of critically ill patients with UTIs. Patients with UTIs who were admitted to ICU from ER were reviewed, and 80 patients who had combined infection or end-stage renal disease were excluded. A total of 122 patients were included in this study and were classified according to the presence of abdominal CT images or urinary obstruction, and then, the groups were compared. CT=computed tomography, ER=emergency room, ICU=intensive care unit, UTI=urinary tract infection.

included ICU-free days, mechanical ventilator-free days, inotropic-free days, renal replacement therapy (RRT)-free days, and mortality.

Furthermore, we investigated whether the timing of intervention for urinary drainage influenced the clinical outcomes. To do so, patients with obstruction were subdivided based on the timing of intervention: those who were intervened within 72 hours and those who received the intervention after 72 hours or never did. The outcomes were examined between the sub-groups.

2.4. Statistical analysis

Continuous variables were expressed as medians and interquartile ranges and were compared using the Mann–Whitney *U* test. Categorical variables were expressed as frequencies and percentages and were compared using the chi-square test. The use of inotropes, ventilator, or RRT and mortality were compared by logistic regression analysis. In addition, clinical outcomes including inotropic-, ventilator-, RRT-, and ICU-free days were evaluated by a linear regression model. Multivariate analyses were conducted after adjustment for each SOFA score (cardiovascular, respiratory, or renal SOFA score), while mortality and ICU-free days were adjusted by the total SOFA score. A *P*-value of <.05 was considered statistically significant. All statistical analyses were conducted using the software package SPSS statistics version 21.0 (IBM Corp., Armonk, NY).

3. Results

3.1. Characteristics in critically ill patients with UTIs

One hundred twenty-two patients who were diagnosed with UTIs were admitted into the ICU from the emergency department. There were 45 men and 77 women, and their median age was 74 (67–80) years. Uropathogens were identified in 91 (74.6%) patients. The most common pathogen was *Escherichia coli* (67.0%), followed by *Klebsiella pneumoniae* (9.9%), and *Proteus mirabilis* (5.5%). The prevalence of extended-spectrum beta-lactamase-producing organisms was 27.5%. Of the included patients, 99 (81.1%) patients underwent CT scans and 23 (18.9%) did not. Patients without CT scans more frequently had quadriplegia and an indwelling urinary catheter than those with CT scans (P=.001 and .01, respectively, Table 1). In addition, the neurological SOFA scores were significantly different (P<.001).

Urinary obstruction was identified in 40 (40.4%) patients among those who had CT scans. The causes of obstruction were identified as follows: 26 (65.0%) had stones, 7 (17.5%) had malignancy, 3 (7.5%) had prostate enlargement, 2 (5.0%) had catheter malfunction, 1 (2.5%) had ureter stricture, and 1 (2.5%) had an unknown cause. Patients with urinary obstruction had higher median admission SOFA scores (10 [7–11] vs 7 [5–9], P=.01) and higher median lactate levels (3.7 [2.2–6.9] mmol/L vs 1.5 [1.0–3.2] mmol/L, P < .001) than those without urinary obstruction (Table 1). On the other hand, history of stone, serum creatinine levels, urine pH, and type of uropathogens did not differ according to urinary obstruction.

3.2. Clinical outcomes according to urinary obstruction in critically ill patients with UTIs

Clinical outcomes were compared between patients with urinary obstruction and patients with intact urinary tract (Table 2). The use of inotropic drugs and mechanical ventilation did not differ between the groups (P = .20 and .34, respectively). Inotropic- and ventilator-free days were also comparable between the 2 groups (P = .13 and .60, respectively). However, patients with urinary obstruction were more likely to require RRT (odds ratio [OR] 2.7; 95% confidence interval [CI] 1.0–7.1; P = .05), although this was not the case in the multivariate analysis (OR 3.8; 95% CI 0.9–15.4; P = .06). The median RRT-free days in patients with obstruction was 3.6 (95% CI 0.7–6.5) days shorter than those without obstruction (P = .02), and it persisted after the adjustment with renal SOFA score (estimate -3.0 days; 95% CI -5.8to -0.1; P = .04).

ICU-free days were also shorter in patients with obstruction, compared with those without obstruction (estimate -4.3 days; 95% CI -7.7 to -0.8; P = .02); however, this did not differ in the multivariate analysis (P = .15). There were 4 (10.0%) deaths in the obstruction group, and 4 (6.8%) deaths in the non-obstruction group. This study did not reveal a difference in the 28-day mortality between patients with and without urinary obstruction (P = .57).

3.3. Impacts of the timing of urinary drainage on outcomes in UTI patients with urinary obstruction

We further investigated whether the timing of urinary drainage influences outcomes in critically ill patients with UTIs who had urinary obstruction. Of the 40 patients with obstruction, 21 (52.5%) received the intervention within 72 hours, and 19 (47.5%) received the intervention after 72 hours or never did. The baseline characteristics are shown in Table 3. Significant differences did not exist between the 2 sub-groups.

We performed linear regression analyses with respect to clinical outcomes (Fig. 2). The study showed that inotropic- and ICU-free days did not differ (P=.29 and .18). Ventilator-free days were insignificantly longer in patients who received early interventions than in those who received late interventions (estimates 5.0; 95% CI -0.9 to 10.8 days; P=.09 in the multivariate analysis). On the other hand, patients who underwent intervention within 72 hours needed shorter durations of RRT than those who underwent intervention after 72 hours in both the univariate and multivariate analyses (estimates, 6.0 days; 95% CI 0.5–11.5; P=.03 in the multivariate analysis). Mortality over 28 days did not differ according to the timing of urinary drainage (P=.27).

4. Discussion

This retrospective study investigated the clinical significance of urinary obstruction in critically ill patients with UTIs during their hospital stays. This study showed that patients with UTIs with urinary obstruction had more severe clinical presentation and that they experienced shorter durations of RRT- and ICU-free days than those without obstruction. Furthermore, among patients with UTIs with urinary obstruction, the intervention for urinary drainage within 72 hours resulted in longer durations of RRT-free days.

Imaging studies are not necessary for diagnosing UTIs in patients visiting the emergency department. However, it is used to identify urinary obstruction, abscess, or emphysematous pyelonephritis. At first, we reviewed the clinical patterns of clinicians that ordered imaging studies in critically ill patients with UTI, which showed that CT was unlikely to be performed when

Table 1

Characteristics in critically ill patients diagnosed as urinary tract infections.

	CT (-) (N=23)	CT (+) Non-obstruction (N = 59)	CT (+) Obstruction (N = 40)
Age, y	74 (63, 82)	74 (68, 81)	74 (62, 80)
Male, n (%)	10 (43.5)	21 (35.6)	14 (35.0)
Comorbidities, n (%)			
Diabetes	10 (43.5)	27 (45.8)	21 (52.5)
Hypertension	12 (52.2)	41 (69.5)	21 (52.5)
Heart failure	1 (4.3)	5 (8.5)	3 (7.5)
Chronic liver disease	0 (0.0)	1 (1.7)	1 (2.5)
Chronic kidney disease	2 (8.7)	9 (15.3)	5 (12.5)
Malignancy	2 (8.7)	9 (15.3)	12 (30.0)
Brain injury	10 (43.5)	17 (28.8)	15 (37.5)
Quadriplegia	4 (17.4)*	2 (3.4)	0 (0.0)
History of urinary stone, n (%)	0 (0.0)	4 (6.8)	6 (15.0)
Urinary catheter use, n (%)	8 (34.8)*	6 (10.2)	7 (17.5)
Previous creatinine, mg/dL ($n = 62$)	0.6 (0.5–1.0)	0.8 (0.5–1.0)	1.0 (0.7–1.6)
SOFA score	8 (5–10)	7 (5–9)	10 (7–11) [†]
Cardiovascular	4 (2-4)	3 (1-4)	4 (2-4) [†]
Respiratory	1 (0-2)	1 (0-2)	2 (0-2)
Neurological	2 (1-4)*	1 (1–1)	1 (1-1)
Liver	0 (0-0)	0 (0-0)	0 (00)
Coagulation	0 (0-1)	1 (0-2)	1 (0-2)
Kidney	1 (0-2)	1 (0-2)	2 (1–3)
Ventilator use, n (%)	3 (13.0)	4 (6.8)	5 (12.5)
Inotropic use, n (%)	18 (78.3)	37 (62.7)	30 (75.0)
Body temperature, °C	37.2 (36.5–38.5)	37.2 (36.3-38.2)	37.1 (36.5–38.3)
Laboratory findings			
White blood cells, /µL	13390 (9800–19420)	13890 (10790-20550)	19675 (8950-26168)
Platelet, ×10 ³ /L	231 (128–332)*	167 (100–234)	138 (83–202)
C-reactive protein, mg/L	117.5 (62.2–219.1)	141.6 (72.0 -220.7)	148.6 (72.2–207.7)
Lactate, mmol/L (n = 100)	2.2 (1.5–3.2)	1.5 (1.0–3.2)	3.7 (2.2–6.9) [†]
Creatinine, mg/dL	1.5 (1.0–2.9)	1.6 (1.1–3.7)	2.0 (1.6–3.9)
Urine pH	5.0 (5.0-6.5)	5.0 (5.0–5.5)	5.0 (5.0-6.5)
Bacteremia, n (%)	11 (47.8)	29 (49.2)	24 (60.0)
Urine culture positive, n (%)	17 (73.9)	47 (79.7)	27 (67.5)
Pathogen			
Escherichia coli	7 (30.4)	34 (57.6)	20 (50.0)
Klebsiella pneumoniae	5 (21.7)	3 (5.1)	1 (2.5)
Gram positive cocci	3 (13.0)	7 (11.9)	1 (2.5)
Others	2 (8.7)	3 (5.1)	5 (12.5)

Continuous variables are expressed as median (25th-75th percentile), and categorical variables are expressed as numbers (percentage). CT = computed tomography, SOFA = sequential organ failure assessment.

*P < .05 compared with patients with CT scans.

 $^{\dagger}\mathit{P}{<}.05$ compared with patients without urinary obstruction.

Table 2	
Clinical outcomes according to urinary obstruction in critically ill patients with urinary tract infections.	

	Univariate analysis		Multivariate analysis [*]	
	Odds ratio or estimates (95% CI)	Р	Odds ratio or estimates (95% CI)	Р
Inotropic				
Use	1.8 (0.7-4.3)	.20	0.1 (0.0-4.2)	.20
Free days	-2.5 (-5.7 to 0.7)	.13	-1.7 (-4.8 to 1.5)	.31
Ventilator				
Use	2.0 (0.5–7.8)	.34	1.3 (0.3-6.0)	.75
Free days	-0.9 (-4.6-2.7)	.60	-0.0 (-3.5-3.5)	.99
RRT				
Use	2.7 (1.0-7.1)	.05	3.8 (0.9–15.4)	.06
Free days	-3.6 (-6.5 to -0.7)	.02	-3.0 (-5.8 to -0.1)	.04
ICU-free days	-4.3 (-7.7 to -0.8)	.02	-2.3 (-5.5-0.8)	.15
28-day mortality	1.5 (0.4–6.5)	.57	1.3 (0.3–5.6)	.75

Cl=confidence interval, ICU=intensive care unit, RRT=renal replacement therapy, SOFA=sequential organ failure assessment.

* Multivariate analyses were conducted after the adjustment for corresponding SOFA score (cardiovascular, respiratory, or renal SOFA score) while mortality and ICU-free days were adjusted by the total SOFA score.

Table 3

Characteristics according to the timing of urinary drainage among patients with urinary tract infections and urinary obstruction.

	Urinary drainage after 72 hours or never N=19	Urinary drainage within 72 hours N=21	Р
Age	74 (68–79)	72 (61–80)	.81
Male, n (%)	9 (47.4)	5 (23.8)	.12
SOFA score	9 (8–11)	10 (6-11)	.49
Cardiovascular	4 (3-4)	3 (2-4)	.32
Respiratory	2 (0-2)	2 (1-2)	.79
Neurological	1 (1-1)	1 (1-1)	.83
Liver	0 (0-0)	0 (00)	.54
Coagulation	1 (0-2)	1 (0-2)	1.00
Kidney	2 (1-3)	1 (1-2)	.13

Continuous variables are expressed as median (25th-75th percentile), and categorical variables are expressed as numbers (percentage). SOFA = sequential organ failure assessment.

patients had quadriplegia, urinary catheter, and high neurological SOFA scores. This might mean that patients having these factors were obviously at risk for UTIs,^[13] so clinicians probably did not feel the need to carry out a further study for identifying urinary obstruction.

Imaging studies are necessary in high-risk patients suspected to have urinary obstruction, abscess, or emphysematous pyelonephritis because early intervention for source control can be required. A recent review article by Johnson et al summarized that risk factors for these complications include known or suspected urolithiasis, a urine pH of 7.0 or higher, a new decrease in the estimated glomerular filtration rate to 40 mL/min or lower, unexplained oliguria, septic shock, worsening clinical status despite aggressive medical therapy, and sickle cell disease, based on 2 previous studies.^[8,14,15] Our study with critically ill patients admitted to the ICU did not correspond with these studies. It is noteworthy that most parameters did not differ between patients with and without urinary obstruction. A history of malignancy and stones slightly differ, but they were statically insignificant (P=.08 and .31, respectively). In addition, serum creatinine levels were not informative. Because a considerable proportion of patients in the ICU experience acute kidney injuries,^[16] it can be difficult to distinguish whether an increase in serum creatinine levels is due to urinary obstruction or acute kidney injury from other reasons. Thus, risk factors identified as predicting urinary obstruction should be reassessed, especially in critically ill patients.

Patients having urinary obstruction had higher baseline severities than those without obstruction in this study. Besides, renal outcomes and ICU-free days were worse in these patients. In other words, urinary obstruction could be a complicating factor in critically ill patients with UTIs.^[17-20] There have been few reports that investigated the hospital courses of patients with UTIs with urinary obstruction. Hamasuna et al^[19] showed that obstructive pyelonephritis as a result of urolithiasis represents an emergent disease with relatively high mortality. Another study by Revner et al^[20] prospectively compared patients with UTIs between those with and without urinary obstruction, similar to our study. In that study, a higher mortality rate was observed in patients with urinary obstruction than in those without obstruction. Although our results did not show an association between urinary obstruction and increased mortality, urinary obstruction seems to aggravate hospital courses in critically ill patients with UTIs. Given the above findings, we extrapolated that imaging studies may be warranted if patients diagnosed with UTIs are severely ill in order to rule out the presence of urologic complications requiring additional interventions.

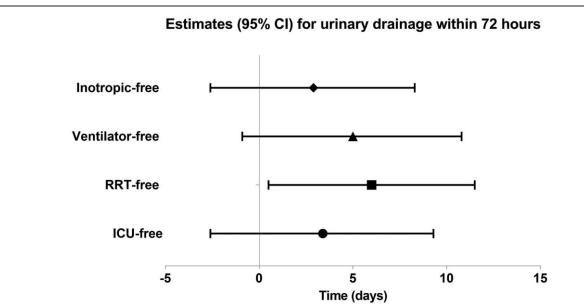


Figure 2. Multivariate linear regression models for outcome-free days according to the time of urinary drainage. Patients with urinary obstruction were subclassified according to the timing of urinary drainage, and the duration of outcome-free days were evaluated. In multivariate analyses adjusting each baseline SOFA score, estimates of urinary drainage within 72 hours were as follows: inotropic-free days of 2.9 (95% CI -2.6-8.3; P=.29); ventilator-free days of 5.0 (95% CI -0.9to 10.8; P=.09), RRT-free days of 6.0 (95% CI 0.5-11.5; P=.03), and ICU-free days of 3.4 (95% CI -2.6 to 9.3; P=.26). Multivariate analyses were conducted after the adjustment for the corresponding SOFA score (cardiovascular, respiratory, or renal SOFA score) while ICU-free days were adjusted by the total SOFA score. CI=confidence interval, ICU=intensive care unit, RRT=renal replacement therapy, SOFA=sequential organ failure assessment.

Source control is an important measure for managing patients with sepsis, and the international guideline recommends that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in these patients. Subsequently, any required source control intervention should be implemented as soon as medically and logistically practical after the diagnosis is made.^[21] However, evidence regarding the impact of the time to source control is lacking. A study by De Pascale et al^[22] confirmed inadequate source control as well as inadequate antimicrobial therapy is predictors of mortality in ICU patients with complicated intraabdominal infections, while another study by Martínez et al^[23] did not show the association between source control after 12 hours and higher mortality. Urinary sepsis accompanied with obstruction clearly corresponds to a situation that requires early control of the infection source. Thus, we lastly investigated whether the time of urinary drainage as source control influences the outcomes in patients with obstruction, and we found that the intervention within 72 hours was associated with longer RRTfree days than that after 72 hours. Mortality did not differ despite a visible trend of difference (P=.27). Nevertheless, we cannot conclude from this study a source control time limit of 72 hours because this study was not a controlled study, and we just randomly used the cut-off value to divide the subjects into 2 subgroups. As far as we know, this was the first study reporting the significant impact of the timing of source control in critically ill patients with urinary sepsis.

The current study has several limitations. First, we used a small sample size from a single center that limited the power of the results and may have ignored some differences. In particular, major outcomes such as ICU-free days and mortality could be weakened, so they need to be reassessed in further larger studies. Second, we used retrospective data, which may result in information bias. However, errors of classification or outcome measurement did not occur, because our data were obtained from electronic medical records. The retrospective design might limit the subjects' recall of previous medical histories including urinary stones. Third, although renal outcomes differed according to the presence of urinary obstruction, the etiologies of kidney injury were not differentiated in this study. The impacts of contrastinduced nephropathy and septic acute kidney injury should be considered. However, the nephrotoxic effect of contrast might be weak because less contrast was used in the obstruction group than in the non-obstruction group (37.5% vs 50.8%). In addition, RRT-free days were shorter in patients with obstruction, independent of the baseline severity of kidney injury. In other words, the study showed that urinary obstruction might have an independent role in the development and duration of renal injury. Fourth, selection bias was considered when comparing the sub-groups according to the timing of urinary drainage. However, there were no significant differences in variables known to affect clinical outcomes, and the benefits on RRT-free days persisted in the multivariate analysis. Nevertheless, some confounders might have been overlooked.

In conclusion, this retrospective study investigated the clinical significance of urinary obstruction in critically ill patients with UTIs. Urinary obstruction could be a complicating factor causing higher probability of RRT implementation and shorter RRT- and ICU-free days in patients with urinary sepsis. Therefore, early identification of the presence of urologic complications should be necessary, especially in severely ill patients with UTIs. In addition, efforts for early intervention such as urinary drainage are needed

to avoid the indiscreet duration of RRT. Future large studies are warranted for establishing the timing of source control in patients with urinary sepsis who have obstruction requiring source control.

Author contributions

Conceptualization: Suk-Won Suh, Jungho Shin. Data curation: Jun Young Hong, Jungho Shin. Formal analysis: Jun Young Hong, Jungho Shin. Investigation: Jun Young Hong, Jungho Shin. Methodology: Suk-Won Suh, Jungho Shin. Supervision: Suk-Won Suh, Jungho Shin. Validation: Jungho Shin. Writing – original draft: Jun Young Hong, Jungho Shin.

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