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ORIGINAL RESEARCH

Presepsin as a predictor of septic shock and mortality in patients with urinary tract infection according to the Sepsis-3 definitions

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Abstract

The objective of this study was to investigate whether presepsin can serve as a useful biomarker for predicting septic shock and mortality rates in patients with urinary tract infections (UTI) as defined by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). This single-center and prospective observational study was carried out between December 2019 and December 2022 and included 171 UTI patients divided into two groups: a non-septic shock group (n = 121) and a septic shock group (n = 50). The primary outcome of this study was the development of septic shock; the secondary outcome was 30-day hospital mortality. Receiver operating characteristic (ROC) curves and multivariate regression analyses were performed to investigate the predictive value of presepsin levels for septic shock and the Cox proportional hazards model was used to determine the risk factors for 30-day hospital mortality in UTI patients. Septic shock patients had significantly higher serum levels of presepsin when compared to the non-septic shock group ($p < 0.001$). In multivariate logistic regression analysis, presepsin demonstrated its independent role as a risk factor for septic shock (odds ratio (OR): 1.002; 95% confidence interval (CI): 1.001–1.002; $p < 0.001$). The multivariate Cox proportional hazards model indicated that presepsin represents a significant predictor of 30-day hospital mortality in septic shock patients (hazard ratio (HR): 1.0005; 95% CI: 1.0001–1.001; $p < 0.05$). The ROC curve for diagnosing septic shock had an area under the curve (AUC) of 0.739 with a cutoff value of 447 pg/mL for presepsin. For the prediction of 30-day hospital mortality in patients with UTI, an optimal presepsin cutoff of 709 pg/mL was determined; ROC curve analysis yielded an AUC of 0.744. When applying the Sepsis-3 criteria, presepsin levels represented a significant independent risk factor for septic shock and 30-day hospital mortality in UTI patients.

Keywords

Presepsin; Septic shock; Urinary tract infection; Emergency department

1. Introduction

Urinary tract infections (UTI) are a prevalent condition that have the potential to progress to sepsis or septic shock, a severe and acute illness that affects millions of individuals worldwide on an annual basis with high mortality rates ranging from 20%–50% [1]. Previous research has shown that urinary and reproductive system infections account for 9%–31% of sepsis cases, with urosepsis making up 20%–30% of all sepsis cases [2]. Therefore, it is imperative to develop methods for the early detection and appropriate treatment of sepsis or septic shock at the onset of UTI.

Various biomarkers have been used for the diagnosis and prognosis of sepsis to facilitate early diagnosis and appropriate treatment. Plasma levels of procalcitonin (PCT) and C-reactive protein (CRP) have been used to facilitate the diagnosis of early sepsis and to estimate its severity and prognosis [1, 3]. Similarly, blood concentrations of lactate can serve as a useful biomarker for septic shock and can also indicate disease severity and prognosis [4, 5].

Over recent years, a series of promising new biomarkers have emerged in the field of medicine; one such biomarker is presepsin, the soluble form of the cluster of differentiation (CD14) protein expressed on the membranes of monocytes and granulocytes [6]. Previous studies have demonstrated that presepsin could represent a valuable biomarker for diagnosing sepsis, evaluating its severity, and predicting its prognosis in various patients, including those with UTI. Several previous studies demonstrated the diagnostic accuracy of presepsin for the early diagnosis of both sepsis [7, 8] and septic shock.

However, in other studies, researchers did not detect a notable difference in the plasma levels of presepsin with regards to septic shock and mortality [9–11], thus creating significant debate.

It is clear that presepsin can produce variable results as a prognostic factor for septic shock. This variation may be caused by numerous factors; one primary factor could be the source of the infection that triggers sepsis. Different infectious sources may lead to the activation of a diverse array of disease pathways and responses, thereby affecting the prognostic value of biomarkers, including presepsin. Unlike many other types of sepsis, which can originate from multiple sources, urosepsis is specifically derived from a UTI [12, 13]. Moreover, many studies focused on the predictive power of presepsin for septic shock in UTI prior to the definitions provided by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3); however, to the best of our knowledge, no studies have applied the sepsis-3 definition with respect to the predictive power of presepsin for septic shock in patients with UTI [1, 6]. Therefore, in this study, we aimed to evaluate the prognostic ability of presepsin, compared with other markers, such as PCT, CRP and lactate, for the prediction of septic shock and in-hospital mortality in UTI patients, as defined by Sepsis-3.

2. Methods

2.1 Study design and setting

We conducted a single-center and prospective observational study between the 01 December 2019 and the 30 December 2022. The study was conducted at a tertiary medical center in Seoul, South Korea, with 835 beds and a regional emergency center that receives approximately 50,000 patients annually.

2.2 Study population

Between December 2019 and December 2022, we included all adult patients (aged $\geq$18 years) who were hospitalized for UTI *via* the emergency room. Patients who had a positive quick sequential organ failure assessment (qSOFA) score upon presentation in the emergency department (ED) were screened for participation; a positive qSOFA score was established when the qSOFA score reached $\geq$2. Our specific inclusion criteria included a qSOFA score that was $\geq$2 points in the ED, irrespective of the current infection and two or more of the following: a high respiratory rate ($\geq$22 breaths/min), an altered mental state (a Glasgow coma score $<$15), and low blood pressure (a systolic blood pressure $\leq$100 mmHg). The final SOFA score is derived from six separate scores (each ranging from 0 to 4) allocated to the respiratory, neurological, cardiovascular, hepatic, coagulation and renal systems, as follows. For the respiratory system, a PaO_2 (partial pressure of oxygen)/FiO_2 (the fraction of inspired oxygen) (mmHg) $\geq$400 = 0, $<$400 = 1, $<$300 = 2, $<$200 with respiratory support = 3, $<$100 with respiratory support = 4. For the nervous system, a Glasgow Coma Scale of 15 = 0, 13–14 = 1, 10–12 = 2, 6–9 = 3 and $<$6 = 4. For the cardiovascular system, a mean arterial pressure (MAP) $\geq$70 mmHg = 0, a MAP $<$70 mmHg = 1, dopamine $<$5 μg/kg/min or dobutamine (any dose) = 2, dopamine $>$5 μg/kg/min or epinephrine $\leq$0.1 μg/kg/min or norepinephrine $\leq$0.1 μg/kg/min = 3, and dopamine $>$15 μg/kg/min or epinephrine $>$0.1 μg/kg/min or norepinephrine $>$0.1 μg/kg/min = 4. For the liver, bilirubin (mg/dL) (μmol/L) $<$1.2 ($<$20) = 0, 1.2–1.9 (20–32) = 1, 2.0–5.9 (33–101) = 2, 6.0–11.9 (102–204) = 3, and $>$12.0 ($>$204) = 4. For coagulation, platelets $\times$ 10^3/mL $\geq$150 = 0, $<$150 = 1, $<$100 = 2, $<$50 = 3 and $<$20 = 4. For the kidneys, creatinine (mg/dL) (μmol/L) $<$1.2 ($<$110) = 0, 1.2–1.9 (110–170) = 1, 2.0–3.4 (171–299) = 2, 3.5–4.9 (300–440) (or a urinary output $<$500 mL/day) = 3 and $>$5.0 ($>$440) (a urinary output $<$200 mL/day) = 4 [14]. The diagnosis of UTI in patients was made by the emergency physician based on the presence of pyuria (urinary sediment with $\geq$5 leukocytes per high-power field by microscopy using centrifuged urine) and the presence of symptoms such as fever ($>$37.8 °C), painful urination with or without frequency, pain in the suprapubic area or visible hematuria, flank pain, shivering, vomiting, costovertebral-angle tenderness, and feelings of nausea [15, 16]. The criteria outlined by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were used to establish the diagnosis of sepsis and septic shock [9]. The exclusion criteria were as follows: (1) aged under 18 years, (2) pregnant, (3) refusal to provide consent, (4) discharge against medical advice, (5) transfer to another hospital, (6) another combined infection focus other than UTI on chest X-ray or chest computed tomography (CT) or abdominal CT, (7) prior antibiotic therapy, defined as the usage of antibiotics for a minimum of 3 days within the last month, (8) patients with compromised immune systems (liver failure, autoimmune disorders, hematological malignancies, organ transplants, AIDS), and (9) those with terminal illnesses (advanced or metastatic cancer, advanced congestive heart failure).

2.3 Measurement of presepsin levels

For the quantification of presepsin levels, blood specimens were promptly collected from a peripheral vein within six hours of admission in the Emergency Department (ED). The samples were centrifuged and subsequently aliquoted into smaller portions to prevent repetitive freeze-thaw cycles. The samples were stored at −70 °C within 2 hours of collection to await analysis. Prior to biomarker measurement, frozen samples were thawed at ambient temperature and gently agitated. The measurement of plasma presepsin levels was conducted with a PATHFAST analyzer (plasma serum, LSI Medience Corporation, Tokyo, Japan); this chemiluminescent enzyme immunoassay offers a detectable range that extends from 0 pg/mL to 10,000 pg/mL.

2.4 Data collection

A range of patient information was gathered systematically, including age, gender, medical history, mean arterial pressure (MAP), body temperature (BT), heart rate (HR), respiratory rate (RR), presepsin and PCT levels, CRP levels, and white blood cell (WBC) count. We also collated the levels of aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (γGPT), bilirubin, blood urea nitrogen (BUN), lactate and creatinine. Vital signs and results from

blood tests were assessed at the time of enrollment.

The primary endpoint of this investigation was the occurrence of septic shock. The secondary endpoint was 30-day hospital mortality.

2.5 Statistical analysis

Continuous variables that were normally distributed are presented as mean and standard deviation (SD), while those that were not normally distributed are described as medians and interquartile ranges (IQRs). Categorical variables are described by frequency (%). Continuous variables were assessed using the Mann-Whitney test, while categorical variables were evaluated through either the Chi-squared or Fisher's exact test, as deemed suitable according to the anticipated frequency. Parameters that showed significant differences among the two groups underwent further assessment through multivariate logistic regression and receiver operating characteristic (ROC) analysis to establish their utility as independent predictors. Upon identifying the optimal cut-off value, we determined the sensitivity and specificity. Univariate and multivariate Cox hazard model analyses were executed to assess risk factors associated with 30-day hospital mortality. A derivation cohort was configured to enable AUC (area under the curve) comparison between presepsin and other predictors with 90% power at the 5% significance level, yielding a calculated sample size of 30 for each group. Accounting for a dropout rate of 20%, the projected total number of patients per group was 37. Statistical analysis was conducted using SPSS version 21.0 and MedCalc version 12.4 (IBM Corp, Armonk, NY, USA), with statistical significance based on a p-value < 0.05.

3. Results

3.1 Baseline characteristics

Over the course of the study, we screened 232 patients with positive qSOFA scores upon presentation to the ED (Fig. 1). Of these, 61 patients were excluded because they were under 18 years-of-age (n = 3), pregnant (n = 1), refused to provide consent (n = 3), discharged against medical advice (n = 14), transferred to another hospital (n = 8), or had another combined infection focus other than UTI on radiography (n = 32). The study ultimately included 171 patients in its population. Of these, 50 patients (29%) were classified into the septic shock group and 121 patients (71%) were classified into the non-septic shock group.

3.2 Prognostic value for septic shock

The septic shock group featured a markedly higher proportion of males (38.0%) than the non-septic shock group (17.4%) ($p = 0.004$). In addition, the septic shock group was associated with a significantly higher age, RR and significantly higher levels of bilirubin, BUN, creatinine, PCT and lactate. Furthermore, the septic shock group showed significantly elevated serum levels of presepsin when compared to the non-septic shock group (1052 *vs.* 451, $p < 0.001$). On the other hand, the non-septic shock group had a higher MAP. However, no statistically significant variances were found between the two groups in regards to WBC count or CRP values (Table 1).

In the multivariable logistic regression model for septic shock, lactate, MAP, RR and presepsin were all identified as independent parameters associated with septic shock. The odds ratio (OR) for lactate was 2.722 (95% CI: 1.716–4.318; $p < 0.001$); the OR for presepsin was 1.002 (95% CI: 1.001–1.002; $p < 0.001$), the OR for MAP was 0.943 (95% CI: 0.912–0.975; $p < 0.001$), and the OR for RR was 1.184 (95% CI: 1.012–1.386; $p = 0.035$). The results derived from the multivariable logistic regression model for septic shock are presented in Table 2.

3.3 Prognostic value for 30-day hospital mortality

With regards to the prognostic value for 30-day hospital mortality, we found that the mortality rate was 8.8% (15/171) when considering all patients. Statistically significant disparities were not observed between the survival and non-survival groups concerning WBC, CPR, PCT and lactate levels. Nonetheless, significant statistical distinctions were evident between the two groups with regards to age, presepsin levels, and the presence of an indwelling catheter, as deduced through univariate analysis. The only significant risk factor identified in the multivariate analysis was the level of presepsin (hazard ratio (HR): 1.0005; 95% CI: 1.0001–1.001; $p = 0.03$). Univariate and multivariate Cox proportional hazards model analyses of the 30-day hospital mortality are presented in Table 3.

3.4 Diagnostic value of presepsin, lactate, WBC, PCT, and CRP

To assess the diagnostic value of presepsin, lactate, PCT, WBC and CRP for septic shock, we calculated the areas under the ROC curves (AUCs) (Fig. 2). Lactate had the highest AUC of 0.887, followed by presepsin with an AUC of 0.739, and PCT with an AUC of 0.680 (Fig. 2). The cutoff for presepsin was determined to be 447 pg/mL, with a sensitivity of 92%, a specificity of 50%, an accuracy of 62%, a positive predictive value (PPV) of 0.43, and a negative predictive value (NPV) of 0.94.

In terms of predicting 30-day hospital mortality, presepsin had the highest AUC of 0.744, followed by lactate (Fig. 3). The cutoff for presepsin was determined to be 709 pg/mL, with a sensitivity of 62.2%, a specificity of 80%, an accuracy of 63.7%, a PPV of 0.97, and a NPV of 0.17.

4. Discussion

In this study, we discovered that an elevated level of presepsin upon admission serves as an independent predictor for both septic shock and 30-day hospital mortality in UTI patients, when applying the Sepsis-3 definition. Moreover, for predicting outcomes, presepsin levels upon admission demonstrated fair discriminative power for septic shock and 30-day hospital mortality, with AUC values of 0.739 and 0.744, respectively. A major strength of our study is that we focused exclusively on patients with UTI infection and focused our research specifically on presepsin levels, excluding other in-

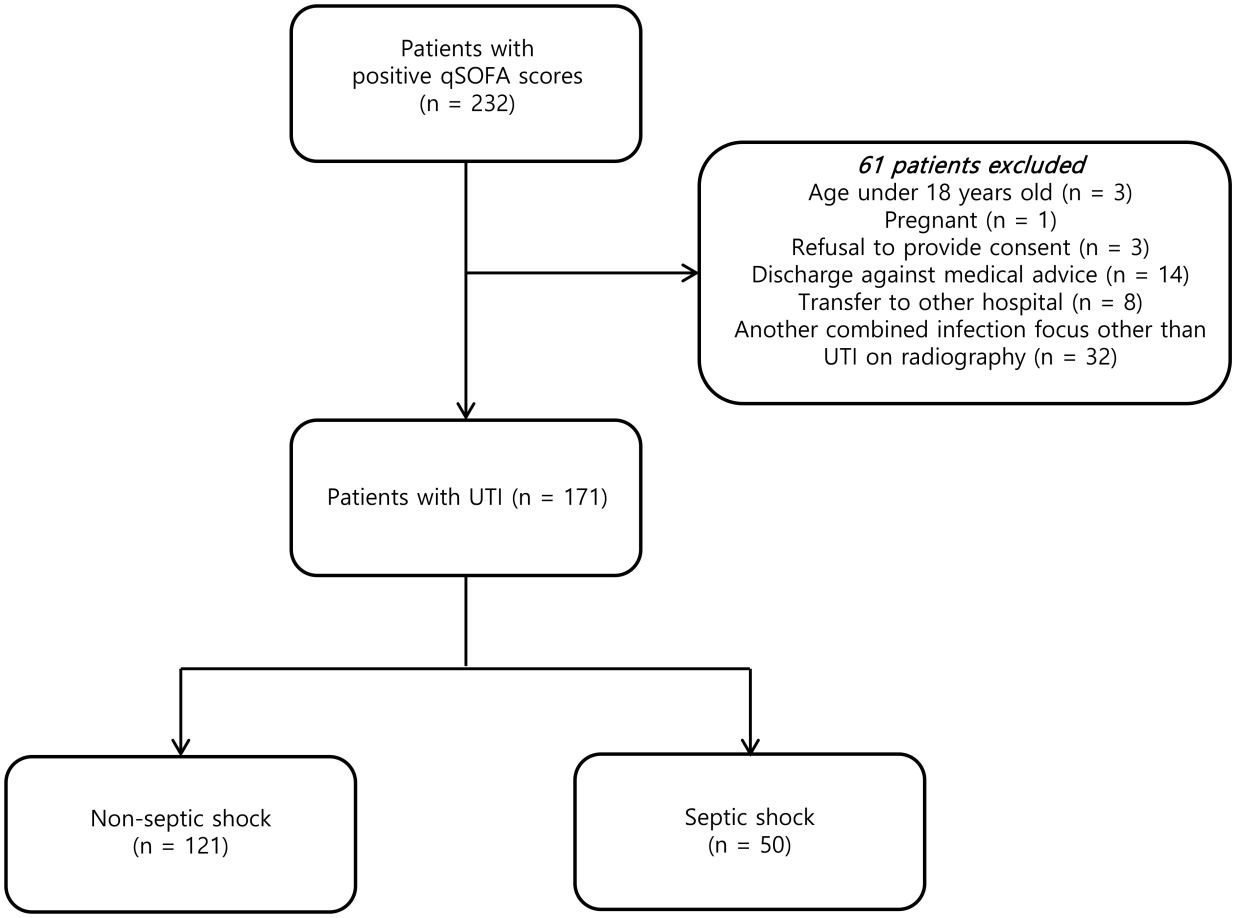

FIGURE 1. Flowchart of the study population. Abbreviations: qSOFA: quick sequential organ failure assessment; UTI: urinary tract infections.

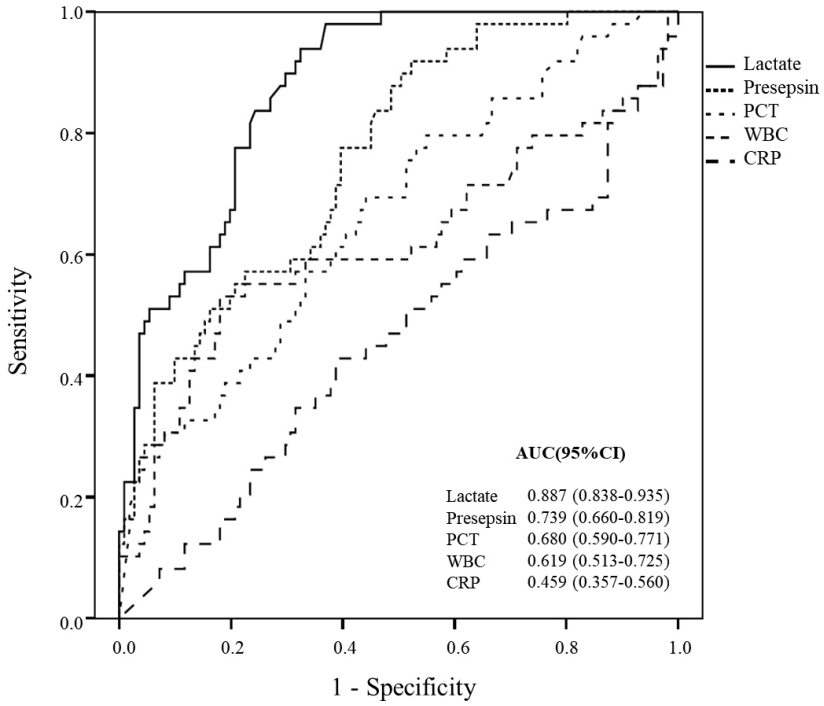

FIGURE 2. ROC curve analysis of presepsin, lactate, PCT, CRP and WBC for the prediction of septic shock. Abbreviations: AUC: area under the curve; CI: confidence Interval; PCT: procalcitonin; WBC: white blood cell; CRP: C-reactive protein.

TABLE 1. Characteristics of patients with or without septic shock on the day of enrollment.

Variable	Total N = 171	Septic shock group N = 50	Non-septic shock group N = 121	*p* value
Age (yr)	76.0 (62.0–82.0)	78.5 (69.0–85.0)	75.0 (61.0–81.0)	0.013
Gender, Male (n, %)	40.0 (23.4)	19.0 (38.0)	21.0 (17.4)	0.004
Clinical characteristics				
MAP (mmHg)	83.33 (69.17–97.67)	68.50 (61.00–80.92)	88.33 (76.33–99.33)	<0.001
HR (bpm)	101.0 (86.0–115.0)	110.50 (89.25–123.00)	100.0 (85.0–112.0)	0.043
RR	20 (18–22)	20.00 (18.00–25.75)	20 (18–22)	0.039
BT (°C)	37.70 (36.95–38.70)	37.60 (37.00–38.27)	37.9 (36.8–38.8)	0.181
Laboratory data				
WBC ($\times 10^3/\mu L$)	13.330 (9.330–18.890)	17.260 (9.360–22.550)	13.020 (9.320–16.940)	0.109
Bilirubin (mg/dL)	0.73 (0.50–1.17)	0.94 (0.63–1.29)	0.67 (0.44–1.09)	0.002
AST (U/L)	31.0 (22.0–44.5)	32.00 (22.25–72.25)	30 (22–41)	0.263
ALT (U/L)	21.0 (13.0–36.5)	18.50 (12.25–39.75)	21 (13–34)	0.808
BUN (mg/dL)	24.9 (16.6–40.3)	29.90 (22.45–44.55)	23.5 (14.1–36.0)	0.001
Creatinine (mg/dL)	1.13 (0.82–1.89)	1.68 (1.12–2.52)	0.99 (0.76–1.62)	<0.001
γGPT (U/L)	38.50 (23.75–77.50)	32.00 (23.00–64.75)	44.00 (24.25–85.75)	0.252
CRP (mg/dL)	14.21 (7.47–22.21)	13.18 (5.04–20.46)	14.84 (8.23–23.38)	0.154
Presepsin (pg/mL)	570.0 (338.0–1128.5)	1052 (570.25–1660.25)	451 (302–879)	<0.001
PCT (ng/mL)	2.04 (0.47–15.77)	8.425 (1.445–34.835)	1.19 (0.36–11.30)	<0.001
Lactate (mmol/L)	2.12 (1.41–3.50)	4.09 (2.82–5.55)	1.66 (1.30–2.52)	<0.001
Medical history (n, %)				
DM	69 (40.4)	25 (50)	44 (36.4)	0.098
HTN	90 (52.6)	30 (60)	60 (49.6)	0.215
Liver disease	13 (7.6)	5 (10)	8 (6.6)	0.447
CHF	5 (2.9)	2 (4.0)	3 (2.5)	0.591
Stroke	4 (2.3)	0 (0)	4 (3.3)	0.193
COPD	24 (14)	9 (18)	15 (12.4)	0.337
CKD	3 (1.8)	1 (2)	2 (1.7)	0.875
Indwelling urinary catheter	16 (9.4)	5 (10)	11 (9.1)	0.853
30-day hospital mortality*	15 (8.77)	10 (20)	5 (4.13)	0.001

**Fisher's exact test, Abbreviations: MAP: mean arterial pressure; HR: heart rate; RR: respiratory rate; BT: body temperature; WBC: white blood cell; AST: aspartate transaminase; ALT: alanine transaminase; BUN: blood urea nitrogen; γGPT: γ-glutamyl transpeptidase; CRP: C-reactive protein; PCT: procalcitonin; DM: diabetes mellitus; HTN: hypertension; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.*

TABLE 2. The prediction of septic shock by logistic regression analysis.

Variable	OR	95% CI	*p* value
Lactate	2.722	1.716–4.318	<0.001
MAP	0.943	0.912–0.975	<0.001
Presepsin	1.002	1.001–1.002	<0.001
PCT	0.987	0.953–1.023	0.504
Age	1.011	0.966–1.058	0.635
Sex (male)	3.166	1.001–10.014	0.049
Creatinine	0.804	0.530–1.219	0.305
RR	1.184	1.012–1.386	0.035
Bilirubin	0.961	0.386–2.388	0.932
HR	0.993	0.964–1.023	0.658

Abbreviations: OR: odds ratio; CI: confidence Interval; MAP: mean arterial pressure; PCT: procalcitonin; RR: respiratory rate; HR: heart rate.

TABLE 3. Predictions of 30-day hospital mortality when applying the Cox proportional hazards model.

Variable	Univariate analysis			Multivariate analysis		
	p value	HR	95% CI	*p* value	HR	95% CI
Sex (male)	0.353	1.714	0.550–5.348			
Age	0.037	1.055	1.003–1.110	0.055	1.053	0.999–1.109
MAP	0.059	0.971	0.942–1.001			
Heart rate	0.982	1.000	0.976–1.026			
RR	0.155	1.074	0.973–1.185			
WBC	0.134	0.937	0.020–0.860			
Bilirubin	0.590	1.227	0.582–2.587			
AST	0.117	1.004	0.999–1.009			
ALT	0.700	0.997	0.982–1.012			
BUN	0.439	1.006	0.991–1.021			
Creatinine	0.447	1.105	0.854–1.430			
γGPT	0.595	1.001	0.996–1.007			
CRP	0.968	0.999	0.944–1.057			
Presepsin	0.030	1.001	1.0001–1.001	0.031	1.001	1.000–1.001
PCT	0.603	1.008	0.977–1.041			
Lactate	0.143	1.126	0.960–1.321			
DM	0.995	2,347,704.107	0–inf*			
HTN	0.536	1.406	0.478–4.141			
Liver disease	0.389	2.696	0.281–25.806			
CHF	0.995	<0.001	0–inf			
Stroke	0.981	0.982	0.207–4.663			
COPD	0.991	<0.001	0–inf			
CKD	0.588	1.550	0.317–7.574			
Indwelling urinary catheter	0.045	3.662	1.030–13.032	0.141	2.706	0.719–10.187

**Infinite. Abbreviations: HR: hazard ratio; CI: confidence Interval; MAP: mean arterial pressure; RR: respiratory rate; WBC: white blood cell; AST: aspartate transaminase; ALT: alanine transaminase; BUN: blood urea nitrogen; γGPT: γ-glutamyl transpeptidase; CRP: C-reactive protein; PCT: procalcitonin; DM: diabetes mellitus; HTN: hypertension; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.*

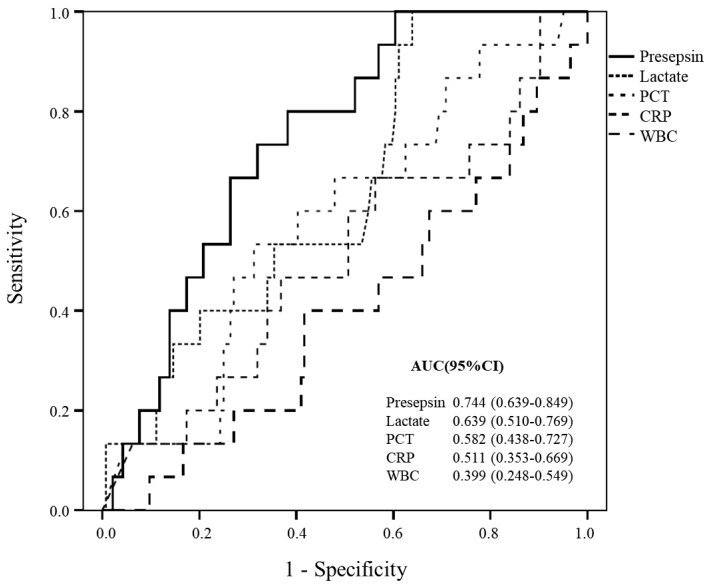

FIGURE 3. ROC curve analysis of presepsin, lactate, PCT, CRP and WBC for the prediction of 30-day hospital mortality. Abbreviations: AUC: area under the curve; CI: confidence Interval; PCT: procalcitonin; WBC: white blood cell; CRP: C-reactive protein.

fections or combined infections, as evidenced by chest X ray or chest/abdominal pelvis CT scans. In addition, our study utilized the Sepsis-3 definition. To the best of our knowledge, the influence of presepsin as a prognostic factor for septic shock and 30-day hospital mortality in only UTI patients, in accordance with the Sepsis-3 definition, has not yet been thoroughly investigated.

Urosepsis is a form of sepsis derived from a UTI and has been a prevalent issue with documented occurrences spanning numerous years [17]. Previous research has shown that in 9%–31% of sepsis patients, the infection source is the urinary tract, and urosepsis frequently arising from UTIs [17]. The universally recognized mortality rate for severe sepsis ranges from 20%–42% [18].

Rapid assessment of the progression to septic shock in patients with infections in the ED can provide valuable assistance in determining appropriate management and subsequent prognosis [19]. However, it remains challenging to assess the progression to septic shock in UTI patients based solely on medical history, physical signs, basic blood tests, and urinary analysis. Moreover, blood and urine culture tests are time-consuming and are therefore not suitable as tools for rapid assessment in the ED [20].

Presepsin, along with PCT, lactate, CRP and other markers, has shown some value in assessing the severity and prognosis of sepsis patients and can provide results within a few hours, thereby making it suitable for use in the ED [21]. In contrast to the more sluggish response of PCT and CRP, which are conventional and established biomarkers for sepsis, presepsin is distinctive in that it responds rapidly to infection. Research has shown that it can take 3–6 hours for PCT levels to escalate, peaking at 6–8 hours, and even longer for CRP, requiring 6 hours to rise and peak between 36–50 hours [22–24]; thus presepsin is a more favorable biomarker of sepsis as it responds far more rapidly. However, while several studies have focused on septic shock, few have investigated the levels of presepsin in patients with UTI [3].

In a previous study, Sekine *et al.* [1] conducted a prospective and observational study on 57 short-stay hospital patients, and reported that presepsin levels ($\geq$500 pg/mL) represented an independent risk factor for septic shock in patients presenting with UTI. However, these authors did not apply the Sepsis-3 definition in their study. In alignment with the findings of Sekine *et al.* [1], our study also demonstrated that presepsin exhibited a higher AUC in ROC analysis when compared to PCT for diagnosing septic shock in UTI patients (0.739 *vs.* 0.680). Intriguingly, the cutoff values for diagnosing septic shock in our study were marginally lower (447 ng/mL) than the values reported by Sekine *et al.* [1] (492 ng/mL). Furthermore, while Sekine *et al.* [1] did not describe any correlation with mortality due to the absence of deaths, our study confirmed the utility of presepsin as a predictor of mortality. It appears that Sekine *et al.* [1] may have enrolled relatively mild patients as this would explain the absence of deaths in their cohort of patients. In contrast, our study had a mortality rate of 8.5% and identified presepsin as a predictor of mortality on its own. These differences in patient population and outcomes further highlights the importance of our study in the context of mortality prediction in UTI patients and emphasizes the potential significance of presepsin as a valuable prognostic factor. This finding is consistent with other studies in which presepsin was shown to predict mortality [25–27].

There are several limitations to this study that need to be considered. First, this study was carried out at a single center and had a limited sample size; these factors could potentially restrict the generalizability of our findings. Second, we did not take renal function into account when establishing the reference values for presepsin and PCT; previous research has indicated that renal function can impact the levels of presepsin [28, 29]. Ideally, future reference values should be set based on an assessment of renal function. However, the necessary adjustments for this have yet to be elucidated. To examine the prognostic utility of presepsin for septic shock and mortality, taking into account renal function, a large number of patients would be required. Third, we only measured plasma presepsin levels in the ED and did not track subsequent changes in these markers. Nevertheless, our study, applying the Sepsis-3 definition that has been used since 2016 and is based on the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) [14], is the first to reveal that presepsin is a stand-alone predictor for both septic shock and mortality in UTI patients under these new guidelines.

5. Conclusions

Using the Sepsis-3 definitions, our study revealed that the level of presepsin at the time of admission serves as an independent predictor for both septic shock and 30-day hospital mortality in patients with UTIs. Our findings emphasize the fair diagnostic and prognostic value of presepsin levels in patients with UTI, particularly in terms of its capacity to identify septic shock and predict in-hospital mortality. To ascertain the most suitable cut-off value for presepsin levels in diagnosing and predicting septic shock and mortality, it is advisable to conduct additional multicenter and prospective studies involving larger cohorts.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

YHL—established the main conception and designed this study. GBY, JWK, KRL, DYH, SOP and SYK—took part in the collection of data. GBY—analysis and interpretation of data; writing first draft. JWK, KRL, DYH, SOP and SYK—review/correction of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study adhered to the principles stipulated in the Declaration of Helsinki and obtained approval from the institutional review board (IRB) of Konkuk University Hospital (IRB approval number: KUMC 2019-04-015). All patients or their legal representatives provided written informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Sekine Y, Kotani K, Oka D, Nakayama H, Miyazawa Y, Syuto T, *et al*. Presepsin as a predictor of septic shock in patients with urinary tract infection. BMC Urology. 2021; 21: 144.

[2] Zhang L, Zhang F, Xu F, Wang Z, Ren Y, Han D, *et al*. Construction and evaluation of a sepsis risk prediction model for urinary tract infection. Frontiers in Medicine. 2021; 8: 671184.

[3] Contenti J, Occelli C, Lemoel F, Ferrari P, Levraut J. Presepsin versus other biomarkers to predict sepsis and septic shock in patients with infection defined by Sepsis-3 criteria: the PREDI study of diagnostic accuracy. Emergencias. 2019; 31: 311–317.

[4] Vincent J, Bakker J. Blood lactate levels in sepsis: in 8 questions. Current Opinion in Critical Care. 2021; 27: 298–302.

[5] Weinberger J, Klompas M, Rhee C. What is the utility of measuring lactate levels in patients with sepsis and septic shock? Seminars in Respiratory and Critical Care Medicine. 2021; 42: 650–661.

[6] Claessens Y, Trabattoni E, Grabar S, Quinquis L, Der Sahakian G, Anselmo M, *et al*. Plasmatic presepsin (sCD14-ST) concentrations in acute pyelonephritis in adult patients. Clinica Chimica Acta. 2017; 464: 182–188.

[7] Kondo Y, Umemura Y, Hayashida K, Hara Y, Aihara M, Yamakawa K. Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult patients: a systematic review and meta-analysis. Journal of Intensive Care. 2019; 7: 22.

[8] Piccioni A, Santoro MC, de Cunzo T, Tullo G, Cicchinelli S, Saviano A, *et al*. Presepsin as early marker of sepsis in emergency department: a narrative review. Medicina. 2021; 57: 770.

[9] Yamamoto T, Nishimura T, Kaga S, Uchida K, Tachibana Y, Esaki M, *et al*. Diagnostic accuracy of presepsin for sepsis by the new Sepsis-3 definitions. The American Journal of Emergency Medicine. 2019; 37: 1936–1941.

[10] Kahveci U, Ozkan S, Melekoglu A, Usul E, Ozturk G, Cetin E, *et al*. The role of plasma presepsin levels in determining the incidence of septic shock and mortality in patients with sepsis. Journal of Infection in Developing Countries. 2021; 15: 123–130.

[11] Kweon OJ, Choi J, Park SK, Park AJ. Usefulness of presepsin (sCD14 subtype) measurements as a new marker for the diagnosis and prediction of disease severity of sepsis in the Korean population. Journal of Critical Care. 2014; 29: 965–970.

[12] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Critical Care Medicine. 2001; 29: 1303–1310.

[13] Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, *et al*. Outcomes of the surviving sepsis campaign in intensive care units in the USA and Europe: a prospective cohort study. The Lancet Infectious Diseases. 2012; 12: 919–924.

[14] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016; 315: 801–810.

[15] Kaur R, Kaur R. Symptoms, risk factors, diagnosis and treatment of urinary tract infections. Postgraduate Medical Journal. 2021; 97: 803–812.

[16] Yang SS, Tsai J, Kanematsu A, Han C. Asian guidelines for urinary tract infection in children. Journal of Infection and Chemotherapy. 2021; 27: 1543–1554.

[17] Guliciuc M, Maier AC, Maier IM, Kraft A, Cucuruzac RR, Marinescu M, *et al*. The urosepsis—a literature review. Medicina. 2021; 57: 872.

[18] Brun-Buisson C. The epidemiology of the systemic inflammatory response. Intensive Care Medicine. 2000; 26: S064–S074.

[19] Bisarya R, Song X, Salle J, Liu M, Patel A, Simpson SQ. Antibiotic timing and progression to septic shock among patients in the ED with suspected infection. Chest. 2022; 161: 112–120.

[20] Gander RM, Byrd L, DeCrescenzo M, Hirany S, Bowen M, Baughman J. Impact of blood cultures drawn by phlebotomy on contamination rates and health care costs in a hospital emergency department. Journal of Clinical Microbiology. 2009; 47: 1021–1024.

[21] Velissaris D, Zareifopoulos N, Karamouzos V, Karanikolas E, Pierrakos C, Koniari I, *et al*. presepsin as a diagnostic and prognostic biomarker in sepsis. Cureus. 2021; 13: e15019.

[22] Lelubre C, Anselin S, Zouaoui Boudjeltia K, Biston P, Piagnerelli M. Interpretation of c-reactive protein concentrations in critically ill patients. BioMed Research International. 2013; 2013: 1–11.

[23] Maruna P, Nedelníková K, Gürlich R. Physiology and genetics of procalcitonin. Physiological Research. 2000; 49: S57–S61.

[24] Singh K, Singh S, Kumar P, Khera D, Sharma P, Toteja N, *et al*. Is there a role of presepsin as a novel biomarker in pediatric sepsis? Indian Journal of Critical Care Medicine. 2022; 26: 712–716.

[25] Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F, Forno D, *et al*. Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study. Critical Care. 2013; 17: R168.

[26] Pizzolato E, Ulla M, Galluzzo C, Lucchiari M, Manetta T, Lupia E, *et al*. Role of presepsin for the evaluation of sepsis in the emergency department. Clinical Chemistry and Laboratory Medicine. 2014; 52: 1395–1400.

[27] Baik SM, Park J, Kim TY, Choi SH, Hong KS. Validation of presepsin measurement for mortality prediction of sepsis: a preliminary study. Acute and Critical Care. 2022; 37: 527–532.

[28] Arakawa K, Saeki A, Ide R, Matsushita Y. Presepsin cut-off value for diagnosis of sepsis in patients with renal dysfunction. PLOS ONE. 2022; 17: e0273930.

[29] Tsuchida T, Ie K, Okuse C, Hirose M, Nishisako H, Torikai K, *et al*. Determining the factors affecting serum presepsin level and its diagnostic utility: a cross-sectional study. Journal of Infection and Chemotherapy. 2021; 27: 585–591.

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