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Utility of urinary presepsin in the diagnosis of pyelonephritis: a cross-sectional study

Ryo Yamashita^{1*}, Yusuke Izumi¹, Koji Nakada² and Jun Hiramoto¹

Abstract

Background Presepsin is produced during the phagocytosis of bacteria by granulocytes. Presepsin increases at the site of infection; however, the significance of urinary presepsin in pyelonephritis is unknown. This study aimed to evaluate whether measuring urinary presepsin can distinguish between pyelonephritis and nonpyelonephritis.

Methods A cross-sectional study of patients with suspected pyelonephritis was conducted. Urinary presepsin at admission was compared between the pyelonephritis and nonpyelonephritis groups using the Mann–Whitney test. The predictive accuracy of urinary presepsin for diagnosing pyelonephritis was evaluated by the area under the receiver operating characteristics (ROC) analysis curve.

Results A total of 35 eligible participants were included in the pyelonephritis group and 25 in the nonpyelonephritis group. The median urinary presepsin level was 2232.0 (interquartile range [IQR], 1029.0–3907.0) pg/mL in the pyelonephritis group and 1348.0 (IQR, 614.5–2304.8) pg/mL in the nonpyelonephritis group. Urinary presepsin concentrations were significantly higher in the pyelonephritis group than in the nonpyelonephritis group ($P=0.023$). ROC analysis of urinary presepsin revealed a cutoff value of 3650 pg/mL to distinguish between the pyelonephritis and nonpyelonephritis groups. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for the diagnosis of pyelonephritis were 0.40 (95% confidence interval [CI], 0.24–0.58), 0.96 (95% CI, 0.79–1.00), 0.93 (95% CI, 0.68–1.00), 0.52 (95% CI, 0.37–0.68), 9.60 (95% CI, 1.35–68.23), and 0.62 (95% CI, 0.47–0.83), respectively.

Conclusions The measurement of urinary presepsin is useful in differentiating pyelonephritis from other diseases.

Keywords Presepsin, Pyelonephritis, Pyuria, Receiver operating characteristics

Background

Pyelonephritis is a common disease that is more likely to occur in young women and older individuals. The symptoms and severity of the disease range widely. In most

patients, the symptoms are mild back pain and fever, but septic shock can also occur [1]. If severe sepsis or septic shock occurs, the mortality rate is reported to be 20%–50% [2, 3]. Accurate diagnosis and early treatment are important. Although there is no consensus on the diagnostic criteria for pyelonephritis [4], detecting bacteria in urine culture is crucial. However, obtaining the results of urine culture can take several days; hence, they are not useful for the early diagnosis of pyelonephritis. In addition, the results of urine culture depend on proper specimen collection; however, improper specimen collection can lead to false-positive results. Pyuria is another characteristic finding of pyelonephritis and can be detected early. However, pyuria can also be detected in

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asymptomatic bacteriuria. Hence, the presence of pyuria does not prove pyelonephritis. There are no tools that can quickly distinguish between pyelonephritis and nonpyelonephritis. New biomarkers which can accurately and rapidly diagnose pyelonephritis are needed. Presepsin, a granulocyte degradation product, is produced when granulocytes phagocytose bacteria [5]. Presepsin has been attracting attention as a useful marker for diagnosis and prognosis in sepsis [6]. Since presepsin production is increased at the site of infection, its measurement in the joint fluid is effective in differentiating pyogenic arthritis from crystalline arthritis [7]. The cerebrospinal fluid presepsin is also useful for the diagnosis and prognosis of post-neurosurgical ventriculitis/meningitis [8]. The significance of urinary presepsin in diagnosing pyelonephritis is unknown. This study aimed to evaluate whether measuring urinary presepsin can distinguish between pyelonephritis and nonpyelonephritis.

Methods

Study design and participants

This was a cross-sectional study performed on 132 patients admitted to Jikei University Daisan Hospital with suspected pyelonephritis from October 2019 to November 2021. The inclusion criteria for the study were (1) patients over 20 years, (2) patients with a fever of 37.5 °C or higher, (3) and patients with a urine sedimentation test showing over 10 leukocytes/high power field. Acute pyelonephritis was defined as a patient having back pain or costovertebral angle tenderness and urine culture revealing a bacterial count of 10^5 /liter or higher. We used midstream urine for urine culture. Patients not meeting the definition of acute pyelonephritis were defined as the nonpyelonephritis group. The exclusion criteria for the study were (1) patients receiving antibiotics within a week before admission, (2) patients with indwelling urinary catheters, (3) patients with anatomical abnormalities in the urinary tract, and (4) patients on dialysis.

Study measurements

The patients' age, gender, body temperature, past medical history, and the results of blood and urine cultures at the time of admission were collected. All patients underwent blood sampling for serum C-reactive protein, procalcitonin, creatinine, and presepsin on admission day. Urinary presepsin was also measured on admission day. Serum and urinary presepsin concentrations were measured by a PathFast immunoanalyzer presepsin kit (LSI Medicine, Tokyo, Japan).

Statistical analysis

The Bell curve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for all the statistical

analyses. The Mann–Whitney U test was used to compare the age, urinary presepsin, serum C-reactive protein, procalcitonin, creatinine, estimated glomerular filtration rate, and serum presepsin. The chi-square test was used to compare the sex, past medical history, and bacteremia. The predictive accuracy of urinary presepsin and serum presepsin for diagnosing acute pyelonephritis was evaluated by the area under the curve (AUC) of ROC analysis. The Youden index was used to calculate optimal cutoff values for each measurement result. The cutoff values were used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR–) for each measure. The *P*-values of <0.05 were considered statistically significant.

Results

Baseline characteristics of participants

Among the 132 participants who met the inclusion criteria, 60 participants were included in this study (41 participants were post-antibiotic, 11 participants had indwelling catheters, 18 participants had anatomical abnormalities in the urinary tract, and two participants were on dialysis). The participants were divided into two groups: acute pyelonephritis ($n=35$) and nonpyelonephritis ($n=25$). The average age of all participants was 77.6 years, and 78.3% of the participants were female patients. There were no significant differences between the two groups for age, sex, background disease, or immunosuppressive drug use. The bacteremia rate was significantly higher in the acute pyelonephritis group ($P=0.044$). There were also no significant differences in the renal function, serum C-reactive protein, presepsin, or procalcitonin between the acute pyelonephritis and nonpyelonephritis groups (Table 1).

The final diagnosis in the non-pyelonephritis group is shown in Table 2.

Comparison of urinary presepsin concentrations in acute pyelonephritis and nonpyelonephritis groups

The median urinary presepsin level was 2232.0 (interquartile range [IQR], 1029.0–3907.0) pg/mL in the acute pyelonephritis group and 1348.0 (IQR, 614.5–2304.8) pg/mL in the nonpyelonephritis group. Urinary presepsin concentrations were significantly higher in the acute pyelonephritis group than in the nonpyelonephritis group ($P=0.023$) (Fig. 1).

Comparison of urinary presepsin levels between patients with and without bacteremia among those with acute pyelonephritis

The median urinary presepsin level was 2463.0 pg/mL (IQR, 1252.8–7215.8) in patients with acute

Table 1 Baseline characteristics of participants

	Acute pyelonephritis (n = 35)	Nonpyelonephritis (n = 25)	P-value
Age (years)	85 [78.0–90.5]	81 [56.0–88.0]	0.064
Female sex	25 (71)	22 (88)	0.125
Diabetes mellitus	9 (26)	4 (16)	0.368
Liver cirrhosis	0 (0)	1 (4.0)	0.233
Chronic heart failure	3 (8.6)	2 (8.0)	0.937
Cerebrovascular disorder	9 (26)	2 (8.0)	0.080
Malignant tumor	3 (8.6)	3 (12)	0.663
Autoimmune disease	8 (23)	5 (20)	0.791
Immunosuppressor	7 (20)	3 (12)	0.412
Bacteremia	8 (23)	1 (4.0)	0.044
Creatinine (mg/dL)	0.90 [0.68–1.25]	0.84 [0.51–1.07]	0.161
eGFR (mL/min/1.73 m ²)	49.0 [38.0–66.5]	64.0 [42.0–100.0]	0.122
C-reactive protein (mg/L)	113.4 [50.3–194.1]	88.9 [29.0–148.9]	0.393
Serum Presepsin (pg/mL)	361 [302–589]	386 [251–650]	0.844
Procalcitonin (ng/mL)	0.38 [0.17–2.06]	0.19 [0.08–0.94]	0.097

Values are expressed as number (%) or median [interquartile range, IQR]
 Abbreviations: eGFR estimated glomerular filtration rate

Table 2 Final diagnosis in the nonpyelonephritis group

Diagnosis	Number of cases (%)
Pneumonia	11 (44)
Enterocolitis	2 (8)
Crystal arthritis	2 (8)
Giant cell arthritis	1 (4)
Microscopic polyangiitis	1 (4)
Adult-onset Still's disease	1 (4)
Viral meningitis	1 (4)
Cholangitis	1 (4)
Histiocytic necrotizing lymphadenitis	1 (4)
Hemophagocytic lymphohistiocytosis	1 (4)
Hematoma	1 (4)
Ovarian hemorrhage	1 (4)
Drug fever	1 (4)

pyelonephritis with bacteremia and 2385.0 pg/mL (IQR, 1138.0–4043.5) in patients with acute pyelonephritis without bacteremia. Urinary presepsin levels were not significantly different between the two groups ($P=0.875$) (sTable 1).

Comparison of urinary presepsin levels between the pyelonephritis and nonpyelonephritis groups among patients without bacteremia

The median urinary presepsin level was 2385.0 pg/mL (IQR, 1138.0–4043.5) in the acute pyelonephritis

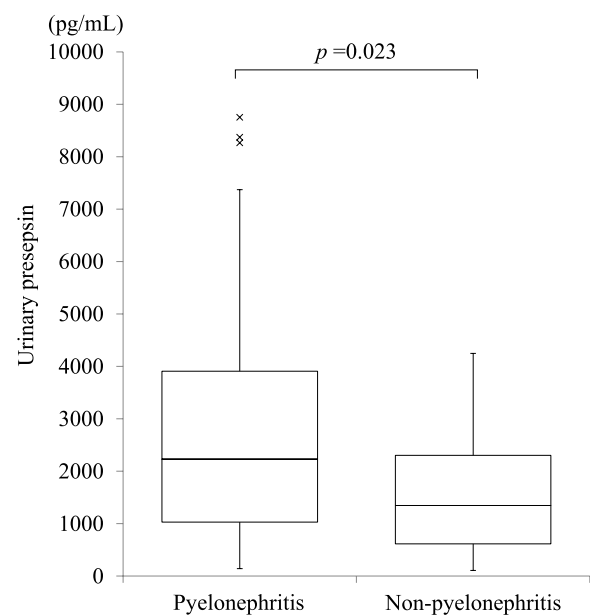


Fig. 1 Comparison of urinary presepsin levels in patients with pyelonephritis and nonpyelonephritis. The Mann–Whitney U test was used for comparing the two groups. Urinary presepsin concentrations were significantly higher in the acute pyelonephritis group than in the nonpyelonephritis group

group without bacteremia and 1339.0 pg/mL (IQR, 594.0–2350.5) in the nonpyelonephritis group without bacteremia. Urinary presepsin was significantly higher in the acute pyelonephritis group without bacteremia

than in the nonpyelonephritis group without bacteremia ($P=0.026$) (sTable 2).

The accuracy of urinary presepsin in the diagnosis of acute pyelonephritis

ROC curve analysis of urinary presepsin revealed a cut-off value of 3650 pg/mL to distinguish the acute pyelonephritis and nonpyelonephritis groups (Fig. 2). The value of AUC was 0.66 (95% confidence interval [CI], 0.52–0.80). Using the calculated cutoff values, sensitivity, specificity, PPV, NPV, LR+, and LR– for the diagnosis of acute pyelonephritis were 0.40 (95% CI, 0.24–0.58), 0.96 (95% CI, 0.79–1.00), 0.93 (95% CI, 0.68–1.00), 0.52 (95% CI, 0.37–0.68), 9.60 (95% CI, 1.35–68.23), and 0.62 (95% CI, 0.47–0.83), respectively. Compared to serum presepsin, urinary presepsin was a more accurate indicator of sensitivity, specificity, PPV, NPV, LR+, and LR– (Table 3).

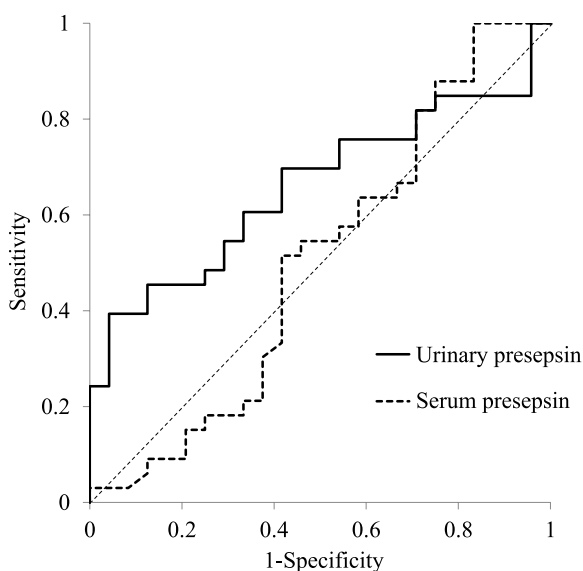


Fig. 2 ROC curves for the sensitivity and specificity of urinary presepsin and serum presepsin in differentiating pyelonephritis from other diseases. The value of AUC was 0.66 (95% confidence interval [CI], 0.52–0.80)

Discussion

This study revealed that urinary presepsin was significantly elevated in the acute pyelonephritis group compared with the nonpyelonephritis group. On the contrary, serum CRP, procalcitonin, and presepsin were not significantly different between the pyelonephritis and the nonpyelonephritis groups. These results suggest that measuring urinary presepsin in patients with fever and pyuria may provide an early indication of pyelonephritis.

When granulocytes phagocytose bacteria, CD14 is taken into the cells and degraded by proteases. The degraded CD14 becomes soluble CD14, which is detected as presepsin [5]. Presepsin is one of the biomarkers elevated in bacterial infections because of this production mechanism [9]. In pyelonephritis with bacteremia, serum presepsin levels are increased [10]. Furthermore, serum presepsin concentration correlates with sepsis severity. It is a more useful biomarker than PCT in predicting disease severity [11]. In pyelonephritis, granulocytes phagocytose bacteria in the urinary tract. This may result in increased local presepsin production and high urinary presepsin levels. For diagnosing pyelonephritis, urine culture results need to be awaited. However, it takes several days to obtain the urine culture results. On the contrary, urinary presepsin can be measured in 15 min. Although the definitive diagnosis of pyelonephritis is based on the identification of bacteria by urine culture, it is undoubtedly important to base antibiotic selection on the results of antibiotic sensitivity testing. Urinary presepsin cannot replace this significant utility of urine culture. However, it may contribute to an earlier diagnosis of pyelonephritis, which may help in reducing unnecessary antibiotic usage.

Our additional analyses revealed no significant difference in urinary presepsin levels between patients with and without bacteremia among those with pyelonephritis. This finding might be due to the fact that urinary presepsin mainly reflects local presepsin production in the urinary tract rather than the effects of bacteremia. In the present study, the comparison of patients with pyelonephritis in the absence of bacteremia and those without pyelonephritis or bacteremia revealed that urinary presepsin levels were significantly high in those with pyelonephritis without

Table 3 Ability of urinary presepsin and serum presepsin to detect acute pyelonephritis

	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Urinary pre-sepsin	0.66 [0.52–0.80]	3650 pg/mL	0.40 [0.24–0.58]	0.96 [0.79–1.00]	0.93 [0.68–1.00]	0.52 [0.37–0.68]	9.60 [1.35–68.23]	0.62 [0.47–0.83]
Serum pre-sepsin	0.50 [0.34–0.66]	1522 pg/mL	0.03 [0.00–0.16]	0.84 [0.64–0.95]	0.20 [0.01–0.72]	0.40 [0.26–0.54]	0.19 [0.02–1.59]	1.15 [0.96–1.38]

Results are expressed as values [95% confidence interval]

Abbreviations: AUC Area under the ROC curve, PPV Positive predictive value, NPV Negative predictive value, LR+ Positive likelihood ratio, LR– Negative likelihood ratio

bacteremia, suggesting that the higher urinary presepsin levels observed in patients with pyelonephritis, as shown in Fig. 1, was not due to a higher percentage of patients with bacteremia.

The results of ROC curve analysis revealed that urinary presepsin has higher sensitivity, specificity, PPV, NPV, LR+, and LR- than serum presepsin in the diagnosis of acute pyelonephritis. Unfortunately, the AUC and sensitivity of urinary presepsin were not high. Therefore, combining urinary presepsin with other laboratory parameters might be more useful for the diagnosis of acute pyelonephritis. Traditionally, the assessment for acute pyelonephritis is often performed using leukocyte esterase, an enzyme released by leukocytes, and nitrites as some bacteria reduce urinary nitrates to nitrites. When either leukocyte elastase or nitrite is positive, a diagnosis of acute pyelonephritis can be made with a sensitivity of 75%, specificity of 82%, LR+ of 4.2, and LR- of 0.3 [12]. Although urinary presepsin is inferior to the combination of leukocyte elastase and nitrites in sensitivity, it may be superior in specificity, LR+, and LR-. Urinary presepsin may be a useful test for making the definitive diagnosis of acute pyelonephritis. For pyelonephritis, we recommend that urinalysis should be initially performed to screen for leukocyte elastase and nitrite and that urinary presepsin levels should be measured in patients with a positive screening result to get closer to the definitive diagnosis.

This study has several limitations. First, the sample size was small because the patients with factors that might affect urinary presepsin levels were excluded from this study. To clarify the generalizability of the results, further investigations are required. Second, this study included patients with fever and pyuria. Patients without fever were not included in this study. In addition, severe cases and older patients with pyelonephritis not presenting with fever were not included in this study. Hence, additional studies are needed. Third, patients with catheter-related urinary tract infections, anatomical abnormalities of the urinary tract, and hemodialysis patients were excluded from this study. It is unclear whether urinary presepsin measurement would be useful in these patients. Fourth, some of the patients in the nonpyelonephritis group might have had cystitis or asymptomatic bacteriuria. To the best of our knowledge, there are no studies comparing urinary presepsin levels between pyelonephritis and other urinary tract infections such as cystitis or asymptomatic bacteriuria, and it is unclear whether these conditions affect urinary presepsin. Further studies are needed to elucidate this aspect. Finally, this study was conducted with a single-center design. Further investigations at other facilities are required.

Conclusion

In conclusion, urinary presepsin measurement is useful in differentiating pyelonephritis from other diseases. We have shown that urinary presepsin has high specificity, PPV, and LR+ in the diagnosis of pyelonephritis. Urinary presepsin provides immediate results and may contribute to appropriate antibiotic use.

Abbreviations

AUC	Area under the curve
LR	Likelihood ratio
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating characteristics

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-023-08353-2>.

Additional file 1: sTable 1. Comparison in pyelonephritis group with and without bacteremia. **sTable 2.** Comparison of pyelonephritis and nonpyelonephritis groups in patients with negative blood cultures.

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Authors' contributions

All authors conceived and designed the study and took responsibility for the accuracy of data analysis. RY and KN measured the samples. RY and YI analyzed and interpreted the data. RY wrote the first version of the manuscript. All authors critically revised the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The used and/or analyzed data during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the Jikei University School of Medicine, and written informed consent was obtained from the participants.

Consent for publication

Not Applicable.

Competing interests

The authors have no conflicts of interest to declare.

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