



Clinical investigation on acute pyelonephritis without pyuria: a retrospective observational study

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Background: The current guidelines for the diagnosis of acute pyelonephritis (APN) recommend that APN be diagnosed based on the clinical features and the presence of pyuria. However, we observed that some of the patients who are diagnosed with APN do not have characteristic clinical features or pyuria at the initial examination. We performed this study to investigate the characteristics of APN without pyuria.

Methods: A retrospective, cross-sectional study was conducted on 391 patients diagnosed with APN based on clinical and radiologic findings, between 2015 and 2019. The clinical features, laboratory results, and computed tomography (CT) findings were compared between patients with normal white blood cell (WBC) counts and those with abnormal WBC counts (WBC of 0–5/high power field [HPF] vs. >5/HPF) in urine.

Results: More than 50% of patients with APN had no typical urinary tract symptoms and one-third of them had no costovertebral angle (CVA) tenderness. Eighty-eight patients (22.5%) had normal WBC counts (0–5/HPF) on urine microscopy. There was a negative correlation between pyuria (WBC of >5/HPF) and previous antibiotic use (odds ratio, 0.249; 95% confidence interval, 0.140–0.441; $p < 0.001$), and the probability of pyuria was reduced by 75.1% in patients who took antibiotics before visiting the emergency room.

Conclusion: The diagnosis of APN should not be overlooked even if there are no typical clinical features, or urine microscopic examination is normal. If a patient has already taken antibiotics at the time of diagnosis, imaging studies such as CT should be performed more actively, regardless of the urinalysis results.

Keywords: Diagnosis; Emergency medical services; Pyelonephritis; Pyuria; Urinalysis

Introduction

Acute pyelonephritis (APN) is characterized by upper urinary tract infection (UTI) symptoms (fever and flank pain) and pyuria [1,2]. However, symptoms related to upper UTI may be ambiguous, and sometimes only fever may appear [3,4]. If the symptoms presented by the patient are ambiguous or no symptoms other than fever are present, an objective test confirming the presence of pyuria is an important factor in the diagnosis of APN [5-7]. However, it is

known that some patients diagnosed with APN do not have pyuria [8], which is frequently encountered in clinical practice.

In this study, we investigated the number of white blood cells (WBC) observed in urine microscopy of female patients who were finally diagnosed with APN, to analyze how many patients with APN do not have pyuria, and to determine the differences in demographics, medical history, clinical features, physical examination findings, laboratory examination results, and abdominal computed

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tomography (CT) findings between APN with and without pyuria.

Methods

Ethical statements: This study was conducted as a retrospective, cross-sectional study after receiving approval from the Institutional Review Board (IRB) of Kangbuk Samsung Hospital (IRB No: 2020-11-030). The patient's name, hospital number, date of birth, and social security number were deleted after assigning a serial number to each to maintain anonymity.

1. Subjects

In addition to the clinical diagnosis of APN, abdominal CT findings compatible with APN were also necessary to target only patients with a clear APN diagnosis. Female patients aged 18 years or older who visited our emergency department (ED) between January 2015 and December 2019 and whose final discharge diagnosis was APN were sought. Then, the CT findings were reviewed to exclude cases that did not have findings compatible with APN or had obvious causes of infection other than APN. In addition, patients who visited the hospital with a double J stent, percutaneous nephrostomy, and an indwelling foley catheter were also excluded (Fig. 1).

2. Outcome measures

The urine WBC counts of the subjects determined by the microscopic study were arbitrarily classified into WBC 0–3/HPF, 4–5/HPF, 6–10/HPF, 11–20/HPF, and > 20/HPF. We investigated the number of patients with APN having urine WBC counts in the normal range (0–5/HPF). After that, we compared the demo-

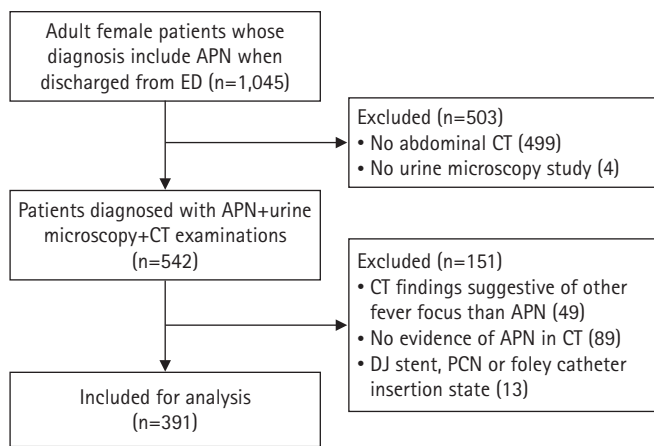


Fig. 1. Flow diagram of the enrolled patients. APN, acute pyelonephritis; ED, emergency department; CT, computed tomography; DJ, Double J; PCN, percutaneous nephrostomy.

graphic characteristics, medical history, clinical features, physical examination findings, laboratory results, and CT findings between patients with normal WBC counts and those with abnormal WBC counts (0–5/HPF vs. > 5/HPF). The patient's age, underlying disease, past APN diagnosis experience, time from symptom onset to diagnosis, and antibiotic use prior to the ED visit were determined under demographic characteristics and medical history. It was not possible to determine the dose, duration, and type of antibiotics administered, and it was defined as "previous antibiotics use" if the patient took antibiotics even once before visiting the emergency room. The symptoms of upper UTI (fever and flank pain) and lower UTI (dysuria, frequency, urgency and residual urine sense) were recorded under clinical features. Costovertebral angle (CVA) tenderness was investigated for physical examination findings. WBC, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin, urine culture results, and blood culture results were investigated for laboratory findings. A positive urine culture test was defined as > 10⁵ colony-forming unit/mL. APN was defined as wedge-shaped low attenuation lesions from the renal medulla to the renal cortex and/or perinephric fat stranding on enhanced CT, and perinephric fat stranding on nonenhanced CT [9,10]. In addition, renal abscess formation and emphysematous change were considered APN. Those who had ureteritis or cystitis without APN were excluded from the study.

3. Statistical analysis

Statistical analysis was performed using STATA (STATA 15.1, StataCorp LLC, College Station, TX, USA). Continuous variables are presented as mean and standard deviation, and categorical variables are described in terms of frequency (%). Continuous variables were compared using the Student *t*-test or Mann-Whitney *U*-test, while categorical variables were compared using the chi-square or Fisher exact test, according to the expected frequency. Statistical significance was set at $p < 0.05$. Logistic regression was performed to confirm the correlation of major variables according to the amount of WBCs observed in the urine microscopic study. Multivariate logistic regression was performed using the variables considered to have an important effect on the presence of pyuria, with a *p*-value of 0.05 or less in univariate analysis.

Results

1. General characteristics

The average age of patients was 58.5 years, and the average time to visit the emergency room after symptom onset was 69.3 hours. Sixty-two patients (15.9%) had already taken antibiotics at least

once before visiting the ED. More than 90% of patients with APN had a fever or a history of fever. Approximately 43.2% of patients had upper UTI symptoms (back pain or flank pain), and only 39.9% of patients had lower UTI symptoms (dysuria, frequency, urgency, and residual urine sense) at the time of ED visit. More than 50% of patients with APN did not have either upper or lower UTI symptoms. On physical examination, CVA tenderness was observed in 269 patients (68.8%), and approximately one-third of patients did not have CVA tenderness despite APN.

A total of 223 patients underwent blood culture, and pathogens were identified in 80 patients (35.9%). Among the 138 patients who underwent urine culture, 99 (71.7%) had pathogenic bacteria.

On abdominal CT, 89 patients did not have findings compatible with APN despite the clinical diagnosis of APN. There were 49 patients who had other causes of infection without APN findings on abdominal CT despite the clinical diagnosis of APN. Abscess formation or emphysematous changes were observed on abdominal

CT in 24 patients (6.1%). There were 175 patients (44.8%) with ureteritis and 131 patients (33.5%) with cystitis (Table 1).

2. Comparison of patients with normal (0–5/HPF) and abnormal WBC count (>5/HPF) in urine microscopic study

Eighty-eight patients (22.5%) had normal WBC counts (0–5/HPF) despite the clinical and CT diagnosis of APN, whereas 77.5% of patients had abnormal WBC counts (>5/HPF) on urine microscopic analysis (Table 2).

When comparing APN with normal WBC (0–5/HPF) and with abnormal WBC (>5/HPF), there were no differences in age, underlying disease, duration from symptom onset to diagnosis, previous history of APN, upper UTI symptoms (fever and flank pain), lower UTI symptoms (dysuria, frequency, urgency, and residual urine sense), physical examination findings, blood WBC count, CRP, procalcitonin, and positive blood culture results. The variables that showed statistical differences were prior use of antibiotics, neutrophil percentage, NLR, and positive urine culture. Abscess formation or emphysematous changes in abdominal CT showed no difference, while ureteritis or cystitis showed a significant difference. Patients with APN accompanied by ureteritis or cystitis on CT showed a significantly higher prevalence of abnormal WBC counts (>5/HPF) on urine microscopic examination (Table 3).

3. Logistic regression analysis

Table 4 shows the results of the univariate and multivariate logistic regression analyses. Among the variables with a $p < 0.05$ in univariate analysis, previous antibiotic use, ureteritis, and cystitis were presumed to have an important effect on pyuria, and multivariate logistic regression analysis was performed using these variables. There was no multicollinearity between ureteritis and cystitis (ϕ coefficient = 0.200). There was a strong and independent negative correlation between WBC of >5/HPF and previous antibiotic use at the time of diagnosis (odds ratio [OR], 0.249; 95%

Table 1. Demographic data

Characteristic	Data
No. of patients	391
Age (yr)	58.5 ± 18.7
Symptom onset to ED (hr)	69.3 ± 109.1
Past medical history	
Diabetes mellitus	118 (30.2)
Hypertension	152 (38.9)
Chronic kidney disease	14 (3.6)
Previous APN history	92 (23.5)
Previous antibiotics use at least once before ED visit	62 (15.9)
Clinical presentation	
Fever	361 (92.3)
Back pain or flank pain	169 (43.2)
Lower UTI symptom	
Dysuria	142 (36.3)
Frequency	185 (47.3)
Urgency	89 (22.8)
Residual urine sense	97 (24.8)
CVA tenderness	269 (68.8)
Abdomen CT finding	
Abscess formation or emphysematous change	24 (6.1)
Ureteritis	175 (44.8)
Cystitis	131 (33.5)
Culture	
Urine culture positive	99/138 (71.7)
Blood culture positive	80/223 (35.9)

Values are presented as number only, mean ± standard deviation, or number (%).

ED, emergency department; APN, acute pyelonephritis; UTI, urinary tract infection; CVA, costovertebral angle; CT, computed tomography.

Table 2. Degree of leukocyte in urine microscopy study among acute pyelonephritis confirmed patients in the emergency department

Degree of WBC	Data
0–3/HPF	46 (11.8)
4–5/HPF	42 (10.7)
6–10/HPF	61 (15.6)
11–20/HPF	68 (17.4)
>20/HPF	174 (44.5)

Values are presented as number (%).

WBC, white blood cell; HPF, high power field.

Table 3. Comparison of patients with normal (0–5/HPF) and abnormal WBC count (>5/HPF) in urine microscopic study

Variable	White blood cell (/HPF)		p-value
	≤ 5 (n = 88)	> 5 (n = 303)	
Age (yr)	57.1 ± 19.5	58.9 ± 18.5	0.425
Diabetes mellitus	31 (35.2)	87 (28.7)	0.241
Hypertension	35 (39.8)	117 (38.6)	0.844
Chronic kidney disease	3 (3.4)	11 (3.6)	1.000
Symptom duration (hr)	65.4 ± 91.8	70.4 ± 113.7	0.706
Previous antibiotics use	29 (33.0)	33 (10.9)	<0.001
Previous APN history	22 (25.0)	70 (23.1)	0.712
Fever	78 (88.6)	283 (93.4)	0.139
Flank pain or back pain	41 (46.6)	128 (42.2)	0.469
CVA tenderness	61 (69.3)	208 (68.7)	0.905
Lower UTI symptom			
Dysuria	31 (35.2)	111 (36.6)	0.809
Frequency	38 (43.2)	147 (48.5)	0.378
Urgency	15 (17.0)	74 (24.4)	0.146
Residual urine sense	25 (28.4)	72 (23.8)	0.374
Laboratory finding			
WBC (counts/μL)	11,566 ± 5,018	12,600 ± 4,653	0.072
Neutrophil (%)	81 ± 8.9	83.7 ± 7.6	0.006
NLR	9.9 ± 6.3	13 ± 9.9	0.006
CRP (mg/dL)	11.1 ± 8	12.6 ± 8.8	0.163
Procalcitonin (ng/mL)	5.6 ± 14.9	5.7 ± 12.5	0.961
Positive urine culture	12/26 (46.2)	87/112 (77.7)	0.001
Ciprofloxacin resistant	8/12 (66.7)	68/87 (78.2)	0.377
ESBL positive	2/12 (16.7)	22/87 (25.3)	0.514
Positive blood culture	11/44 (25.0)	69/179 (38.5)	0.093
CT finding			
Abscess formation or emphysematous change	9 (10.2)	15 (5.0)	0.069
Ureteritis	27 (30.7)	148 (48.8)	0.003
Cystitis	17 (19.3)	114 (37.6)	0.001

Values are presented as mean ± standard deviation or number (%).

WBC, white blood cell; HPF, high power field; APN, acute pyelonephritis; CVA, costovertebral angle; UTI, urinary tract infection; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; ESBL, extended-spectrum β-lactamase; CT, computed tomography.

confidence interval [CI], 0.140–0.441; $p < 0.001$). If antibiotics were used at least once before visiting the emergency room, the chance of pyuria in urinalysis was reduced by 75.1%. None of the clinical signs or symptoms correlated with pyuria. Among the blood test results, neutrophil percentage and NLR showed a minimal positive correlation. For every one-unit increase in neutrophil percentage and NLR, the probability of pyuria was predicted to increase by 3.3% and 5.1%, respectively. The probability of pyuria was significantly higher in cases with ureteritis or cystitis on CT than in those without ureteritis or cystitis. In particular, in bilateral ureteritis, the OR for pyuria reached 9.7 (95% CI, 2.2–41.7; $p = 0.002$) compared to cases without ureteritis.

Discussion

This study showed that a relatively large proportion of patients with a confirmed diagnosis of APN based on clinical and radiological findings did not have typical clinical features and WBC counts on urine microscopic examination were within the normal range. Unlike the current guidelines for diagnosing APN based on clinical features and pyuria, this result suggests that it is difficult to exclude the diagnosis of APN based on clinical features and pyuria alone.

Eighty-eight patients (22.5%) had normal WBC counts (0–5/HPF) on urine microscopic examination despite the clinical and CT diagnosis of APN. Among the several variables investigated, even a single use of antibiotics before visiting the ED was found to

Table 4. Logistic regression analysis

WBC of > 5/HPF	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Previous antibiotics use	0.249 (0.140–0.441)	<0.001	0.249 (0.138–0.45) ^{a)}	<0.001
Fever	1.814 (0.816–4.035)	0.144	1.916 (0.821–4.469) ^{a)}	0.133
Flank pain or back pain	0.838 (0.520–1.351)	0.469	1.033 (0.618–1.727) ^{a)}	0.900
Dysuria	1.063 (0.647–1.745)	0.809	1.089 (0.63–1.883) ^{a)}	0.760
Frequency	1.240 (0.769–2.000)	0.378	1.176 (0.7–1.976) ^{a)}	0.539
Residual urine sense	0.785 (0.461–1.339)	0.375	0.904 (0.507–1.611) ^{a)}	0.731
Urgency	1.573 (0.851–2.907)	0.149	1.513 (0.787–2.908) ^{a)}	0.214
CVA tenderness	0.969 (0.580–1.620)	0.905	1.105 (0.639–1.912) ^{a)}	0.721
WBC (× 1,000/ μ L)	1.05 (0.995–1.108)	0.073	1.054 (0.996–1.115) ^{a)}	0.068
Neutrophil (%)	1.038 (1.009–1.068)	0.009	1.033 (1.003–1.065) ^{a)}	0.030
NLR	1.059 (1.018–1.102)	0.005	1.051 (1.009–1.094) ^{a)}	0.017
Lactate	1.140 (0.659–1.973)	0.639	1.04 (0.595–1.817) ^{a)}	0.891
CRP	1.021 (0.992–1.051)	0.164	1.014 (0.984–1.045) ^{a)}	0.374
Procalcitonin	1.001 (0.977–1.025)	0.960	1.001 (0.975–1.026) ^{a)}	0.964
Abscess formation or emphysematous change	0.457 (0.193–1.084)	0.075	0.511 (0.201–1.301) ^{a)}	0.159
Ureteritis	2.157 (1.301–3.578)	0.003	2.244 (1.328–3.789) ^{b)}	0.003
Unilateral ureteritis	1.574 (0.928–2.672)	0.093	1.645 (0.95–2.848) ^{b)}	0.076
Bilateral ureteritis	9.445 (2.226–40.072)	0.002	9.663 (2.239–41.698) ^{b)}	0.002
Cystitis	2.519 (1.413–4.490)	0.002	2.412 (1.334–4.36) ^{b)}	0.004

WBC, white blood cell; HPF, high power field; OR, odds ratio; CI, confidence interval; CVA, costovertebral angle; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

^{a)}Adjusted for previous antibiotics use, ureteritis, and cystitis. ^{b)}Adjusted for previous antibiotics use.

be highly correlated with normal urine WBC counts despite having APN. Therefore, prior use of antibiotics before ED visit should always be checked while taking a patient's history for APN diagnosis. If the patient has already taken antibiotics, it is reasonable to diagnose APN based on the results of imaging tests such as CT rather than the results of urinalysis.

On the other hand, the presence of abnormal WBC count showed a significant positive correlation with the presence of accompanying ureteritis or cystitis on CT. UTI is a retrograde ascending infection in which uropathogens arising from fecal flora, progress through the urethra and bladder to the ureter and kidney [11,12]. Clinical features appear in the form of urethritis and cystitis at the onset of UTI; hence, typical symptoms of lower UTI, such as dysuria, frequency, residual urine sense, and urgency are observed. However, as UTI progresses to ureteritis and pyelonephritis, upper UTI symptoms (fever and flank pain) appear. As lower UTI progresses to APN, the uropathogens may move from the lower urinary tract to the upper region of the tract; hence, bacteria and inflammation no longer remain in the lower urinary tract. However, in other cases, bacteria and inflammation may remain in the lower urinary tract. We assumed that if bacteria and inflammation remain in the lower urinary tract in patients with APN, cystitis should be observed along with APN findings on CT, and urine WBC count may be high.

This study showed that more than half of patients with APN had neither upper UTI symptoms nor lower UTI symptoms, and approximately one-third of patients had no CVA tenderness. It is known that elderly patients with APN can only have a fever without typical symptoms of UTI [3,4]. However, in this study, the subjects were from a relatively younger age group with an average age of 58.5 ± 18.7 years, which indicates that even in young female patients, typical upper UTI symptoms and lower UTI symptoms may not appear in APN. Physicians should always keep in mind that clinical features and physical examination may be ambiguous, and pyuria may not be present in patients with APN.

The current APN diagnosis and treatment guidelines recommend that APN be diagnosed clinically based on the clinical features and the presence of pyuria, and to perform imaging studies only if the patient does not show clinical improvement after 72 hours of antibiotic treatment [1,2,13]. However, complicated APN requiring intervention or maintenance on a longer period of antibiotic treatment (kidney abscess, emphysematous change, ureter stone, etc.) is only identified after CT scans [8,14-16]. Moreover, as shown in the results of this study, there were many cases without APN findings or other infection sources than APN on CT, despite the clinical suspicion of APN. In this study, 16.4% of cases (89 of 542) had no evidence of APN on CT, and 9.0% of patients (49 of 542) with the clinical suspicion of APN had other sources

of infection than APN on CT. For these reasons, the effectiveness of CT in APN diagnosis is gradually increasing. The authors recommend to actively perform CT on patients from their initial visit if APN cannot be ruled out, rather than insisting on the current guidelines that defer imaging studies.

The main limitation of this study could be the selection bias. First, since this study was not intended for all patients with clinically suspected APN, but only for patients who had confirmed APN based on CT scan, there is a possibility that a selection bias could have occurred. Some patients may not have undergone CT because their symptoms, physical examination findings, and urine microscopy results were clearly suggestive of APN. These patients could have been included in the study if they had undergone CT. Second, this study included only patients who visited the ED; hence, patients who visited the outpatient clinic were excluded. Third, this was a single-center, retrospective study. Additionally, we have not studied whether there are differences in treatment and clinical prognosis between patients with and without pyuria.

More than half of the patients with confirmed APN did not have typical symptoms or signs of UTI, and about one-quarter of the patients did not have pyuria. Usage of antibiotics before ED visit was strongly and independently correlated with normal WBC counts on urinalysis. The diagnosis of APN should not be overlooked even if there are no typical clinical features, or a urine microscopic analysis is normal. If no other cause of fever can be found and APN cannot be completely excluded, imaging tests such as CT should be more actively performed regardless of clinical features or presence of pyuria, especially if the patient has already taken antibiotics at the time of diagnosis.

Notes

Conflicts of interest

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

Author contributions

Conceptualization: all authors; Data curation, Investigation: HKS, JHL, DHS, JUN; Formal analysis: HKS, JHL, JUN, SKH, PCC; Supervision: DHS, JUN, SKH, PCC; Writing-original draft: HKS, JHL; Writing-review & editing: HKS, JHL, DHS, JUN, SKH, PCC.

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