

# Clinical Usefulness of Contrast-Enhanced Computed Tomography in Patients with Non-Obstructive Acute Pyelonephritis

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**Objectives:** The aim of this study is to investigate the clinical utility of contrast-enhanced computed tomography (CE-CT) in patient with non-obstructive acute pyelonephritis (APN).

**Methods:** From 2007 to 2013, 537 APN patients who underwent a CE-CT scan within 24 hours after hospital admission were enrolled. We divided these patients into greater (50% or greater involvement, n = 143) and lesser (less than 50% involvement, n = 394) groups based on renal parenchymal involvement in CE-CT examination. We compared clinical characteristics between two groups and analyzed the clinical value of CE-CT scan as a reliable marker for predicting clinical severity and disease course in patient with non-obstructive APN.

**Results:** The mean estimated glomerular filtration rate was  $70.6 \pm 25.5$  mL/min/1.73m<sup>2</sup>. Compared with patients in lesser group, the patients in greater group had lower serum albumin levels ( $3.5 \pm 0.5$  vs  $3.8 \pm 0.6$ ,  $P < 0.01$ ) and longer hospital stay ( $10.1 \pm 4.7$  vs  $8.8 \pm 4.5$ ,  $P < 0.05$ ). In addition, acute kidney injury (AKI) (23.1% vs 11.4%,  $P < 0.005$ ) and bacteremia (36.4% vs 26.8%,  $P = 0.02$ ) were frequently developed in greater group, respectively. The overall incidence of AKI was 14.8% based on RIFLE criteria. In a multivariate logistic regression analysis for predicting AKI, age, presence of diabetes mellitus and the presence of renal parenchymal involvement of greater than 50% in CE-CT were significant predictors of AKI.

**Conclusions:** The CE-CT scan could be useful to predict the clinical severity and course in non-obstructive APN patients with preserved renal function.

**Key Words:** Acute kidney injury, Computed tomography, Pyelonephritis

Acute pyelonephritis (APN) is defined as an acute inflammation of the upper urinary tract, including renal parenchyma, calyces, and pelvis. APN usually presents as mild diseases, but it sometimes causes substantial morbidity and mortality.<sup>1</sup> Several parameters including old age, immunosuppression, health care associated infection, obstructive uropathy, decreases in

platelet count, serum albumin level, high C-reactive protein, and bacteremia have been proposed as prognostic factors predicting poor prognosis in patients with APN.<sup>2-4</sup>

Contrast-enhanced computed tomography (CE-CT) is used for diagnosis of APN, and can provide important information on the range of inflammation and other accompanying compli-

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cations to help to establish a precise diagnosis.<sup>5,6</sup> There are some specific CT findings observed in APN patients. The most common radiologic CE-CT finding of APN is a striated or wedge-shaped area of hypoperfusion after contrast injection.<sup>7,8</sup> However, there have been few studies about correlation between the extent of infection in renal parenchyma and non-obstructive APN severity.<sup>7,8</sup> In the present study, we evaluated the clinical utility of CE-CT for predicting clinical severity in patient with non-obstructive APN.

## MATERIALS AND METHODS

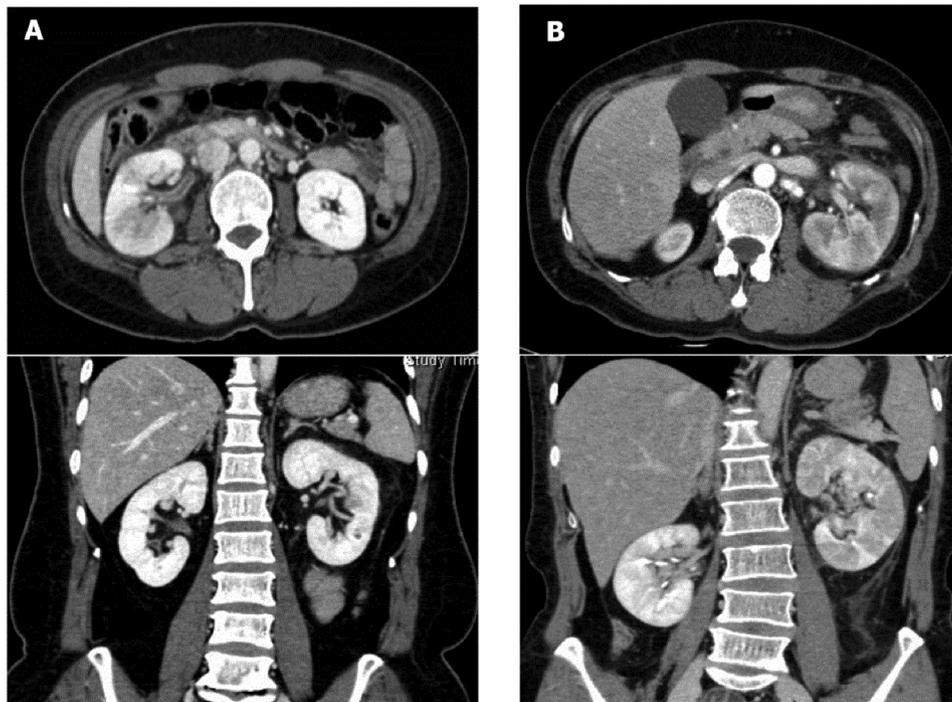
### Patient selection

From January 2007 to December 2013, we enrolled 556 APN patients who underwent a CE-CT scan within 24 hours after hospital admission before starting antibiotic treatment. Patients were excluded if they were younger than 18 years or had an hydronephrosis or renal abscess on CT scan. We also excluded the patients with post-contrast induced-acute kidney injury (CI-AKI) or low-quality image due to various causes. A clinical diagnosis of APN was made in patients with more than three of the following five diagnostic criteria: (1) clinical symptoms such as fever, chills, vomiting, or flank pain (2) costovertebral angle tenderness (3) fever of higher than 37.5 °C (4) leukocytosis in the complete blood count (5) abnormal urine test results (pyuria: white blood cell of  $\geq 10$ /high-power field or positive urine culture of  $10^5$  colony-forming unit/mL). A total of 537 patients were included

in this study. Two experienced radiologist divided these patients into two groups by approximately quantifying renal parenchymal low density extent on CE-CT. APN extent was approximately quantified on CE-CT by calculating number of slices that contained less enhancing lesion divided by total number of slices that contained normal renal parenchyma (Fig. 1). We also checked the status of renal parenchymal involvement. In cases with bilateral APN of different grades in each kidney, the higher grade was recorded. Patients were divided into two groups: greater group (greater than 50% involvement, n = 143) and lesser group (lesser than 50% involvement, n = 394). This study was approved by the Institutional Review Board of the Presbyterian Medical Center, Jeonju, South Korea (IRB No. 2019-05-014).

### Clinical and laboratory information

All patients had a detailed clinical history and examination, a standard set of investigations including complete blood counts, liver function tests, serum creatinine, urea, electrolytes, chest radiograph, three peripheral blood smears for malaria, urinalysis, and two blood cultures. AKI was defined based on the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria,<sup>9</sup> and patients were categorized into the R, I or F categories. We defined CI-AKI with the RIFLE criteria as a relative increment in serum creatinine of  $\geq 50\%$ , or a decrease in estimated glomerular filtration rate of  $\leq 25\%$  from baseline, or an episode of oliguria lasting  $\geq 6$  hours within 48 to 72 hours following



**Fig. 1. Acute pyelonephritis grades according to CT findings. (A) lesser grade, lesser than 50% of renal involvement (B) greater grade, greater than 50% of renal involvement.**

contrast administration.<sup>10</sup> The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.<sup>11</sup> When the baseline serum creatinine was not available, it was calculated using the standard four-variable MDRD formula assuming eGFR of 75 mL/min/1.73 m<sup>2</sup>. The RIFLE class was determined based on the worst among serum creatinine levels, eGFR, and urine output criteria. Renal replacement therapy was initiated using the standard indications. Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of renal infection. The CT images were reviewed by two radiologists who unaware of clinical information; the final decision of grade was reached by consensus.

### CT technique

CT scan was conducted on a 16-channel multi-detector row scanner (Somatom Sensation 16, Siemens Medical Solutions, Erlangen, Germany) with setting of 3 mm slice thickness. The CT findings were evaluated in the nephrographic phases. Intravenous contrast material was administered in an antecubital vein with injector at a dose of 1.5 mL/Kg body weight at a rate of 3 mL/s to a maximum of 120 mL. Nephrographic-phase scans were started 90 to 100 seconds after contrast injection.

### Statistical analysis

All data are presented as means  $\pm$  standard deviations unless otherwise specified. The baseline characteristics of patients in the greater and

**Table 1. The clinical and laboratory findings of the 537 patients with nonobstructive acute pyelonephritis**

| Characteristics                            |             |
|--|-------------|
| Age, years                                 | 55.2 ± 17.9 |
| Female, n (%)                              | 504 (93.9)  |
| Co-morbidity                               |             |
| Diabetes, n (%)                            | 82 (15.3)   |
| Hypertension, n (%)                        | 157 (29.2)  |
| Duration of hospital stay, days            | 9.2 ± 4.6   |
| Sepsis, n (%)                              | 7 (1.3)     |
| Serum creatinine, (mg/dl)                  | 0.9 ± 0.3   |
| eGFR adm, ml/min/1.73m <sup>2</sup>        | 70.6 ± 25.5 |
| Total WBC count, ( × 10 <sup>3</sup> / mL) | 12.7 ± 12.3 |
| Serum albumin, (mg/dl)                     | 3.8 ± 0.6   |
| Bilateral involvement, n (%)               | 98 (18.2)   |
| Bacteremia, n (%)                          | 158 (29.4)  |
| AKI, n (%)                                 | 78 (14.5)   |

eGFR adm: eGFR at the time of admission

WBC: white blood cell

AKI: acute kidney injury

lesser groups were compared using t tests for continuous variables and chi-square tests for categorical variables. Clinically relevant parameters or the variables that were significantly associated with the presence of AKI in the univariate analysis were included in the multivariate analysis. A *P*-value of < 0.05 was considered to be statistically significant. All statistical analyses were carried out using SPSS version 22.0.

## RESULTS

### Baseline characteristics

The baseline characteristics of the 537 study subjects are presented in Table 1. The patients included 504 (93.9%) men and 33 (6.1%) women, with a mean age of 55.2 ± 17.9 years. The mean

estimated glomerular filtration rate was 70.6 ± 25.5 mL/min/1.73m<sup>2</sup>. The initial white blood cell count (WBC) and serum albumin levels were 12.7 × 10<sup>3</sup>/mL and 3.8 g/dL, respectively. The mean hospital stay was 9.2 ± 4.6 days. Bilateral renal involvement in CE-CT and bacteremia were noted in 18.2% and 29.4% of the patients, respectively. Of 537 participants, 78 (14.5%) experienced AKI during hospitalization period.

### Comparison of clinical characteristics between greater and lesser group

When we compared clinical characteristics between greater (n = 143) and lesser (n = 394) groups, the patients in greater group had lower serum albumin levels (3.5 ± 0.5 vs 3.8 ± 0.6, *P* < 0.01) and longer hospital stay (10.1 ± 4.7 vs 8.8 ± 4.5, *P* < 0.05). Furthermore, bilateral renal in-

**Table 2. Comparison of baseline characteristics between non-AKI and AKI group**

|   | Greater<br>(n = 143) | Lesser<br>(n = 394) | P-value |
|---|----------------------|---------------------|---------|
| Age   | 57.5 ± 16.6          | 54.4 ± 18.3         | NS      |
| Female, n (%)                                   | 137 (95.8)           | 367 (93.1)          | NS      |
| Comorbidity                                     |                      |                     |         |
| Diabetes, n (%)                                 | 26 (18.2)            | 56 (14.2)           | NS      |
| Hypertension, n (%)                             | 50 (35.0)            | 107 (27.2)          | 0.05    |
| Duration of hospital stay, days                 | 10.1 ± 4.7           | 8.8 ± 4.5           | < 0.05  |
| Sepsis, n (%)                                   | 1 (0.70)             | 6 (1.51)            | NS      |
| eGFR <sub>adm</sub> , ml/min/1.73m <sup>2</sup> | 63.8 ± 23.3          | 72.8 ± 25.8         | < 0.05  |
| eGFR <sub>dis</sub> , ml/min/1.73m <sup>2</sup> | 71.4 ± 20.5          | 76.5 ± 23.5         | NS      |
| Total WBC count, ( × 10 <sup>3</sup> / mL)      | 13.8 ± 12.8          | 12.3 ± 12.0         | NS      |
| Serum albumin, (mg/dl)                          | 3.5 ± 0.5            | 3.8 ± 0.6           | < 0.05  |
| Bilateral involvement, n (%)                    | 40 (10.2)            | 58 (40.6)           | < 0.05  |
| Bacteremia, n (%)                               | 52 (36.4)            | 106 (26.9)          | < 0.05  |
| AKI, n (%)                                      | 33 (23.1)            | 45 (11.4)           | < 0.05  |

eGFR<sub>adm</sub>: eGFR at the time of admissioneGFR<sub>dis</sub>: eGFR at the time of discharge

WBC: white blood cell

AKI: acute kidney injury

**Table 3. Predictors of development of AKI (univariate and multivariate analysis)**

|   | Univariate<br>HR (95% CI) | P-value | Multivariate<br>HR (95% CI) | P-value |
|---|---------------------------|---------|-----------------------------|---------|
| Age   | 1.037 (1.021 - 1.054)     | < 0.001 | 1.024 (1.005 - 1.043)       | 0.014   |
| Diabetes mellitus   | 2.835 (1.622 - 4.954)     | < 0.001 | 2.005 (1.080 - 3.724)       | 0.028   |
| Hypertension  | 3.277 (2.004 - 5.358)     | < 0.001 | 1.592 (0.879 - 2.886)       | 0.125   |
| Serum albumin, (mg/dl)                                      | 0.367 (0.232 - 0.583)     | 0.019   | 0.660 (0.387 - 1.132)       | 0.125   |
| Total WBC count<br>( × 10 <sup>3</sup> / mL)                | 1.049 (1.012 - 1.087)     | 0.006   | 1.031 (0.997 - 1.067)       | 0.073   |
| 50% or greater renal<br>parenchymal<br>involvement in CE-CT | 2.327 (1.414 - 3.827)     | 0.001   | 1.901 (1.092 - 3.309)       | 0.023   |

AKI: acute kidney injury

WBC: white blood cell

CE-CT: contrast enhanced computed tomography

involvement (40.6% vs 10.2%,  $P < 0.05$ ) and bacteremia (36.4% vs 26.9%,  $P < 0.05$ ) were frequently developed in greater group, respectively

(Table 2). AKI (23.1% vs 11.4%,  $P < 0.05$ ) occurred more frequently in greater group than lesser group. According to the RIFLE criteria, 52

(66.6%) and 26 (33.4%) in our study fell into the R and I categories, respectively. By univariate analysis, age, presence of diabetes mellitus or hypertension, serum albumin, total leukocyte count, bilateral renal involvement and 50% or greater renal parenchymal involvement in CT scan were significant predictors of AKI. Adjusting for these factors in a multivariate logistic regression analysis, older age and CT finding of 50% or greater renal parenchymal involvement were the only significant predictors of AKI (Table 3).

## DISCUSSION

In the present study, we show that the patients in greater group had longer hospital stay than lesser group. In addition, compared with lesser group, AKI and bacteremia were frequently developed in greater group. Our findings provide a rationale for using CE-CT scan as a tool for predicting clinical severity in patients with non-obstructive APN.

APN is the most common form of upper urinary tract infection, and usually occurs secondary to an ascending infection of gram-negative bacteria in women.<sup>12</sup> Although APN is easily treated by antibiotics, its clinical course and severity varies.<sup>1</sup> Several risk factors are associated with the more severe presentations of urinary tract infection. Of these, urinary tract obstruction was independent predictor of septic shock.<sup>3,13</sup> To evaluate urinary tract obstruction due to various causes, radiological tests including CT or ultrasound are needed. In case of non-obstructive

APN, the most common radiologic CT finding is a striated or wedge-shaped area of hypoperfusion or mass-like lesion after contrast injection.<sup>7,8</sup> However, there are few data about such CT finding as a marker reflecting APN severity.<sup>7,8,14</sup>

Paick et al. graded APN into 4 groups according to the extent of renal involvement; no renal parenchymal involvement as grade 1; less than 25% involvement as grade 2; 25% to 50% involvement as grade 3; and greater than 50% as grade 4, and reported clinical usefulness of CT grade for predicting clinical course of APN.<sup>14</sup> In presenting study, we classified the subjects into two groups based on modification of method reported by Paick et al. Initially, we also classified the subjects into four groups according to APN grade reported by Paick et al, however, there were no statistically significant differences among groups (the data were not shown). This finding might be due to the difference of enrolled participants. In the study by Paick et al, the mean age of the study population was 39.3 years and there were no patients with AKI. On the other hand, the mean age in our study was 55.2 years, and the overall incidence of AKI was 14.5%. Thus, large prospective randomized controlled study is needed to check whether the association of the extent of renal involvement in CT and clinical severity can differ based on renal function. However, the increase in hospital stay of greater group, which is shown in our study, was also observed in the study reported by Paick et al. Urothelial thickening, diffuse peritoneal thickening, perinephric fat infiltration and the presence of two or more abnormal CT findings were

more frequently observed in patients with bacteremic APN.<sup>15</sup> However, there are few data about correlation between bacteremia and extent of renal involvement.<sup>16</sup> In case of patients with APN, blood cultures have been reported to be positive in 18-32% of APN cases.<sup>16-18</sup> In our study, 158 (29.4%) patients out of 537 have positive blood culture, and bacteremia (36.4% vs 26.9%,  $P < 0.05$ ) were frequently developed in greater group. During treatment of APN, it is important to differentiate bacteremic urinary tract infection (UTI) patients from non-bacteremic UTI patients since complication of bacteremic UTI can lead to sepsis or death. Thus, our data show that CT finding may be helpful to predict bacteremia in patients with APN.

Old age, arteriosclerosis, diabetic vasculopathy, chronic hypertension, and chronic kidney disease are regarded as risk factors for renal failure due to impairment of the vasodilatory response in the afferent arteriole.<sup>19,20</sup> In our study population, old age and 50% or greater renal parenchymal involvement in CT examination were significant risk factors for predicting APN-associated AKI. In this study, all patients with AKI recovered without renal replacement therapy after appropriate antibiotics and supportive care. According to our data, CT finding could be helpful to predict AKI in APN patients with preserved renal function.

Our study had certain limitations. First, this was a retrospective single center study. Thus, a large, prospective, randomized, controlled multicenter study is needed in the future. Second, the subjects in present study had relatively preserved

renal function since patients with poor renal function did not undergo CE-CT due to CI-AKI. Third, although several CT findings were observed in APN,<sup>15</sup> we only investigated renal parenchymal involvement in CT. Thus, a large study using various CT findings in APN patients is needed in the future.

In our study, the patients with 50% or greater renal parenchymal involvement in CE-CT had severe type of APN based on hospital stay, presence of bacteremia and AKI. Therefore, CE-CT could be helpful to discriminate patients with severe from non-severe APN patients in non-obstructive patients with preserved renal function.

### **Declaration of interest**

All authors have no conflicts of interest to declare.

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