Usefulness of computed tomography in the diagnosis of acute pyelonephritis in older patients suspected of infection with unknown focus

学　位　論　文

Usefulness of computed tomography in the diagnosis of acute pyelonephritis in older patients suspected of infection with unknown focus

（感染巣が自明でない感染症疑いの高齢者に対する急性腎盂腎炎の診断における CT の有用性）

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Abstract

Background: In elder patients, the diagnosis of acute pyelonephritis can be difficult because the lack of specific symptoms or specific test results. The diagnostic performance of computed tomography (CT) signs has not been studied thoroughly to date.

Purpose: To assess the performance of CT signs to diagnose acute pyelonephritis in elder patients suspected of infection without self-evident focus.

Material and Methods: This study targeted patients admitted from 2015 through 2018. I included patients aged ≥65 years who underwent blood cultures, urine culture, and non-contrast or contrast-enhanced CT on admission. I excluded cases with clinically evident infection focuses prior to CT. Five CT signs were independently reviewed by two radiologists blinded to clinical information: perirenal fat stranding, pelvicalyceal wall thickening and enhancement, renal enlargement, thickening of Gerota's fascia, and area(s) of decreased attenuation. A clinical expert panel decided the final clinical diagnoses.

Results: Among 473 eligible patients, acute pyelonephritis cases were 61. The positive and negative likelihood ratios of the perirenal fat stranding were 4.0 (95% confidence interval [CI] 2.3–7.0) and 0.8 (95%CI 0.7–0.9) in non-contrast CT, respectively, as the laterality of findings between left and right kidneys were considered. The diagnostic performances were similar in the other signs in non-contrast CT with positive and negative likelihood ratios of 3.5–11.3 and 0.8–0.9, respectively.

Conclusion: The diagnosis of acute pyelonephritis in older patients suspected of infection with unknown focus can be facilitated with CT signs.

Abbreviation: APN = acute pyelonephritis; CECT = contrast-enhanced computed tomography; CI = confidence interval; CT = computed tomography; IQR = interquartile range; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NCCT = non-contrast computed tomography; qSOFA = quick Sequential Organ Failure Assessment

Introduction

Acute pyelonephritis (APN) is a common bacterial infection (1). In cases with bacterial infection, information about the focus of infection is vital for selecting the appropriate antibiotic regimen. The recommended duration of treatment for APN is usually longer than that for other common infectious conditions (e.g., pneumonia) (2), therefore correct diagnosis of APN is important to avoid undertreatment.

In older population, the diagnosis of APN can be difficult. Clinical presentation of APN typically includes lower urinary tract symptoms (dysuria, urgency, and polyuria), flank pain, costovertebral tenderness, pyuria, and bacteriuria (2–4). Unfortunately, the sensitivity of flank pain is not very high (5), nor is that of bacteriuria in elder patients (6). Therefore, physical examination and urine tests do not help with diagnosis of APN in them. Some experts have insisted that computed tomography (CT) and other imaging modalities are of great use to detect obstruction, but of little use to detect the infection of urinary tracts (7,8). Nonetheless, other experts suggest that some CT findings should be useful in the diagnosis of APN. Yet, the CT signs for diagnosis of APN has not been thoroughly studied. High sensitivity of CT signs for the diagnosis of APN was suggested in some studies, but they lacked information on specificity. In these studies, as the likelihood ratio (LR) cannot be calculated, it was difficult to determine if CT signs were useful (9–11). Fukami et al. reported that perirenal fat stranding, one of the most common CT signs for the diagnosis of APN, had poor diagnostic performance (12). However, the control group of their case-control study was consisted of patients who underwent renal biopsy. This could have caused the underestimation of the diagnostic performance of CT (12). In order to explore further , I aimed in this study to evaluate the diagnostic performance of CT signs for APN in elder patients who were suspected to have bacterial infection without self-evident focus.

Material and Methods

This retrospective cross-sectional study was performed following the Standards for Reporting of Diagnostic Accuracy Studies statement for diagnostic accuracy studies (13). This study was approved by the ethics committee of Fukushima Medical University (30070).

Setting and patients

I conducted the study in the department of general medicine of Shirakawa Kosei General Hospital (471-bed capacity) from April 2015 to March 2017. I targeted patients aged

≥65 years who were admitted and suspected to have a bacterial infection without any self-evident focus. The physicians' decision to order a urine culture and two or more sets of blood cultures on admission was regarded as a surrogate marker of clinical suspicion for bacterial infection, as in previous studies (14,15). Then, not only the cases who did not undergo CT, but also those whose clinically evident focus of infection was mentioned in the comment of CT order were excluded. The cases with a single kidney were also excluded as I could not compare the left and right kidneys.

Index test

Possibly useful CT signs were chosen from the former literature by a group consisting of two radiologists, a general internist, and an emergency physician, all of whom have board certifications. The chosen signs were perirenal fat stranding (9,11,16,17), pelvicalyceal wall thickening and enhancement (16), renal enlargement (11,16–19), thickening of Gerota's fascia (16), and area(s) of decreased attenuation (11,16,17,19). "Striated nephrogram" is classically referred to as an imaging marker, which we considered as a variation of the area(s) of decreased attenuation.

Two radiologists independently reviewed the CT images and evaluated the presence of the chosen APN signs, without access to relevant clinical information. Every sign was evaluated both in the left and right kidneys. All cases underwent non-contrast CT (NCCT), but necessity of addition of contrast-enhanced CT (CECT) was arbitrarily decided by clinicians. If the two radiologists disagreed on the presence of certain signs, they discussed to reach an agreement. They did not see the existing radiological reports issued in the actual clinical practice.

According to former studies, CT signs are considered to be nonspecific (16). Therefore, I focused on the laterality of the CT signs in this study. To achieve this, I compared two analyses based on different definitions of positive CT signs (laterality-sensitive and laterality-insensitive analyses). If and only if the difference of a CT sign between left and right kidney was obvious, then the sign was regarded as positive in the laterality-sensitive analysis. In contrast, if a CT sign was present, regardless of the findings of contralateral kidney, then the signs was regarded as positive in the laterality-insensitive analysis. I calculated diagnostic characteristics of the CT signs both in NCCT and CECT, except in the area(s) of decreased attenuation which can be evaluated only in CECT.

Reference standard

No definite criteria have been established for the diagnosis of APN, and diagnostic criteria used in existing studies on APN treatment were different from one another (20–23). A gold standard for APN would ideally be a pathological assessment, but it is far from realistic especially because APN is mostly curable with proper antibiotic treatment. In addition, neither clinical signs and symptoms, nor microbiological tests are accurate in the diagnosis of APN in elder patients (24). In such case that no definite diagnostic criteria exist, the best possible reference standard is known to be an expert panel diagnosis (25), which I used in this study.

Two physicians, a board-certified general internal physician, and a board-certified emergency physician, made a clinical expert panel. Each panelist independently reviewed the extracted medical charts, which included age, sex, history, vital signs, physical findings, laboratory data of blood and urine, clinical course after admission, results of the urine and blood culture, and survival on the 30th day of admission. A research assistant edited CT reports issued in the actual clinical practice to eliminate any comments on kidneys to avoid information bias. The clinical expert panel classified the cases into two diagnostic categories: APN and other conditions. If the two panelists' diagnoses did not agree, they reached the final diagnosis with discussion.

Statistical analysis

I used a commercial software program (STATA, version 15.1 SE; StataCorp LP, College Station, Texas) for the analysis. The estimated sensitivity of a CT sign was 80%, the alpha level of 0.05, the power of 0.8, and the marginal error of 10% were used to assess the sample size. According to these parameters, this study needed 62 cases of APN.

Sensitivity, specificity, and positive and negative likelihood ratios (LR+ and LR-, respectively), as point estimates with 95% confidence intervals (CI) were calculated for each CT signs. If specificity was 100%, I adopted the substitution formula to evaluate positive likelihood ratios, i.e., 0.5 is added to all cell frequencies before calculation (26). Moreover, to improve sensitivity, I also evaluated the diagnostic performance of the "presence of any of the CT findings".

I assessed the consistency between the panelists of radiology expert panel and of the clinical expert panel with the kappa coefficient. I adopted the interpretation of kappa value as follows: ≤ 0, no agreement; 0.01–0.20, none to slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.0, almost perfect agreement (27).

Results

Characteristics of study subjects

Among the screened 1,137 cases, 664 were excluded (Fig. 1). Twenty-one cases, nine of which had APN, were excluded because the infection focus was already evident before undergoing CT. I included the remaining 473 cases. NCCT was performed in all the 473 cases, while CECT was performed in only 101 cases.

Table 1 shows basic characteristics of the cases. In APN cases, women outnumbered men. APN cases had higher rate of positive blood cultures than the others.

Clinical diagnosis and a judgment by the clinical expert panel

The consistency of the two panelists of clinical expert panel was almost perfect with kappa coefficient of 0.82. The two panel members disagreed in 22 among 473 cases (4.5%). Among the 61 cases categorized into the APN group by the clinical expert panel, the diagnosis in the actual clinical practice was consistent in 55 patients (90.2%), and the remaining six patients had been diagnosed with other conditions including pneumonia. Among 412 cases which were categorized into the non-APN group by the clinical expert panel, as few as five (1.2%) had the diagnosis of urinary tract infection in the actual practice. The diagnoses in the actual practice among the non-APN group were most commonly respiratory diseases including pneumonia (295 patients, 71.6%), followed by abdominal diseases, bone-and-joint diseases, and lymphoma and other malignant diseases.

Diagnostic performance of CT findings

The consistency of the two panelists of the radiological expert panel was shown in Table 2 with kappa coefficients. All CT signs except the thickening of Gerota's fascia showed fair to substantial inter-rater agreement (28).

Table 3 and 4 showed the results of the laterality-sensitive and laterality-insensitive analyses. The specificity of the CT signs was generally high, but the sensitivity was not. The CT signs showed higher LR+ in the laterality-sensitive analyses than in the laterality-insensitive ones. In the laterality-sensitive analyses, decreased attenuation in CECT showed the highest LR+ of 33.2 (95% CI: 4.3-254.0). In the laterality-insensitive analyses, the perirenal fat stranding showed the lowest LR- as a single sign in both NCCT and CECT (0.5 [0.4-0.7]

and 0.3 [0.1-0.7], respectively). The presence of any of the CT signs showed the lowest LR- of all, which was 0.3 (0.2-0.6) in CECT in the laterality-insensitive analyses.

Discussion

Summary of the findings

I evaluated the diagnostic performance of five CT signs for APN in elder patients suspected of infection without self-evident focus. The perirenal fat stranding and the pelvicalyceal wall thickening/enhancement showed moderately high LR+, especially when laterality was considered. Though the enlargement of kidney and the thickening of Gerota's fascia showed high LR+, the judgement of the thickening of Gerota's fascia was not consistent between the two radiological experts. The decreased attenuation cannot be evaluated with NCCT but only with CECT, which showed high LR+ in both the laterality-sensitive and the insensitive analyses. The perirenal fat stranding in laterality-insensitive CECT showed the lowest LR- as a single CT sign.

Comparison with existing literature

According to a former case-control study by Fukami et al., which included 89 patients with APN as cases and 319 patients who underwent renal biopsy as controls, the diagnostic performance of the perirenal fat stranding was poor (12). In this study, patients who underwent NCCT and CECT were analyzed altogether (51 patients among 89 patients with APN underwent CECT, while all patients in the control group underwent NCCT). The sensitivity, specificity, and LR+ of the perirenal fat stranding were reported as 72%, 71%, and 2.5, respectively. Given the results of this study, the diagnostic performance of the perirenal fat stranding in the study by Fukami et al. could have been better if the laterality of the finding between left and right kidneys had been considered.

In this study, the perirenal fat stranding showed a moderately high LR+ especially with laterality-sensitive analysis, but bilateral APN cases may have been miscategorized as negative. According to the report by Lee et al., 33.4% of the area(s) of hypoattenuation-positive APN had bilateral lesions (29), but in the present study, bilateral hypoattenuation was found in only 11.7% of the APN cases with CECT. This difference might be due to the heterogeneity of the study population. For instance, the patients were much younger in Lee et al.'s study (50.4±20.6 and 59.3±19.4 years for unilateral and bilateral APN cases, respectively) than in the present study (85.8±10.4 and 77.0±9.4, respectively). Given that the bilateral hypoattenuation

was relatively rare in the present study, the impact of false-negatives due to the bilateral lesions may have not been large.

Clinical implication

CT signs can help physicians diagnose APN in elder patients suspected of infection without self-evident focus. The laterality-sensitive interpretation of the CT signs is particularly useful for ruling in the diagnosis of APN. While CT is unnecessary for patients with an evident focus of infection, it can be a reasonable option to evaluate the possibility of APN when elder patients present with non-specific signs and symptoms.

Limitations

This study had several limitations. First, this was a single-center, retrospective study. Therefore, these findings should be further assessed in multi-center, prospective studies. Second, the external validity of this study could have been limited by the study design. I used the physicians' decision to order blood/urine cultures as a surrogate marker of clinical suspicion for bacterial infection. Moreover, I regarded the patients who underwent CT as those without an evident focus of infection unless a focus of infection was mentioned in the comment of the CT order. Such inclusion criteria based on the physicians' decision could be subjective and difficult to reproduce. Future studies with more objective inclusion criteria need to be performed to validate the findings of this study. Third, CT is not always readily available in other settings. In Japan, its generous accessibility to CT allows physicians to order CT rather freely. Therefore, validation studies in other countries are necessary. Finally, the results in CECT should be interpreted with caution, because only 101 cases underwent CECT.

Conclusion

To conclude, CT signs of APN in elder patients can be useful, especially for ruling in the diagnosis, when the infectious focus is not self-evident. Large, prospective studies in other settings are needed to validate the findings in this study.

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Tables

Table 1. The characteristics of the cases

APN, acute pyelonephritis; HPF, high-power field; IQR, interquartile range; qSOFA, quick Sequential Organ Failure Assessment

*The values of qSOFA were missing in four of the APN cases and in 48 of the non-APN cases, due to the lack of respiratory rate documentation.

**Urine culture was counted as positive if the number of colonies was 10^5 colony-forming units per milliliter or greater.

	APN n = 61	non-APN n = 412	Total n = 473
Age (yr), median (IQR)	83 (76–89)	85 (79–89)	85 (79–89)
Men, n (%)	20 (32.8)	202 (49.0)	222 (46.9)
Lower urinary tract symptoms, n (%)	3 (4.9)	12 (2.9)	15 (3.2)
Chronic kidney disease, n (%)	2 (3.3)	14 (3.4)	16 (3.4)
Diabetes, n (%)	16 (26.2)	64 (15.5)	80 (16.9)
Former use of antibiotics, n (%)	6 (9.8)	58 (14.1)	64 (13.5)
qSOFA ≥ 2, n (%)*	21 (34.4)	113 (27.4)	134 (28.3)
Serum creatinine (μmol/L), median (IQR)	88.4 (65.4–120.2)	76.9 (58.3–106.5)	80.4 (59.2–109.6)
Positive blood culture, n (%)	26 (42.6)	53 (12.9)	79 (16.7)
Positive urine culture, n (%)**	57 (93.4)	205 (49.8)	262 (55.4)

Table 2. Kappa coefficient of each CT sign between the two independent radiologists

CECT, contrast-enhanced computed tomography; CT, computed tomography; NCCT, non-contrast computed tomography

	Kappa coefficient in laterality-sensitive analyses ± standard error	Kappa coefficient in laterality-insensitive analyses ± standard error
Signs on NCCT (n = 473)		
- Perirenal fat stranding	0.51 ± 0.03	0.42 ± 0.04
- Pelvicalyceal wall thickening	0.37 ± 0.04	0.40 ± 0.04
- Enlargement of kidney	0.78 ± 0.04	0.53 ± 0.04
- Thickening of Gerota's fascia	0.22 ± 0.03	0.18 ± 0.03
Signs on CECT (n = 101)		
- Perirenal fat stranding	0.66 ± 0.08	0.52 ± 0.09
- Pelvicalyceal wall thickening or enhancement	0.55 ± 0.08	0.48 ± 0.10
- Enlargement of kidney	0.89 ± 0.08	0.64 ± 0.09
- Thickening of Gerota's fascia	0	0
- Decreased attenuation	0.57 ± 0.07	0.74 ± 0.10

Table 3. Diagnostic performance of CT signs in the laterality-sensitive analyses

CECT, contrast-enhanced computed tomography; CI, confidence interval; CT, computed tomography; NCCT, non-contrast computed tomography

*Substitution formula was used to calculate the positive likelihood ratio, as specificity was 100%.

	Sensitivity, % (95%CI)	Specificity, % (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)
Unilaterally dominant finding on NCCT (n = 473)				
- Perirenal fat stranding	26.2 (15.8–39.1)	93.4 (90.6–95.6)	4.0 (2.3–7.0)	0.8 (0.7–0.9)
- Pelvicalyceal wall thickening	24.6 (14.5–37.3)	93.0 (90.0–95.2)	3.5 (2.0–6.1)	0.8 (0.7–0.9)
- Enlargement of kidney	11.5 (4.7–22.2)	98.1 (96.2–99.2)	5.9 (2.2–15.7)	0.9 (0.8–1.0)
- Thickening of Gerota's fascia	8.2 (2.7–18.1)	99.3 (97.9–99.8)	11.3 (2.8–45.9)	0.9 (0.9–1.0)
- Any of the 4 signs present	39.3 (27.1-52.7)	87.4 (83.8-90.4)	3.1 (2.1-4.7)	0.7 (0.6-0.9)
Unilaterally dominant finding on CECT (n = 101)				
- Perirenal fat stranding	44.4 (21.5–69.2)	90.1 (82.1–95.4)	4.5 (2.0–10.1)	0.6 (0.4–0.9)
- Pelvicalyceal wall thickening or enhancement	52.6 (28.9–75.6)	85.7 (76.8–92.2)	3.7 (1.9–7.1)	0.6 (0.3–0.9)
- Enlargement of kidney	15.8 (3.4–39.6)	98.9 (94.0–100.0)	14.4 (1.6–131.0)	0.9 (0.7–1.0)
- Thickening of Gerota's fascia	11.1 (1.4–34.7)	100.0 (96.0–100.0)	24.2 (1.2–484.0)*	0.9 (0.8–1.0)
- Decreased attenuation	36.8 (16.3–61.6)	98.9 (94.0–100.0)	33.2 (4.3–254.0)	0.6 (0.5–0.9)
- Any of the 5 signs present	78.9 (54.4-93.9)	80.2 (70.6-87.8)	4.0 (2.5-6.4)	0.3 (0.1-0.6)

Table 4. Diagnostic performance of CT signs in the laterality-insensitive analyses

CECT, contrast-enhanced computed tomography; CI, confidence interval; CT, computed tomography; NCCT, non-contrast computed tomography *Substitution formula was used to calculate the positive likelihood ratio, as specificity was 100%.

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Unilateral or bilateral finding on NCCT (n = 473)				
- Perirenal fat stranding	60.7 (47.3–72.9)	75.7 (71.2–79.7)	2.5 (1.9–3.3)	0.5 (0.4–0.7)
- Pelvicalyceal wall thickening	37.7 (25.6–51.0)	90.5 (87.3–93.2)	4.0 (2.6–6.2)	0.7 (0.6–0.8)
- Enlargement of kidney	14.8 (7.0–26.2)	98.1 (96.2–99.2)	7.6 (3.1-18.9)	0.9 (0.8–1.0)
- Thickening of Gerota's fascia	8.2 (2.7–18.1)	98.8 (97.2–99.6)	6.8 (2.0–22.7)	0.9 (0.9–1.0)
- Any of the 4 signs present	68.9 (55.7-80.1)	69.9 (65.2-74.3)	2.29 (1.8-2.9)	0.4 (0.3-0.7)
Unilateral or bilateral finding on CECT (n = 101)				
- Perirenal fat stranding	77.8 (52.4–93.6)	73.6 (63.3–82.3)	3.0 (1.9–4.5)	0.3 (0.1–0.7)
- Pelvicalyceal wall thickening or enhancement	68.4 (43.4–87.4)	76.9 (66.9–85.1)	3.0 (1.8–4.8)	0.4 (0.2–0.8)
- Enlargement of kidney	15.8 (3.4–39.6)	97.8 (92.3–99.7)	7.2 (1.3–40.1)	0.9 (0.7–1.1)
- Thickening of Gerota's fascia	11.1 (1.4–34.7)	100.0 (96.0–100.0)	24.2 (1.2-484.0)*	0.9 (0.8–1.0)
- Decreased attenuation	47.4 (24.4–71.1)	97.8 (92.2–99.7)	21.3 (5.0–90.9)	0.5 (0.4–0.8)
- Any of the 5 signs present	94.1 (71.3-99.9)	3.6 (0.7-10.1)	1.0 (0.8-1.1)	2.0 (0.3-12.8)

Figure captions

Fig. 1 Study population

CT = computed tomography; CECT = contrast-enhanced computed tomography; NCCT = non-contrast computed tomography.

*There are some overlaps among three categories.