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Serum procalcitonin predicts development of acute kidney injury in patients with suspected infection

Abstract

Background: Procalcitonin (PCT) is an early, sensitive, and accurate marker for diagnosing infection and sepsis. As sepsis and septic shock are dominant causes of acute kidney injury (AKI), we investigated whether PCT is an early predictor of AKI in patients with symptoms of infection.

Methods: Between January 2011 and October 2011, 1361 inpatients in West China Hospital who displayed infection symptoms were enrolled in our study. Levels of PCT, serum amyloid A (SAA), C-reactive protein (CRP), interleukin-6 (IL-6), and white blood cell count (WBC) were determined and participants' renal function was monitored for 3 consecutive days.

Results: The rate of AKI occurrence 3 days after enrollment was 14.6%. Higher PCT levels were correlated with higher AKI occurrence rates and higher levels of serum urea, creatinine, and cystatin C ($p<0.05$). The area under the receiver-operating characteristic (ROC) curve (AUC) for PCT was 0.823, making it more predictive ($p<0.0001$) than SAA, CRP, IL-6, or WBC. The cut-off value of 1.575 ng/mL for PCT had the highest validity for predicting AKI in patients with infection symptoms. The sensitivity, specificity, negative-predictive value (NPV), positive-predictive value (PPV), negative-likelihood ratio (LR-), and positive-likelihood ratio (LR+) for this cut-off value were 61.7%, 84.6%, 93.6%, 37.5%, 0.415, and 4.98, respectively.

Conclusions: PCT can be used as a predictive marker for sepsis-induced acute kidney injury in patients with symptoms of infection.

Keywords: acute kidney injury; procalcitonin; receiver-operating characteristic curve.

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Introduction

Acute kidney injury (AKI) is an increasingly common clinical problem in hospitalized patients that independently predicts poor outcome [1–7]. Although AKI is often a complex multifactorial syndrome, sepsis and septic shock are its dominant causes [8]. Sepsis-induced acute kidney injury (S-AKI) increases patient morbidity, predicts higher mortality, affects multiple organ functions, is associated with an increased length of stay in the intensive care unit (ICU), and hence consumes considerable healthcare resources [6]. Considering that AKI affects approximately 10%–60% of all septic patients [5, 9, 10, 11], the importance of understanding the pathogenesis of S-AKI, as well as of sepsis and AKI as a clinical and public health issue, is clear. However, early and timely diagnosis of S-AKI is still difficult, and there is no clearly superior marker for predicting S-AKI.

In recent years, various laboratory parameters, such as differential blood count or acute phase reactants like C-reactive protein (CRP), serum amyloid A (SAA), procalcitonin (PCT), or interleukin-6 (IL6), have been put forward as potential markers for early identification of infection. PCT, a 116 amino acid propeptide of calcitonin with a long half-life in blood, has proven to be an early, sensitive, and accurate marker for identifying bacterial infection and judging the severity of infections and sepsis [12]. In light of this, we asked whether PCT might also be useful for AKI prediction in patients suspected of having infections. The aims of this study were: 1) determine whether PCT measurement is useful for early prediction of AKI in patients with infection symptoms; and 2) compare PCT with other inflammation markers for AKI prediction.

Materials and methods

Between January 2011 and October 2011, all inpatients in West China Hospital, Sichuan University who were clinically suspected of having an infection by three approved internists were included in this study. Diagnoses were based on clinical manifestations, laboratory tests and imaging of the patients, such as labile temperature (armpit temperature <36.5°C or >38.0°C); feeding intolerance, defined as vomiting or gastric residuals ≥20% of the amount fed; white blood cells (WBC) in a normally sterile body fluid (e.g., polymorphonuclear count ≥250/mm^3 in ascitic fluid); perforated viscus; radiographic evidence of pneumonia associated with purulent sputum; or a syndrome associated with a high probability of infection (e.g., ascending cholangitis). Proven bacterial infection was defined as positive microbiological results, while unproven infection refers to infection suspected by three internists but with negative microbiological results.

Signed informed consents were obtained from all participants or their guardians, and the study was approved by the Ethics Committee of West China Hospital, Sichuan University.

Exclusion criteria were: 1) absence of information on baseline renal function (i.e., available outpatient results from within 1 month before hospitalization); 2) chronic kidney disease, stage 1–5 [13]; 3) abnormal renal function at admission (a new kidney injury); or 4) age younger than 18 years old. The diagnostic criteria of AKI were an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h; an increase in serum creatinine to ≥1.5 times baseline which is known or presumed to have occurred within the prior 7 days; or a urine volume <0.5 mL/kg/h for 6 h, as specified in the KDIGO Guideline [14]. Figure 1 shows how many patients were screened and how many excluded.

All clinical manifestations were meticulously documented at the time of patient enrollment, and blood samples were taken immediately. Serum samples for PCT, SAA, CRP, and IL-6 tests were obtained from unanticoagulated tubes by means of centrifugation at 1006.2 *g* for 15 min. Whole blood from EDTA-anticoagulated tubes was used to test for WBC. PCT and IL-6 were determined via E170 (Roche Diagnostics, Germany), SAA via BNα (Siemens, Germany), and CRP via Immage 800 (Beckman Coulter, USA). WBC was tested on an XE 2100 Auto Hematology Analyzer (Sysmex Corporation, Japan). The treating clinicians were aware of the results of all measurements.

Serum samples of all included patients were collected on 3 consecutive days for routine renal function tests (urea, creatinine, and cystatin C). The renal function indicators were tested on a Modular-P800 Auto Biochemical Analyzer (Roche Diagnostics, Germany).

Frequency of symptoms and laboratory parameters were compared by the χ^2-test, Wilcoxon rank sum test, ANOVA test, or Student's t-test. Two-sided statistical tests were used for all analyses; $p<0.05$ was considered significant. All statistical computations were performed by SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Receiver-operating characteristic curves (ROC) for PCT, SAA, CRP, IL-6, and WBC were plotted by SigmaPlot 10.0 (Systat Software Inc., CA, USA). Their AUCs were compared using the Mann-Whitney U-test [$U=(AUC_1-AUC_2)/(\text{Standard Error}_{AUC1}{}^2+\text{Standard Error}_{AUC2}{}^2)^{\wedge(1/2)}$, AUC and Standard Error$_{AUC}$ were obtained using SPSS 13.0]. The sensitivity and specificity of PCT were calculated by SPSS 13.0. The PCT cut-off value was obtained from the ROC according to the principle of maximizing Youden's index (sensitivity+specificity–1). The positive-predictive value (PPV), negative-predictive value (NPV), positive-likelihood ratio (LR+), and negative-likelihood ratio (LR-) were also computed.

Results

Patient characteristics

Of the patients, 846 were male and 515 female (Table 1). The median age of all patients was 58 years (range 18–99). Seven hundred and sixty-six patients (56.3% of

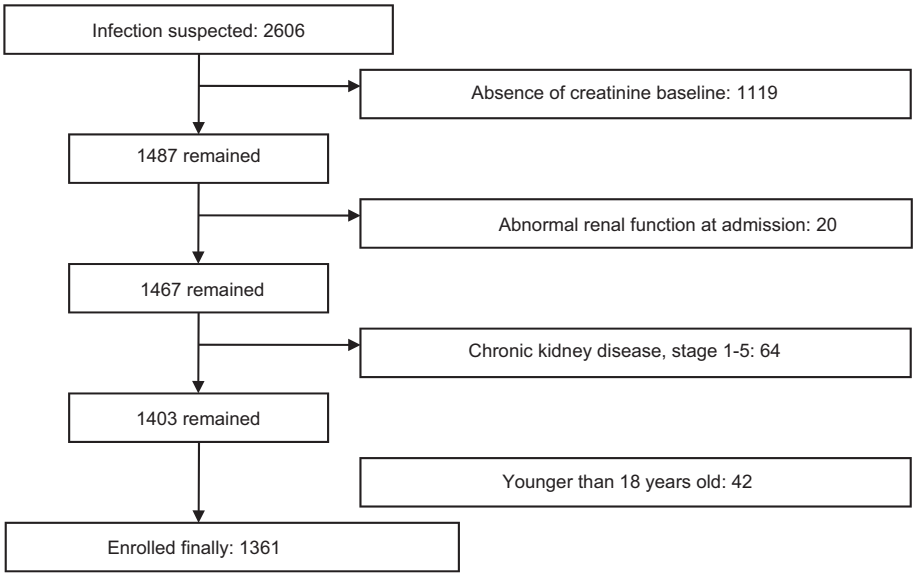

Figure 1 Flow diagram of inclusion and exclusion.

Table 1 Clinical characteristics of enrolled patients.

Total number	1361
Sex, male/female	846/515
Median age, years (range)	58 (18–99)
Proven bacterial infection	766
Pulmonary, n/%	478/62.4
Intra-abdominal, n/%	97/12.7
Gastrointestinal tract, n/%	59/7.7
Skin or soft tissue, n/%	54/7.0
Biliary tract, n/%	34/4.4
Urinary tract, n/%	9/1.2
Articular cavity, n/%	6/0.7
Other, n/%	29/3.8
Positive blood culture	23
Unproven infection	595
Renal function baseline	
Urea, μmol/L (mean±SD)	6.02±3.56
Creatinine, μmol/L (mean±SD)	68.06±21.94
Cystatin C, mg/L (mean±SD)	1.18±0.44

the cohort) had positive microbiology results, of whom only 23 had positive blood cultures. The majority of the patients presented with pulmonary infection (62.4%) or intra-abdominal infection (12.7%). Average baseline serum urea, creatinine, and cystatin C of enrolled patients were (6.02±3.56) μmol/L, (68.06±21.94) μmol/L, and (1.18±0.44) mg/L, respectively.

PCT, SAA, CRP, IL-6 levels and WBC of AKI and non-AKI group

A total of 199 patients (14.6% of the cohort, the AKI group) were diagnosed with AKI during the 3-day follow-up, while the others (85.4% of the cohort, the non-AKI group) were not. The PCT, SAA, CRP, and IL-6 levels and WBC of the AKI group at the time of enrollment were significantly ($p<0.05$) higher than those of the non-AKI group (Table 2).

AKI occurrence and renal function at different PCT levels

Patients were divided into four groups by PCT level (ng/mL): $PCT \leq 0.5$, $0.5<PCT \leq 2$, $2<PCT \leq 10$, and $PCT>10$. The rates of AKI occurrence among the groups were significantly different ($p<0.0001$), and higher PCT levels were correlated with higher AKI occurrence (Table 3). Renal function indicators, including serum urea, creatinine, and cyastatin C levels, were also significantly different among the four groups ($p<0.05$) (Table 4), and were positively correlated with PCT levels. A log transformation of creatinine levels was made to fit to normality to enable a parametric test (Table 4).

PCT, SAA, CRP, IL-6, and WBC for predicting AKI

AUC [95% confidence interval (CI), p] of PCT, IL-6, CRP, WBC and SAA for predicting AKI in patients with suspected infection were 0.830 (0.796–0.863, $p<0.0001$ against the AUC 0.5 line), 0.695 (0.653–0.738, $p<0.0001$ against the AUC 0.5 line), 0.647 (0.605–0.689, $p<0.0001$ against the AUC 0.5 line), 0.607 (0.564–0.650, $p<0.0001$ against the AUC 0.5 line), and 0.549 (0.507–0.591, $p=0.0270$ against the AUC 0.5 line), respectively (Figure 2). Among them, PCT was clearly ($p<0.0001$) superior to the others (Table 5). According to the principle of maximizing Youden's Index (sensitivity+specificity-1), the cut-off value of 1.575 ng/mL of PCT had the highest validity in predicting AKI in these patients. For this cut-off value the sensitivity was 63.82%, specificity 87.18%, NPV 93.37%, PPV 45.97%, LR- 0.415, and LR+4.98.

Table 2 Procalcitonin, serum amyloid A, C-reactive protein, interleukin-6 levels and white blood cell count of AKI and non-AKI group.

	AKI group	Non-AKI group	p-Value
	Median (interquartiles range)	Median (interquartiles range)	
PCT, ng/mL	4.27 (0.54, 26.64)	0.16 (0.06, 0.62)	$p<0.0001^a$
SAA, mg/L	244 (77.90, 563.00)	200 (44.83, 523.00)	$p=0.0270^a$
CRP, mg/L	93.5 (36.40, 181.00)	50.00 (14.35, 108.00)	$p<0.0001^a$
IL-6, pg/mL	104.6 (31.16, 448.40)	32.64 (12.52, 89.09)	$p<0.0001^a$
WBC, 10^9/L	10.82 (6.95, 14.74)	8.12 (5.80, 12.23)	$p<0.0001^a$

AKI, acute renal injury; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; SAA, serum amyloid A; WBC, white blood cell count. Data were compared by Wilcoxon rank sum test. $^a p<0.05$.

Table 3 Acute renal injury occurrence for different procalcitonin levels.

PCT level, ng/L	Patient number	AKI, n/%	p-Value
PCT≤0.5	882	47/5.3	
0.5<PCT≤2	233	36/15.5	
2<PCT≤10	132	37/28.0	
PCT>10	114	79/69.3	
Total	1361	199/14.6	p=0.0000[a]

AKI, acute renal injury; PCT, procalcitonin. Data were compared by the χ^2-test. [a]p<0.05.

Discussion

To the best of our knowledge, this is the first study to assess the clinical utility of PCT, SAA, CRP, IL-6, and WBC in predicting AKI in patients with symptoms of infection. Our results indicate that PCT level alone is a highly accurate predictor of AKI in such patients, with an ideal cut-off value of 1.575 ng/mL.

Several observational studies of septic critically ill patients have found that AKI occurred in between 11% and 64% of the patients [5, 9–11, 15–17]. In our study, 14.6% of the patients with infection symptoms developed AKI. However, as chronic kidney disease is a widely known risk factor for AKI [18], our exclusion of patients with chronic kidney disease and those without baseline creatinine likely lowered the AKI incidence rate in this study.

In the present study, we also found that patients with infection symptoms who developed AKI, most of whom had negative microbiology results, displayed significantly elevated PCT, SAA, CRP, and IL-6 levels and WBC counts at enrollment, which preceded the rise in serum urea, creatinine, and cystatin C levels on the 3 consecutive monitoring days. Several studies have similarly reported significantly elevated levels of serum acute phase reactants, especially PCT, in patients with sepsis compared to those without, with higher sensitivity and less time cost for the PCT test than for microbiological determination [19–28]. Furthermore, some of these studies found that elevated PCT also was associated with sepsis-induced organ dysfunction, including renal injury [23, 27]. Our study also found that AKI occurrence, serum creatinine, and cystatin C levels were positively correlated with PCT levels. As sepsis and septic shock are AKI's dominant causes [8], risk identification, timely recognition, and early diagnosis of infection and sepsis are vital, as they may directly impact patient outcomes. An early definite diagnosis of sepsis suggests high risk of AKI. Furthermore, the more severe the sepsis, the greater the potential harm to the kidneys. Therefore, patients with higher levels of PCT experience more severe damage to their renal function. Generally speaking, PCT can be considered a marker of severity of infection, which correlates with severity of AKI.

Our ROC analysis determined that among PCT, SAA, CRP, IL-6, and WBC, PCT had the best accuracy in predicting AKI in patients with suspected infection. The reason for PCT's utility as a predictive marker for AKI is an important consideration. Previous studies have demonstrated that PCT is a useful and accurate biomarker for infection and sepsis and is more useful than other common inflammatory markers because elevated IL-6, WBC, CRP and SAA can also be caused by inflammation not linked to infection [20, 22, 27, 29]. In addition, the kinetics of PCT, IL-6, WBC, CRP, and SAA differ substantially from one another [30]. Their serum levels are associated with their peak time of release into the blood and their half-lives. Any of these factors can affect their clinical utility. After an inflammatory stimulus, PCT is detectable sooner than the other inflammatory markers – as soon as 3–4 h, peaking at 14–24 h after the stimulus. After removal of the inflammatory stimulus, PCT half-life ranges from 22 to 35 h, the longest of any inflammatory marker [30, 31]. Rapid and sustained

Table 4 Renal function of patients with different procalcitonin levels.

Group	PCT level, ng/L				p-Value
	PCT≤0.5 (n=908)	0.5<PCT≤2 (n=241)	2<PCT≤10 (n=136)	PCT>10 (n=118)	
Urea, μmol/L (mean±SD)	5.92±3.66	8.57±6.27	11.59±9.62	16.37±10.25	p<0.001[a]
Creatinine, μmol/L [mean(range)]	65.85 (11.70–823.5)	72.30 (18.00–506.00)	83.10 (36.10–649.80)	143.9 (24.00–933.00)	
Ln (creatinine), μmol/L (mean±SD)	4.22±0.42	4.35±0.60	4.61±0.66	5.04±0.78	p<0.001[a]
Cystatin C, mg/L (mean±SD)	1.22±0.56	1.57±1.07	1.82±1.07	2.35±1.36	p<0.001[a]

PCT, procalcitonin. Data were based on peak urea, creatinine and cystatin C levels over the 3 consecutive monitoring days and compared by ANOVA test. [a]p<0.05.

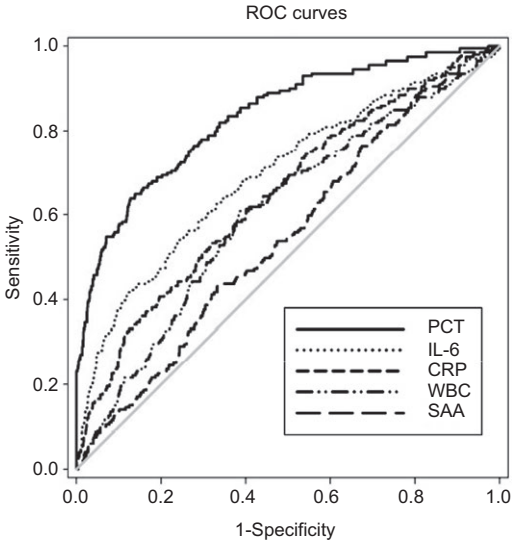

Figure 2 ROC curves of procalcitonin, interleukin-6, C-reactive protein, white blood cell count, and serum amyloid A for predicting acute kidney injury.
CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; SAA, serum amyloid A; WBC, white blood cell count.

up-regulation of serum PCT occurs early in sepsis, making it a useful marker for the presence and severity of infection. Therefore, the high predictive power of PCT for AKI in patients with infection symptoms is not surprising.

With a cut-off value of 1.575 ng/mL, PCT was found to have a specificity of 87.18% for predicting infection, and could help doctors decide whether to enhance antimicrobial treatment to prevent AKI. However, our results suggest that PCT has relatively low sensitivity and PPV for predicting AKI. This may be the result of our excluding patients at high risk of AKI, such as those with chronic kidney disease. It should also be noted that our findings are based on a single measurement. Thus, it is possible that sequential combined testing of CRP, IL-6, WBC, and PCT might improve their diagnostic value.

In recent years, a variety of kidney injury biomarkers have been studied, including neutrophil gelatinase associated lipocalin (NGAL), cystatin-C (Cys-C), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), monocyte chemotactic peptide-1 (MCP-1), netrin-1, and liver-type fatty acid binding proteins (L-FABP). Among these, NGAL, which is up-regulated in kidney tubules soon after ischemic, toxic, septic, autoimmune, and post-transplant injury, has globally shown the best promise for AKI detection over a growing spectrum of disorders [32–38]. Although plasma NGAL is freely filtered by the glomerulus, it is largely reabsorbed in the proximal tubules by efficient megalin-dependent endocytosis [37]. Thus, any urinary excretion of NGAL indicates a concomitant proximal renal tubular injury that precludes NGAL reabsorption and/or increases de novo NGAL synthesis. A recent study suggests that urinary NGAL may be a more sensitive, specific, and reliable biomarker than serum CRP and PCT in the diagnosis of late onset sepsis in preterm newborns [39]. Therefore, NGAL may also be better than PCT for predicting AKI in patients with infection symptoms. We plan to address this question in future studies.

Conclusions

In conclusion, PCT is a more useful predictive marker than IL-6, CRP, WBC, or SAA for AKI in patients suspected of having infections. PCT can also be used as a biomarker to guide timely antibiotic therapy in patients with infection or sepsis, thus preventing AKI.

Table 5 Difference of the area under the ROC curve for procalcitonin, interleukin-6, C-reactive protein, white blood cell count and serum amyloid A for predicting acute kidney injury.

	PCT	IL-6	CRP	WBC	SAA
PCT	/	0.134 (0.081, 0.188) p<0.0001[a]	0.183 (0.129, 0.237) p<0.0001[a]	0.222 (0.168, 0.277) p<0.0001[a]	0.281 (0.227, 0.334) p<0.0001[a]
IL-6	/	/	0.048 (−0.012, 0.108) p=0.1134	0.088 (0.028, 0.148) p=0.0042[a]	0.146 (0.086, 0.206) p<0.0001[a]
CRP	/	/	/	0.040 (−0.021, 0.100) p=0.1967	0.098 (0.038, 0.158) p=0.0013[a]
WBC	/	/	/	/	0.058 (−0.002, 0.118) p=0.0585
SAA	/	/	/	/	/

CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; SAA, serum amyloid A; WBC, white blood cell count. Data were shown as mean area difference (95% confidence interval) between two indicators. [a]p<0.05 by Mann-Whitney U-test.

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Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research funding played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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