Association between admission serum procalcitonin and the occurrence of acute kidney injury in patients with septic shock: A retrospective cohort study

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Abstract
Background: Procalcitonin (PCT) is an effective and sensitive diagnostic biomarker that can facilitate the early detection of infection and septicemia, but whether it can similarly be utilized to predict the development of acute kidney injury (AKI) in patients suffering from septic shock remains to be established. Herein, the relationship between serum PCT at admission and the onset of AKI in septic shock patients was thus evaluated following adjustment for other potential covariates.

Methods: This was a retrospective cohort study of 303 septic shock patients treated in a Chinese hospital between May 2015 and May 2019. All patients in whom PCT levels were measured on admission and who did not exhibit AKI or chronic kidney disease at the time of admission were assessed for AKI development within one week following intensive care unit (ICU) admission as per the KDIGO criteria. The relationship between serum PCT at admission and AKI incidence was then assessed for these patients.

Results: These 303 patients were an average of 64 years old, and were 59.7% male. Of these patients, 50.5% developed AKI within the first 7 days following ICU admission. A dully-adjusted binary logistic regression analysis revealed PCT levels at admission to be associated with AKI following adjustment for potential confounding factors (odds ratio (OR) = 1.01, 95%CI (1.01,1.02), p = 0.0007). Receiver operating characteristic curve analysis further indicated that a PCT cutoff

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level of 52.59 ng/ml at admission was able to predict the incidence of AKI with respective sensitivity and specificity values of 50% and 84%. Interaction analysis revealed no significant interactive relationship between PCT and AKI, suggesting that serum PCT levels represent an early predictor of AKI incidence in septic shock patients.

**Conclusions:** Serum PCT at the time of admission can be used as a predictor of AKI in patients suffering from septic shock.

**Keywords**
Septic shock, procalcitonin, acute kidney injury, retrospective cohort study

**Introduction**

Acute kidney injury (AKI) develops in upwards of 60% of patients admitted to intensive care unit (ICU), and the overall incidence of AKI is rising, with severe sepsis and septic shock being the two primary causes of this serious condition. AKI is associated with a marked increase in mortality rates among patients suffering from septic shock, and patients that survive are at a significantly elevated risk of developing chronic kidney disease (CKD), which is itself associated with significant morbidity and mortality. Sepsis-associated AKI is a complex syndrome with a multifactorial etiology that can contribute to the rapid onset of renal damage and associated pathophysiology. No pharmacological agents have been developed to date capable of preventing or treating AKI, with renal replacement therapy (RRT) remaining the only definitive treatment available for the complications of this debilitating condition. It is thus essential that effective approaches to identifying patients at a high risk of developing AKI be developed in order to guide intervention, treatment, and monitoring strategies.

Serum biomarkers are of great value as tools for predicting and monitoring disease progression in individuals suffering from sepsis and septic shock. Procalcitonin (PCT) is a polypeptide precursor of calcitonin that has been successfully utilized as a diagnostic biomarker capable of sepsis, enabling researchers and clinicians to accurately and sensitively detect infection and associated septicemia in its early stages and to gauge sepsis patient prognosis. Whether PCT levels can also be used to assess the risk of AKI in septic shock patients, however, remains controversial. The present study was thus designed to determine whether serum PCT levels are associated with the risk of subsequent AKI onset in septic shock patients following adjustment for other covariates.

**Materials and methods**

**Study population**

This was a single-center retrospective analysis of patients >18 years old at the Affiliated Hospital of Jining Medical University suffering from septic shock between May 2015 and May 2019. Septic shock patients were identified as those patients with septicemia that required vasopressors to maintain a MAP of ≥65 mmHg and that had a serum lactate level of >2 mmol/l (18 mg/dl) despite adequate volume resuscitation.
Patients were excluded from this study if they had CKD (estimated glomerular filtration rate <30 ml/min/1.73 m²), were undergoing maintenance hemodialysis or peritoneal dialysis, had been diagnosed with malignant tumors, did not have a complete medical history, or did not undergo PCT evaluation at baseline. AKI was defined as per the Kidney Disease Improving Global Outcomes (KDIGO) consensus criteria as an increase

**Figure 1.** Flow diagram of inclusion and exclusion.
in serum creatinine levels by 0.3 mg/dl (26.5 μmol/l) within 48 h or an increase by a minimum of 1.5-fold above baseline within 7 days, or a urine volume of <0.5 ml/kg/h for >6 h.\textsuperscript{21} Patient inclusion and exclusion in the present study are detailed in Figure 1.

Patient follow-up was conducted until the time of hospital discharge in order to evaluate the onset of AKI within 7 days and the length of ICU stay. The Ethics Committee of the Affiliated Hospital of Jining Medical University approved the present study (2020C018). The requirement for informed consent was waived owing to the anonymous and retrospective nature of this study.

**Data collection**

All patient demographic and laboratory data were retrieved from our hospital electronic medical system. Collected demographic data included demographic (age, sex, BMI, smoking, and drinking history), disease severity (APACHE II, SOFA score, norepinephrine max, mechanical ventilation, lactate), vital signs, preexisting conditions, source of infection, laboratory inspection, and ICU mortality. PCT levels were measured with an E170 instrument (Roche Diagnostics, Germany), while indicators of renal function were assessed with a Modular-P800 Auto Biochemical Analyzer (Roche Diagnostics, Germany).

**Statistical analysis**

All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software version 13.\textsuperscript{22} Categorical data are given as frequencies (percentages), while continuous data are given as means ± standard deviation (SD). Stratified analyses, interaction tests, and covariate screening were conducted, and the relationship between PCT concentrations and AKI was assessed via binary logistic regression analyses. For this analysis, AKI was treated as a binary variable, while PCT was treated as a continuous variable grouped into the following categories: <0.5 ng/ml; ≥0.5 ng/ml but <2.0 ng/ml; ≥2.0 ng/ml but <10 ng/ml; and ≥10 ng/ml. Data were reported as odds ratios (ORs) and 95% confidence intervals (CIs) following adjustment for covariates including medical history, age, sex, body mass index (BMI) vital signs, site of infection, and SOFA scores. Interaction and stratified analyses were also conducted according to patient age, sex, lactate levels, SOFA scores, BMI, smoking history, and drinking history. A two-tailed \(p<0.05\) was the significance threshold for this study.

**Results**

**Patient characteristics**

In total, 400 patients suffering from septic shock were admitted to the Affiliated Hospital of Jining Medical University China from May 2015 to May 2019, of whom 303 were eligible for inclusion in the present study (Figure 1). The demographics and characteristics of these patients at the time of admission are compiled in Table 1. Of these patients, 181
Table 1. Baseline characteristics of participants.\textsuperscript{a}

| Variable                        | All patients (N = 303) | No AKI (N = 150) | AKI (N = 153) | p-value |
|---------------------------------|------------------------|------------------|---------------|---------|
| Demographic                     |                        |                  |               |         |
| age (years)                     | 64.36 ± 15.62          | 63.93 ± 15.76    | 64.78 ± 15.51 | 0.636   |
| Men, N (%)                      | 181 (59.74%)           | 88 (58.67%)      | 93 (60.78%)   | 0.707   |
| BMI (kg/m\(^2\))               | 22.81 ± 4.37           | 22.42 ± 4.18     | 23.20 ± 4.53  | 0.119   |
| Drinking, N (%)                 | 203 (67.00%)           | 108 (72.00%)     | 95 (62.09%)   | 0.067   |
| Smoking, N (%)                  | 101 (34.44%)           | 42 (28.00%)      | 59 (38.82%)   | 0.046   |
| Disease severity                |                        |                  |               |         |
| APACHE II score                 | 20.82 ± 7.69           | 18.71 ± 7.30     | 22.90 ± 7.51  | <0.001  |
| SOFA score                      | 9.15 ± 3.57            | 8.19 ± 3.38      | 10.09 ± 3.50  | <0.001  |
| Norepinephrine max (µg/kg/min)  | 0.50 ± 0.58            | 0.38 ± 0.39      | 0.62 ± 0.70   | <0.001  |
| Mechanical ventilation, N (%)   | 184 (60.93%)           | 81 (54.00%)      | 103 (67.76%)  | 0.014   |
| Lactate (mmol/L)                | 4.53 ± 3.36            | 3.81 ± 2.81      | 5.23 ± 3.70   | <0.001  |
| Vital signs                     |                        |                  |               |         |
| Mean arterial pressure, (mmHg)  | 73.39 ± 15.85          | 73.69 ± 15.48    | 73.10 ± 16.25 | 0.747   |
| Heart rate (/min)               | 113.95 ± 22.50         | 111.54 ± 20.93   | 116.31 ± 23.77| 0.024   |
| Body temperature (°C)           | 37.31 ± 2.82           | 37.26 ± 1.05     | 37.13 ± 1.62  | 0.969   |
| PAO2/FIO2 (mmHg)                | 207.83 ± 77.56         | 208.19 ± 76.49   | 207.48 ± 78.85| 0.937   |
| Pre-existing conditions, N (%)  |                        |                  |               |         |
| Hypertension                    | 96 (31.68%)            | 44 (29.33%)      | 52 (33.99%)   | 0.384   |
| Coronary heart                  | 64 (21.12%)            | 33 (22.00%)      | 31 (20.26%)   | 0.711   |
| Diabetes                        | 63 (20.79%)            | 34 (22.67%)      | 29 (18.95%)   | 0.426   |
| Stroke                          | 39 (12.87%)            | 24 (16.00%)      | 15 (9.80%)    | 0.107   |
| Arrhythmia                      | 16 (5.28%)             | 6 (4.00%)        | 10 (6.54%)    | 0.442   |
| COPD                            | 14 (4.62%)             | 6 (4.00%)        | 8 (5.23%)     | 0.786   |
| Source of infection, N (%)      |                        |                  |               |         |
| Lung                            | 145 (47.85%)           | 79 (52.67%)      | 66 (43.14%)   | 0.097   |
| Abdominal                      | 118 (38.94%)           | 49 (32.67%)      | 69 (45.10%)   | 0.027   |
| Urinary tract                   | 17 (5.61%)             | 9 (6.00%)        | 8 (5.23%)     | 0.808   |
| Skin or soft tissue             | 12 (3.96%)             | 5 (3.33%)        | 7 (4.58%)     | 0.770   |
| Other                           | 11 (3.63%)             | 7 (4.67%)        | 4 (2.61%)     | 0.375   |
| Laboratory inspection           |                        |                  |               |         |
| WBC (10\(^3\)/mm\(^3\))       | 15.05 ± 11.98          | 13.06 ± 9.13     | 17.00 ± 13.98 | 0.004   |
| PCT (ng/ml)                     | 36.95 (0.01–22.60)     | 41.01 (0.04–115.00) | <0.001 |
| CRP (mg/dl)                     | 127.51 ± 76.25         | 118.52 ± 78.49   | 136.39 ± 73.16| 0.028   |
| Creatinine (mg/dl)              | 131.25 ± 83.06         | 89.06 ± 44.73    | 172.61 ± 90.93| <0.001  |
| Urea nitrogen (mg/dl)           | 12.52 ± 7.98           | 9.47 ± 5.33      | 15.51 ± 8.98  | <0.001  |
| Clinical outcome                |                        |                  |               |         |
| ICU time (day)                  | 8.27 ± 10.66           | 9.60 ± 13.22     | 6.97 ± 7.13   | 0.032   |
| ICU mortality, %                | 166 (54.79%)           | 56 (37.33%)      | 110 (71.90%)  | <0.001  |
| 28-day mortality, %             | 179 (59.08%)           | 64 (42.67%)      | 115 (75.16%)  | <0.001  |

\textsuperscript{a}Plus-minus values are means ± SD. \textit{p} values were calculated by comparing characteristics between two groups.

BMI: body mass index (calculated as weight in kilograms divided by height in meters squared); SOFA score: Sequential Organ Failure Assessment score; APACHE II score: Acute Physiology and Chronic Health Evaluation II score; COPD: chronic obstructive pulmonary disease; WBC: white blood cell count; PCT: procalcitonin; CRP: C-reactive protein; ICU: intensive care unit.
were male and 122 were female, with a median age of 64 years (range: 18–95). Of these patients, 50.5% developed AKI within 7 days of ICU admission. Most patients presented with either pulmonary infection (47.85%) or intra-abdominal infection (38.94%), and the mean SOFA score for this population was 9.15 ± 3.57. The median PCT level at admission in these patients was 15.74 ng/ml, and the PCT levels were significantly higher in patients that did not develop AKI relative to patients that did develop AKI (p < 0.001).

Serum PCT levels at admission are predictive of AKI development

As shown in Figure 2, we found that increasing PCR levels were associated with an increased risk of AKI. To accurately gauge the ability of PCT to predict AKI incidence, we next performed stratified analyses, interaction tests, and covariate screening. Any risk factor that resulted in a >10% change in the regression coefficient following introduction into the basic model was adjusted for, following screening. Significant risk factor covariates identified via this approach included age; sex; body mass index (BMI); drinking; smoking; C-reactive protein (CRP); Sequential Organ Failure Assessment (SOFA) score; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; heart rate; PAO2/FIO2; lactic (LAC); norepinephrine max; mechanical ventilation; mean arterial pressure; and body temperature. A receiver operating characteristic (ROC) curve was utilized to assess the predictive utility of serum PCT levels upon admission (Figure 3). The area under the ROC curve (AUC) for this analysis was 0.704 (95% CI 0.65–0.76, p < 0.001). The PCT cutoff value identified via this approach was 52.59 ng/ml, and was associated with respective sensitivity and specificity values of 50% and 84%. The positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value for this analysis were 3.1%, 0.6%, 76%, and 62%, respectively.

We next utilized binary logistic regression models to evaluate the prognostic relevance of serum PCT levels at admission after adjusting for confounding variables as shown in Table 2. This analysis revealed PCT to be significant associated with AKI incidence (OR = 1.01, 95% CI: 1.00–1.02) such that every 1 ng/ml increase in serum PCT was associated with a 1% increase in the odds of AKI development in septic shock patients. For patients in the fourth PCT level quartile (≥10 ng/ml), each 1 ng/ml increase in PCT level was associated with a 3.07-fold higher risk of AKI (OR = 3.83, 95% CI: 1.30, 11.25) after adjusting for multiple confounders relative to patients with a PCT level in the 1st quartile (≤0.5 ng/ml). A stratified analysis yielded results consistent with those of our multivariate logistic regression analysis with respect to the relationship between PCT and AKI incidence, while an interaction analysis detected no interactive association between PCT and AKI (Table 3 and Figure 4).

Discussion

The present analysis was designed to gauge the relationship between serum PCT levels at admission and AKI incidence in septic shock patients. We found that patients who developed AKI exhibited higher baseline PCT values and that the risk of AKI rose with increasing serum PCT levels in these patients. We found that each 1 ng/ml increase in serum PCT level was associated with a 1% higher risk of AKI development.
The global AKI-EPI study determined that AKI developed in 57.3% of critically ill patients within 7 days of ICU admission in 97 sites,\textsuperscript{23} whereas another study found this AKI incidence rate to be just 36.8%.\textsuperscript{24} Herein, we found that 50.50% of septic shock patients developed AKI within 7 days of ICU admission as determined based upon KDIGO diagnostic criteria.

In a recent meta-analysis of the prognostic relevance of PCT levels in septicemic patients, a significant difference in day-1 PCT values was detected between individuals who did and did not survive this condition ($p = 0.02$).\textsuperscript{25} As AKI is the primary cause of death among patients suffering from septic shock, these findings align well with those of the present study. Other studies have similarly found serum PCT levels to be useful for the diagnosis of infection and the prediction of AKI risk and overall prognosis in sepsis patients,\textsuperscript{25–27} whereas other studies have produced conflicting evidence suggesting that PCT is of limited prognostic utility in this pathological context.\textsuperscript{13,28} Still, other studies have shown that elevated PCT levels can impact impaired renal function, but have failed to establish the value of PCT as a prognostic biomarker for AKI.\textsuperscript{29–32} One Japanese study determined that PCT values were higher for AKI patients relative to those that did not develop this condition but found the measurement of PCT at time of admission to offer no improvements to their overall predictive model of AKI risk,\textsuperscript{33} and a separate study yielded largely identical results.\textsuperscript{34}

\textbf{Figure 2.} Smooth curve fitting of AKI in patients with septic shock and serum PCT. AKI: acute kidney injury; PCT: procalcitonin.

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Figure 3. ROC curve of PCT predicting AKI in septic shock patients. AKI: acute kidney injury; PCT: procalcitonin; ROC: receiver operating characteristic.

Table 2. Multivariable logistic regression analyses models evaluating the association between PCT and AKI.

| Variable          | Crude          | Adjust         |   |
|-------------------|----------------|----------------|---|
|                   | OR (95% CI) p  | OR (95% CI) p  |   |
| PCT ≤0.5 ng/ml    | Ref            | Ref            |   |
| 0.5 < PCT ≤2 ng/ml| 1.55 (0.68, 3.53) 0.2985 | 1.51 (0.63, 3.60) 0.3522 |   |
| 2 < PCT ≤10 ng/ml | 2.32 (1.00, 6.00) 0.0266 | 1.83 (0.84, 3.99) 0.1266 |   |
| PCT >10 ng/ml     | 2.94 (1.53, 5.62) 0.0011 | 2.33 (1.55, 4.72) <0.0183 |   |

PCT: procalcitonin; AKI: acute kidney injury; OR, odds ratio; CI: confidence interval.
Non-adjusted model adjust for: None.
Adjust model adjust for: age; sex; body mass index (BMI); drinking; smoking; C-reactive protein (CRP); Sequential Organ Failure Assessment (SOFA) score; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; heart rate; PAO2/FIO2; lactic (LAC); norepinephrine max; mechanical ventilation; mean arterial pressure; and body temperature.
Some researchers have proposed that the inherent complexity of the etiology of inflammatory AKI makes it challenging to accurately identify individual biomarkers capable of predicting the incidence of this condition or the prognosis of affected patients. In contrast, combining multiple biomarkers may represent a more objective approach to judging the prognosis of critically ill patients. As such, when assessing the relationship between PCT and AKI incidence in septic shock patients, we adjusted our regression equations for potential confounding variables including age; sex; body mass index (BMI); drinking; smoking; C-reactive protein (CRP); Sequential Organ Failure Assessment (SOFA) score; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; heart rate; PAO2/FIO2; lactic (LAC); norepinephrine max; mechanical ventilation; mean arterial pressure; and body temperature. The relationship between PCT and AKI in our hierarchical analysis was consistent with that in our multivariate logistic regression analysis, and we detected no significant correlation between PCT and AKI.

**Limitations**

There were multiple limitations to the present study. First, this was a single-center retrospective study, and it is thus susceptible to potential selection bias. Second, we utilized

**Table 3.** Stratified analysis of the association of PCT on the risk of AKI in patients with septic shock (PCT as a continuous variable).

| Subgroup     | N  | OR (95% CI)   | p value  | p for interaction |
|--------------|----|---------------|----------|-------------------|
| **Age**      |    |               |          |                   |
| <60          | 100| 1.01 (1.00, 1.02) | 0.0030   |                   |
| ≥60          | 203| 1.02 (1.01, 1.03) | <0.0001  |                   |
| **Sex**      |    |               |          |                   |
| Female       | 122| 1.02 (1.00, 1.03) | 0.0021   |                   |
| Male         | 181| 1.02 (1.00, 1.03) | <0.0001  |                   |
| **Smoking**  |    |               |          |                   |
| No           | 201| 1.02 (1.01, 1.03) | <0.0001  |                   |
| Yes          | 101| 1.02 (1.01, 1.03) | 0.0010   |                   |
| **Drinking** |    |               |          |                   |
| No           | 100| 1.02 (1.01, 1.03) | 0.0012   |                   |
| Yes          | 203| 1.02 (1.01, 1.03) | <0.0001  |                   |
| **Lactate**  |    |               |          |                   |
| Low (<4 mmol/L) | 99 | 1.01 (1.00, 1.02) | 0.0042   |                   |
| High (≥4 mmol/L) | 102| 1.02 (1.01, 1.03) | <0.0001  |                   |
| **SOFA**     |    |               |          |                   |
| Low (0–6)    | 81 | 1.02 (1.00, 1.04) | 0.0273   |                   |
| Mid (7–8)    | 116| 1.01 (1.00, 1.03) | 0.1390   |                   |
| High (9–18)  | 106| 1.03 (1.01, 1.04) | <0.0001  |                   |
| **BMI**      |    |               |          |                   |
| ≤24          | 187| 1.02 (1.01, 1.03) | <0.0001  |                   |
| >24          | 116| 1.02 (1.01, 1.03) | 0.0014   |                   |

BMI: body mass index; SOFA: Sequential Organ Failure Assessment score. Adjusted for age, sex, drinking, smoking, lactate, SOFA score, and BMI.
the KDIDO criteria to diagnose AKI, but we did not record the severity of AKI in affected patients. Further research will thus be required to evaluate the relationship between PCT and AKI progression in septic shock patients. Third, serum PCT levels in these patients were only evaluated upon admission, and no dynamic analyses of the relationship between PCT levels over time and AKI risk in septic shock patients were conducted. Future studies should thus aim to address these limitations in an effort to validate and expand upon our results.

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**Figure 4.** Stratified analysis of the association of PCT on the risk of AKI in patients with septic shock. BMI: body mass index; SOFA: Sequential Organ Failure Assessment score; LAC: lactic; AKI: acute kidney injury; PCT: procalcitonin.
Authors’ contributions
CH, QH, and LZ contributed to the study concept and design. YZ, HX, and SZ acquired the data. CH and LC analyzed the data. All authors interpreted the data. CH, LZ, and QH wrote the manuscript. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Ethics approval and consent to participate
We conducted a single-center, retrospective cohort study utilizing a population-based, ICU database of adult patients with severe sepsis or septic shock admitted to Affiliated Hospital of Jining Medical University. Data were electronically extracted from electronic health records (EHR) by data management personnel blinded to the study. The protocol was approved by the institutional review board of Affiliated Hospital of Jining Medical University (2020C018).

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