Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(5) 1–11

DOI: 10.1177/0300060520922456
journals.sagepub.com/home/imr
SAGE

Elevated PCT at ICU discharge predicts poor prognosis in patients with severe traumatic brain injury: a retrospective cohort study

Yu-rong Wang, Qing-bin Zheng, Guang-fa Wei, Li-jun Meng, Qing-ling Feng, Wen-jie Yuan, Jin-lei Ou, Wei-li Liu and Yong Li

Abstract

Purpose: Disease severity and inflammatory response status are closely related to a poor prognosis and must be assessed in patients with severe traumatic brain injury (STBI) before intensive care unit (ICU) discharge. Whether elevated serum procalcitonin (PCT) levels can predict a poor prognosis in STBI patients before ICU discharge is unclear.

Methods: This retrospective observational cohort study enrolled 199 STBI patients who were in the ICU for at least 48 hours and survived after discharge. Based on serum PCT levels at discharge, patients were divided into the high-PCT group (PCT $\geq$ 0.25 ng/mL) and the low-PCT group (PCT $<$ 0.25 ng/mL). We assessed the relationship between serum PCT levels and a poor prognosis.

Results: The high-PCT group had a higher rate of adverse outcomes compared with the low-PCT group. Multivariate logistic regression analysis showed that the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, white blood cell (WBC) count, C-reactive protein (CRP) level, and PCT level at discharge were significantly associated with adverse outcomes.

Conclusions: Elevated PCT levels at ICU discharge were associated with a poor prognosis in STBI patients. The serum PCT level as a single indicator has limited value for clinical decision-making.

Department of Critical Care Medicine, The Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China

Corresponding author:
Yong Li, Department of Critical Care Medicine, The Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China.
Email: yzliyong0304@163.com

Keywords
Procalcitonin, ICU discharge, severe traumatic brain injury, readmission, prognosis, inflammatory response, adverse outcomes

Date received: 22 October 2019; accepted: 7 April 2020

Introduction

Transferring critically ill patients from the intensive care unit (ICU) to a general ward to continue treatment is challenging and involves high-risk decision-making. This difficulty may result from the shift from an intensive treatment team to a team with fewer staff members.[1] Patients with traumatic brain injury constitute a special group in the ICU, who often require early tracheotomy to reduce the pneumonia incidence.[2] These patients often have different degrees of pulmonary, urinary tract, and bloodstream infections in the ICU.[3] Even if patients with traumatic brain injuries can be transferred out of the ICU to a general ward, they often experience inflammatory responses. The most common cause of ICU readmission is pulmonary infection.[4] Therefore, these patients must be fully evaluated before ICU discharge to reduce the need for ICU readmission because of complications such as infections, which will help to reduce the mortality rate. Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and other scores that are commonly used in ICUs can be used to assess critical patients at ICU admission, but such scores reflect an overall assessment of a patient's condition and cannot be used to assess risk factors at ICU discharge.[5,6] Identifying a valid marker to effectively assess the severity of a patient's inflammatory response state before ICU discharge will improve safety for patients with severe brain trauma who are transferred out of the ICU.

Body temperature, white blood cell (WBC) counts, C-reactive protein (CRP) levels, plasma inflammatory factor levels, and chest imaging are often used to evaluate patients' inflammatory states before ICU discharge, but these indicators have limitations. For example, body temperature and WBC counts have low specificity. Chest imaging examinations have a time lag that does not reflect the inflammatory state at the time of ICU discharge. Studies have shown that high levels of the circulating endothelial adhesion molecules E- and P-selectin are associated with sepsis in trauma patients.[7] Patients with traumatic brain injury are readmitted to the ICU because of systemic complications such as infection, and the pathogenic microorganisms are mainly bacteria. Procalcitonin (PCT) levels are highest in patients with acute bacterial infections and sepsis and are decreased in those with autoimmune-mediated inflammation or local infections, such as abscesses or empyema.[8] Studies have confirmed that for diagnosing sepsis and lower respiratory tract infections, PCT levels combined with other diagnostic tools and clinical examinations are more sensitive and specific compared with other biomarkers (including interleukin (IL)-6, CRP, and lactate).[9–11] CRP is secreted 4 to 6 hours after stimulation by bacterial infection and peaks within the following 36 hours; however, serum PCT levels can persist for long periods, providing an opportunity to track changes in the disease's clinical manifestations. Thus, PCT can be used to predict the inflammatory states of critically ill patients.

We designed a retrospective cohort study to investigate the predictive value of elevated PCT levels at the time of ICU discharge in patients with traumatic brain injury and

to identify a reliable indicator for clinical decision-making for these patients.

Methods

Subjects and protocol

This was a single-center retrospective cohort study of an adult ICU at the Affiliated Hospital of Yangzhou University (22 beds). From January 2013 to October 2018, patients who were admitted to the ICU and met the inclusion criteria for severe brain trauma (Glasgow Coma Scale [GCS] score 3 to 8 in the emergency room) were enrolled. When these patients were in stable condition and no longer needed monitoring or treatment by ICU professionals for organ failure, they were considered for transfer out of the ICU. Patients were included if they were older than 18 years, survived after discharge from the ICU, and had been hospitalized in the ICU for more than 48 hours. If a patient had been admitted to the ICU multiple times, only the first ICU admission was included in the study. Patients were excluded if they had a history of neurological disease or mental illness, did not have their PCT levels monitored upon discharge from the ICU, were discharged from the ICU and subsequently treated at another hospital, or were lost to follow-up. The Ethics Committee at the Affiliated Hospital of Yangzhou University approved this study. Informed consent was obtained from all subjects or their relatives before enrollment.

Data collection

After the patients were enrolled, demographic and baseline characteristics, including age, gender, and APACHE II, SOFA, and GCS scores, were recorded. Each patient's surgical status, mechanical ventilation time, receipt of continuous renal replacement therapy (CRRT), and length of ICU stay were recorded. Indicators that were analyzed for their predictive value for adverse outcomes included APACHE II, SOFA, and GCS scores, PCT and CRP levels, and body temperature.

The patients were divided into two groups based on the PCT levels that were measured at the time of ICU discharge: the high-PCT group had PCT levels $\geq$0.25 ng/mL and the low-PCT group had PCT levels $<$0.25 ng/mL.[12] Generally, when the PCT level is less than 0.25 ng/mL and no systemic inflammatory reaction or infection is present, antibiotic treatment is not recommended. PCT $>$0.25 ng/mL may indicate infection, and antimicrobial treatment may be initiated if additional evidence supports infection. Moreover, elevated PCT also indicates organ function disorders. The primary adverse outcomes that were evaluated in this study included readmission to the ICU and death in the general ward after discharge from the ICU. Patients who had planned readmissions to the ICU and patients who were discharged from the ICU and were no longer being actively treated and died on the general ward were excluded.

Blood sampling and measurements

Serum PCT levels were measured the morning after ICU admission. During the ICU stay, the number of PCT measurements was determined based on the patient's condition. Serum PCT levels were routinely tested before discharge from the ICU. PCT concentrations were measured in serum samples using an immunofluorescence assay (Getein Biotech, Inc., Nanjing, China). WBC counts and CRP levels were immediately measured in the clinical chemistry laboratory of the Affiliated Hospital of Yangzhou University.

Statistical analysis

All analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as the mean ± standard deviation (SD) or as the median and interquartile range (IQR), based on testing for a normal distribution using the Kolmogorov–Smirnov test. Categorical variables are presented as percentages (%). For two-group comparisons, the independent samples *t*-test was used for normally distributed data, and the Mann–Whitney *U*-test was used for non-normally distributed data. To compare data from three or more patient groups, a one-way analysis of variance (ANOVA) was used, and when indicated, the Student–Newman–Keuls method was used as a post hoc test. Multivariate logistic regression was used to identify variables independently associated with adverse outcomes. All tests were two-tailed, and $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics and patient outcomes

There were 199 patients with severe brain trauma who were admitted to the ICU at our hospital and who had an ICU length of stay (LOS) >48 hours (Figure 1). Ninety-six patients with severe brain trauma were enrolled into the study, with an average age of 53.73 ± 16.21 years, a GCS score of 6.24 ± 1.84, an APACHE II score of 18.86 ± 6.25, a SOFA score of 8.70 ± 2.56, and serum PCT of 1.97 ± 1.09 ng/mL, and the overall mortality was 26% (n = 18). Twenty-seven patients had serum PCT levels ≥0.25 ng/mL upon ICU discharge. Sixty-nine patients had serum PCT levels <0.25 ng/mL. Baseline characteristics did not differ significantly between the two groups (Table 1).

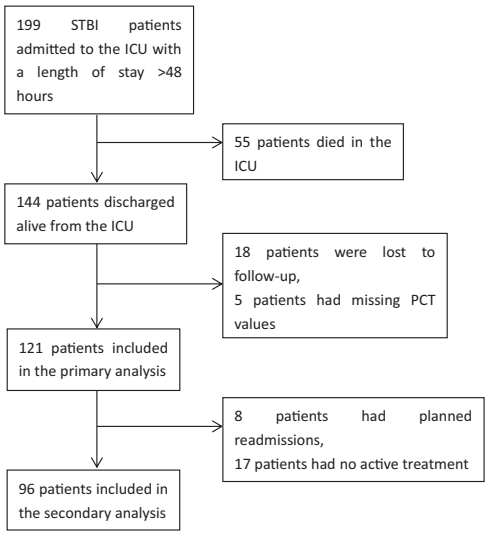

Figure 1. Flowchart.

The readmission rate in the high-PCT group was 33%, which was significantly higher compared with the low-PCT group (33% vs. 13%, P = 0.038). The high-PCT group had a higher rate of adverse outcomes (37% vs. 16%, P = 0.025), a higher APACHE II score (10.85 ± 2.80 vs. 7.87 ± 2.37, P<0.001), and a lower GCS score at ICU discharge (10.30 ± 3.24 vs. 11.75 ± 2.61, P = 0.025) compared with the low-PCT group. The low-PCT group had a shorter LOS in the ICU compared with the high-PCT group (12.61 ± 11.68 vs. 18.48 ± 13.44, P = 0.037). The renal support rates in the high- and low-PCT groups were 37% and 13%, respectively (P = 0.020; Table 2).

No significant difference was found between the two groups in the number of days between ICU discharge and readmission (5.24 ± 3.16 vs. 5.62 ± 3.27 days).

Correlations of PCT levels with disease severity and outcomes

Figure 2 shows the Spearman correlation analysis of PCT levels with APACHE II,

Table 1. Characteristics of the traumatic brain injury study population stratified by primary outcome measures (high PCT/low PCT).

Characteristics	Total (n = 96)	High PCT (n = 27)	Low PCT (n = 69)	P value
Age, years	53.73 ± 16.21	51.37 ± 16.22	54.65 ± 17.24	0.397
Male sex (%)	67.71	70.37	66.67	0.811
GCS score at study entry	6.24 ± 1.84	5.96 ± 1.89	6.35 ± 1.82	0.353
Systolic blood pressure (mmHg)	118.25 ± 14.93	114.75 ± 16.27	121.03 ± 15.42	0.081
APACHE II score at admission	18.86 ± 6.25	19.15 ± 4.60	18.78 ± 6.81	0.796
SOFA score at admission	8.70 ± 2.56	8.56 ± 2.19	8.75 ± 2.71	0.745
PCT level at admission (ng/mL)	1.97 ± 1.09	2.07 ± 1.12	1.90 ± 0.79	0.404
CRP level at admission (mg/L)	55.27 ± 42.52	48.70 ± 39.44	57.44 ± 48.63	0.408
WBC count at admission ($\times 10^9$)	14.98 ± 6.27	16.14 ± 6.98	14.52 ± 5.96	0.257
Temperature at admission (°C)	36.70 ± 0.49	36.63 ± 0.44	36.73 ± 0.51	0.373
Mechanism of injury, %				
Motor vehicle accident	50 (52)	15 (56)	35 (51)	0.670
Auto–pedestrian accident	10 (10)	2 (7)	8 (11)	0.546
Fall	25 (26)	8 (30)	17 (26)	0.391
Assault	11 (12)	2 (7)	9 (12)	0.436
Craniotomy, n (%)	67 (70)	20 (74)	47 (68)	0.568
Associated injuries, n (%)	67 (70)	18 (67)	49 (71)	0.677
Mortality, n (%)	18 (26)	8 (30)	10 (14)	0.088

Data are presented as the mean ± SD (for normally distributed data), the median and IQR (for non-normally distributed data) or a percentage (%) (for categorical variables).
APACHE, Acute Physiologic and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell.

Table 2. Primary and secondary outcomes.

	Total (n = 96)	High PCT (n = 27)	Low PCT (n = 69)	P value
Readmission, n (%)	18 (19)	9 (33)	9 (13)	0.038
Adverse outcome, n (%)	21 (22)	10 (37)	11 (16)	0.025
PCT levels at discharge (ng/mL)	1.74 ± 1.52	2.27 ± 1.68	0.14 ± 0.07	<0.001
CRP levels at discharge (ng/mL)	19.06 ± 17.16	26.43 ± 20.55	16.18 ± 14.82	0.008
APACHE II score at discharge	8.71 ± 2.82	10.85 ± 2.80	7.87 ± 2.37	<0.001
GCS score at discharge	11.34 ± 2.86	10.30 ± 3.24	11.75 ± 2.61	0.025
Mechanical ventilation, n (%)	88 (92)	25 (93)	63 (91)	0.837
ICU LOS (days) (n)	14.26 ± 12.41	18.48 ± 13.44	12.61 ± 11.68	0.037
Renal support, n (%)	22 (23)	10 (37)	9 (13)	0.020

Data are presented as the mean ± SD (for normally distributed data), the median and IQR (for non-normally distributed data) or a percentage (%) (for categorical variables).
PCT, procalcitonin; ICU, intensive care unit; adverse outcome, ICU readmission and/or in-hospital mortality after ICU discharge; ICU LOS, ICU length of stay; APACHE, Acute Physiologic and Chronic Health Evaluation; IQR, interquartile range.

SOFA, and GCS scores. PCT levels were significantly positively correlated with APACHE II scores ($r = 0.425$, $P < 0.001$) and SOFA scores ($r = 0.468$, $P = 0.001$) in all severe traumatic brain injury (STBI) patients. Additionally, PCT levels were negatively correlated with GCS scores, but the correlation was not significant ($r = -0.197$).

Figure 3 shows the receiver operating characteristic (ROC) curves for PCT and CRP levels, and WBC counts and APACHE II and SOFA scores for predicting pulmonary and non-pulmonary infections. The area under the ROC curve (AUC) of PCT levels for predicting pulmonary and non-pulmonary infections was 0.789 (95% confidence interval [CI], 0.684–0.893). The AUC for CRP levels was 0.758 (95% CI, 0.633–0.883), the AUC for WBC counts was 0.639 (95% CI, 0.509–0.769), the AUC for the APACHE II score was 0.755 (95% CI, 0.649–0.861), and the AUC for the SOFA score was 0.769 (95% CI, 0.666–0.872) (Figure 3a). To further refine the scoring system, we eliminated SOFA and APACHE II scores because we considered these parameters to be less specific for predicting whether a patient truly had a pulmonary infection. Therefore, we analyzed the total bioscore of each patient (using only PCT and CRP levels and WBC counts) using a ROC curve. The AUC was 0.823 (95% CI, 0.735–0.946) (Figure 3b).

The multivariate logistic regression analysis showed that at discharge, the APACHE II and SOFA scores, WBC count, and CRP and PCT levels were significantly associated with adverse outcomes (Table 3).

Ethics

All study procedures involving human participants were performed in accordance with the ethical standards of The Affiliated Hospital of Yangzhou University and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants or their representatives before enrollment in the study.

Discussion

Patients with brain trauma are generally thought to remain in an inflammatory

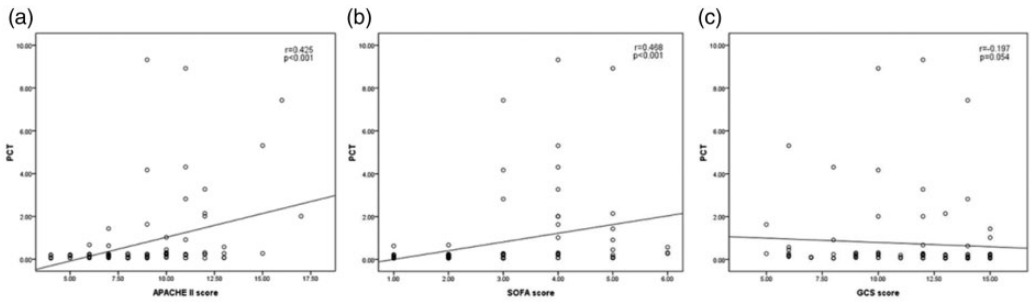

Figure 2. Relationships between PCT levels and APACHE II, SOFA, and GCS scores in patients with STBI. Spearman rank correlations were used to evaluate the relationships between variables. PCT was positively correlated with the APACHE II (a) and SOFA (b) scores and negatively correlated with the GCS score (c) in STBI patients.

PCT, procalcitonin; APACHE, Acute Physiologic and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; STBI, severe traumatic brain injury.

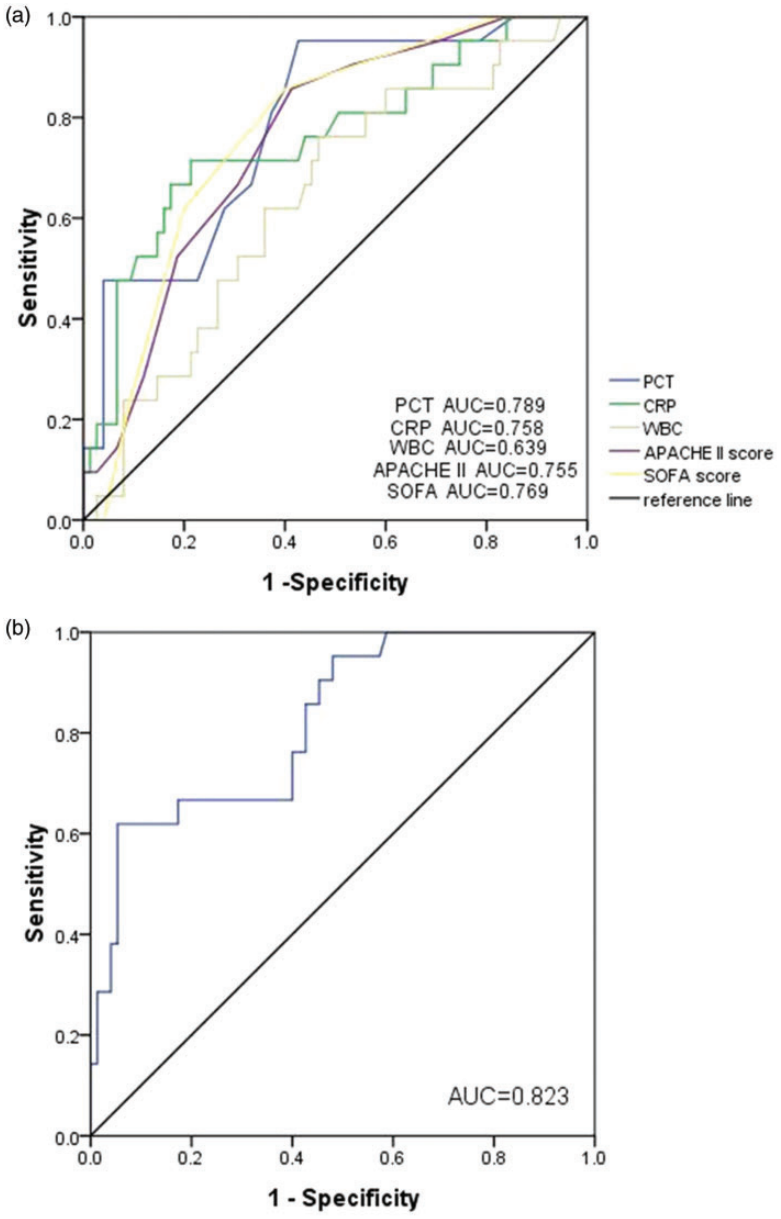

Figure 3. (a) ROC curves for PCT and CRP levels, WBC counts, and APACHE II and SOFA scores for predicting pulmonary and non-pulmonary infections in patients with STBI. (b) The AUC for combined multiple inputs (PCT and CRP levels and WBC counts).
ROC, receiver operating characteristic; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell; APACHE, Acute Physiologic and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; STBI, severe traumatic brain injury; AUC, area under the ROC curve.

Table 3. Logistic regression analysis of adverse outcome prediction in patients with STBI.

	Multivariate analysis	
Variables	Odds ratio (95% CI)	P value
APACHE II score at discharge	1.07 (0.76–1.50)	0.001
SOFA score at discharge	1.31 (0.72–2.36)	0.007
WBC count at discharge	1.35 (1.10–1.66)	0.013
CRP levels at discharge	1.05 (0.98–1.12)	0.033
PCT levels at discharge	1.95 (1.13–3.36)	0.016
Temperature at discharge	0.57 (0.22–1.50)	0.025

WBC, white blood cell; PCT, procalcitonin; adverse outcome, ICU readmission and/or in-hospital mortality after ICU discharge; APACHE, Acute Physiologic and Chronic Health Evaluation; CI, confidence interval.

state when transferred out of the ICU. An aggravated inflammatory response increases the probability that a patient will be readmitted to the ICU, resulting in increased patient mortality. The predictive value of serum PCT levels at ICU discharge for adverse outcomes in patients with traumatic brain injury is unconfirmed. This study used the PCT level as an indicator to predict a poor prognosis among patients with STBI who were discharged from the ICU. Our study found that patients with high PCT levels had significantly higher ICU readmission rates and a poorer prognosis compared with those with low PCT levels. However, overall mortality did not significantly differ between the two groups. Spearman correlation analysis revealed correlations between serum PCT levels before ICU discharge and APACHE II, SOFA, and GCS scores, which may be related to the evaluation of PCT in some organ failure states.[13] In addition, a recent prospective cohort investigation showed that elevated PCT levels at admission were independently associated with unfavorable clinical outcomes in intracerebral hemorrhage patients, which may be used to help predict the prognosis in patients with various severe brain injuries.[14] These findings suggest a correlation between elevated PCT levels before ICU discharge and a poor prognosis among patients with STBI.

Patients with traumatic brain injury are often readmitted to the ICU because of aggravated bacterial infections, such as pulmonary infections, after tracheotomy. PCT is a biomarker with the potential to distinguish between bacterial and viral infections and non-infectious inflammation. If a secondary bacterial infection occurs, serum PCT levels will increase in 3 to 4 hours, peak in 12 to 24 hours, and persist longer than other biomarkers.[15] Other clinically common inflammatory markers such as IL-6 and tumor necrosis factor-α reach their peaks in 5 to 10 hours and then rapidly decrease to normal levels within 20 hours.[16] However, serum CRP levels peak at approximately 36 hours.[11] These features limit the clinical use of these inflammatory markers to track changes in patients' conditions. For diagnosing sepsis, serum PCT levels have higher sensitivity and specificity than IL-6, CRP, and lactic acid.[17,18] Serum PCT levels are positively correlated with the degree of the inflammatory response in patients.[19] Therefore, the 2016 Surviving Sepsis Campaign and the 2016 Infectious Diseases Society of America (IDSA) guidelines recommend using serum PCT levels to determine which antibiotics should be used for hospital-acquired pneumonia and ventilator-associated pneumonia.[20,21] Current evidence suggests that PCT levels

have more clinical value for predicting respiratory infections compared with other infections.[22] Our study found that the serum PCT level before ICU discharge had the greatest predictive value for infection development in both groups, with an AUC of 0.789, which was higher compared with those for CRP levels and APACHE and SOFA scores. PCT levels had a higher predictive value for infection. Infection development and severity are associated with a poor prognosis in patients with severe head injuries.[23]

Clinically, a poor prognosis of patients with traumatic brain injury may also be related to non-infectious factors, such as aggravated underlying diseases and other complications. PCT levels also have diagnostic value in some non-infectious diseases. For example, PCT levels can predict the occurrence of deep vein thrombosis.[24] Changes in serum PCT levels also have predictive value for determining the severity of acute pancreatitis.[25] Serum PCT levels can also be used to assess the severity of illness in patients with chronic obstructive pulmonary disease and serve as a reference for antibiotic treatment.[26] Elevated serum PCT levels predict the risk of short-term mortality in patients with heart failure.[27] In addition, PCT levels are superior to CRP levels and pro-adrenomedullin (MR-proADM) levels for predicting adverse cardiovascular events and all-cause mortality in patients with type 2 diabetes.[28] Recent studies have suggested that PCT is an independent marker of fat accumulation and metabolic parameters associated with obesity status.[29] The adverse prognosis of severe craniocerebral trauma is complicated and it is associated with common infectious factors and related to other complications, basic disease status, and other factors. Our logistic regression analysis revealed that serum PCT levels before ICU discharge are closely related to a poor prognosis, which may be related to the association of PCT levels with non-infectious diseases in these patients.

Patients in the high-PCT group may have been predisposed to infection before being transferred out of the ICU; these patients had higher PCT levels compared with the low-PCT group. However, patients will continue to require antibiotic treatment after leaving the ICU. If the inflammatory response is controllable, these patients should not require readmission to the ICU for treatment. Therefore, PCT has a limited value in assessing the conditions of patients with traumatic brain injury after ICU discharge. We suggest that for patients with STBI without multiple injuries or comorbidities and with a serum PCT level >0.25 ng/mL before ICU discharge, clinicians must be careful when deciding whether to transfer such patients out of the ICU because patients with simple STBI are generally believed to have a lower state of inflammation compared with patients without multiple injuries or comorbidities. A serum PCT level >0.25 ng/mL before ICU discharge in patients with simple STBI indicates a high likelihood of a poor prognosis.

The limitations of this study are as follows: 1) Only one criterion was used for patient enrollment, and the enrolled patients were limited to ICU patients with STBI. Whether the conclusions of this study are applicable to other critically ill patients is unclear; 2) The condition of patients with STBI is complex and variable. Serum PCT levels can predict a poor prognosis in these patients, but PCT levels are susceptible to interactions with multiple factors and false-positive and false-negative results;[30] 3) The value of a single index for predicting the prognosis of patients with STBI after ICU discharge is limited. To improve the predictive value, combined monitoring of several indicators or dynamic monitoring of serum PCT levels is needed after patients leave the ICU,[25] as was investigated in our research. We found

that the AUC for the combination of PCT, CRP, and WBC counts was 0.823, which is better compared with that of the PCT indicator alone. However, whether this combination represents an accurate and reasonable strategy requires further confirmation; and 4) Serum PCT levels have a higher predictive value for infection compared with other outcomes. Further studies with a larger sample size are necessary to verify the value of PCT for predicting a poor prognosis in patients with severe head injury after ICU discharge. Because of the limitations of the study design, although serum PCT levels reflect a patient's inflammatory state, the causal relationship between serum PCT levels and a poor prognosis remains unclear; thus, a well-designed study is needed to further verify the predictive value of PCT levels.

Conclusion

Elevated serum PCT levels upon ICU discharge are associated with a poor prognosis in patients with STBI, but the clinical value of PCT levels for predicting outcomes after ICU discharge for individual patients is limited.

Authors' contributions

Yu-rong Wang, Wei-li Liu, and Yong Li participated in the study design and data collection and interpretation, and they wrote the study protocol. Qing-bin Zheng, Guang-fa Wei, Li-jun Meng, Qing-ling Feng, Wen-jie Yuan, and Jin-lei Ou contributed to the study design, analyzed the data, and performed the statistical analyses. Yong Li drafted the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Please contact the author for data requests.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The protocol was financially supported by funds from the Yangzhou Social Development Project (grant number YZ2017080).

ORCID iD

Yong Li https://orcid.org/0000-0001-9256-6690

References

1. Li P, Stelfox HT and Ghali WA. A prospective observational study of physician handoff for intensive-care-unit-to-ward patient transfers. *Am J Med* 2011; 124: 860–867.
2. Lu Q, Xie Y, Qi X, et al. Is early tracheostomy better for severe traumatic brain injury? A Meta-Analysis. *World Neurosurg* 2018; 112: e324–e330.
3. Dettenkofer M, Ebner W, Hans FJ, et al. Nosocomial infections in a neurosurgery intensive care unit. *Acta Neurochir (Wien)* 1999; 141: 1303–1308.
4. Chen LM, Martin CM, Keenan SP, et al. Patients readmitted to the intensive care unit during the same hospitalization: Clinical features and outcomes. *Crit Care Med* 1998; 26: 1834–1841.
5. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829.
6. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26: 1793–1800.
7. Vassiliou AG, Mastora Z, Orfanos SE, et al. Elevated biomarkers of endothelial dysfunction/activation at ICU admission are associated with sepsis development. *Cytokine* 2014; 69: 240–247.
8. Nakamura M, Kono R, Nomura S, et al. Procalcitonin: Mysterious protein in sepsis. *J Basic Clin Med* 2013; 2: 7–11.
9. Müller B, Beck K, Schächinger H, et al. Calcitonin precursors are reliable markers

of sepsis in a medical intensive care unit. *Crit Care Med* 2000; 28: 977–983.
10. El-Azeem A, Hamdy G, Saraya M, et al. The role of procalcitonin as a guide for the diagnosis, prognosis, and decision of antibiotic therapy for lower respiratory tract infections. *Egypt J Chest Dis Tuberc* 2013; 62: 687–695.
11. Simon L, Gauvin F, Amre DK, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. *Clin Infect Dis* 2004; 39: 206–217.
12. Soreng K and Levy HR. Procalcitonin: An emerging biomarker of bacterial sepsis. *Clin Microbiol Newsl* 2011; 33: 171–178.
13. Choi JJ and McCarthy MW. Novel applications for serum procalcitonin testing in clinical practice. *Expert Rev Mol Diagn* 2018; 18: 27–34.
14. He D, Zhang Y, Zhang B, et al. Serum procalcitonin levels are associated with clinical outcome in intracerebral hemorrhage. *Cell Mol Neurobiol* 2018; 38: 727–733.
15. Meisner M. Current status of procalcitonin in the ICU. *Neth J Crit Care* 2013; 17: 4–12.
16. Latifi S and Levine A. Kinetics of interleukin 6 synthesis predictive of outcome in sepsis. *Crit Care Med* 1999; 27: A102.
17. Wu C, Wu J, Chen C, et al. Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis. *Support Care Cancer* 2015; 23: 2863–2872.
18. Mustafić S, Brkić S, Prnjavorac B, et al. Diagnostic and prognostic value of procalcitonin in patients with sepsis. *Med Glas (Zenica)* 2018; 15: 93–100.
19. de Boer RA, Daniels LB, Maisel AS, et al. State of the art: Newer biomarkers in heart failure. *Eur J Heart Fail* 2015; 17: 559–569.
20. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock. *Intensive Care Med* 2017; 43: 304–377.
21. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63: e61–e111.
22. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2017; 10: CD007498.
23. Li Y, Liu C, Xiao W, et al. Incidence, risk factors, and outcomes of ventilator-associated pneumonia in traumatic brain injury: A meta-analysis. *Neurocrit Care* 2019. doi: 10.1007/s12028-019-00773-w.
24. Rast AC, Knobel D, Faessler L, et al. Use of procalcitonin, C-reactive protein and white blood cell count to distinguish between lower limb erysipelas and deep vein thrombosis in the emergency department: A prospective observational study. *J Dermatol* 2015; 42: 778–785.
25. Sager R, Kutz A, Mueller B, et al. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Med* 2017; 15: 15.
26. Pantzaris ND, Spilioti DX, Psaromyalou A, et al. The use of serum procalcitonin as a diagnostic and prognostic biomarker in chronic obstructive pulmonary disease exacerbations: A literature review update. *J Clin Med Res* 2018; 10: 545–551.
27. Aïssou L, Sorbets E, Lallmahomed E, et al. Prognostic and diagnostic value of elevated serum concentration of procalcitonin in patients with suspected heart failure. A review and meta-analysis. *Biomarkers* 2018; 23: 407–413.
28. Landman GW, Kleefstra N, Groenier KH, et al. Inflammation biomarkers and mortality prediction in patients with type 2 diabetes (ZODIAC-27). *Atherosclerosis* 2016; 250: 46–51.
29. Boursier G, Avignon A, Kuster N, et al. Procalcitonin, an independent marker of abdominal fat accumulation in obese patients. *Clin Lab* 2016; 62: 435–441.
30. Christ-Crain M and Muller B. Procalcitonin in bacterial infections–hype, hope, more or less? *Swiss Med Wkly* 2005; 135: 451–460.