ORIGINAL RESEARCH

Prognostic Value of Serum Procalcitonin Based Model in Moderate to Severe Traumatic Brain Injury Patients

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Objective: Procalcitonin (PCT) is an acknowledged marker of systemic inflammatory response. Previous studies have not reached agreement on the association between serum PCT and outcome of traumatic brain injury (TBI) patients. We designed this study to confirm the prognostic value of PCT in isolated TBI and those with extracranial injury, respectively.

Methods: Patients hospitalized in our hospital for moderate-to-severe TBI between March 2015 and December 2019 were included. Logistic regression analysis was performed to validate the association between PCT and in-hospital mortality in these patients. AUC (area under the receiver operating characteristics curve) of PCT and constructed model were calculated and compared.

Results: Among the included 211 patients, 81 patients suffered a poor outcome, with a mortality rate of 38.4%. Non-survivors had a higher level of serum PCT (2.73 vs 0.72, $p<0.001$) and lower GCS (5 vs 7, $p<0.001$) on admission than survivors. AUC of single PCT for predicting mortality in isolated TBI and those with extracranial injury were 0.767 and 0.553, respectively. Multivariate logistic regression showed that GCS (OR=0.744, $p=0.008$), glucose (OR=1.236, $p<0.001$), cholesterol (OR=0.526, $p=0.002$), and PCT (OR=1.107, $p=0.022$) were independently associated with mortality of isolated TBI. The AUC of the prognostic model composed of GCS, glucose, cholesterol, and PCT was 0.868 in isolated TBI.

Conclusion: PCT is an efficient marker of outcome in isolated moderate-to-severe TBI but not those with extracranial injury. A prognostic model incorporating PCT is useful for clinicians to make early risk stratification for isolated TBI.

Keywords: procalcitonin, traumatic brain injury, extracranial injury, prognosis

Introduction

Traumatic brain injury (TBI) is still a widely concerning public health problem, which severely impairs patients' quality-of-life and brings a heavy economic burden to society. It has recently been estimated that TBI would occur approximately 69 million times annually all over the world.[1] Although many novel therapies aimed at preventing secondary brain injury have been proposed and proved, the mortality of moderate-to-severe TBI remains relatively high. To prevent possible adverse progress in these patients, early risk stratification is necessary for clinicians to evaluate patients' condition and, therefore, adjust treatment strategies. Having been widely used to assess injury severity in the past four decades, the Glasgow Coma Scale (GCS) has gradually been found to have some deficiencies, including an inaccurate estimation during sedation and intubation.[2,3] Recently, a growing number of studies have explored the prognostic value of biomarkers in serum or cerebrospinal fluid, such as glial fibrillary acidic protein (GFAP), S100 calcium binding protein B (S100B), neurofilament protein-light (NfL), ubiquitin carboxy-terminal hydrolase L1 (UCHL1), and Tau.[4] And some studies developed multimodal prognostic calculators such as the Corticosteroid Randomization After Significant Head injury

(CRASH) and International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT).[5,6] In addition to develop novel predictive models, utilizing other markers to modify the GCS is also an effective alternative method which could make up deficiencies of conventional GCS and improve the stability of severity estimation. Previous researchers have tried combining some markers with GCS to increase the predictive value, such as age, shock index, and neutrophil-to-lymphocyte ratio.[7–10] As a widely used diagnostic marker of severe infection and sepsis, procalcitonin (PCT) has been confirmed to be associated with mortality in many clinical settings, such as sepsis, cancer, and trauma.[11–17] Moreover, the prognostic value of serum PCT in patients with neurological diseases including subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage and epilepticus status have been explored.[18–22] Although several researchers have illustrated the prognostic value of PCT in TBI patients, the sample size of these studies were relatively small and included subjects were not limited to homogenous moderate-to-severe TBI patients.[23–26] Another important defect is that the predictive value of only a single PCT level but not a predictive model incorporating PCT and other significant factors were evaluated in these studies. Therefore, we designed this study to explore the prognostic value of PCT alone and predictive model incorporating PCT in moderate-to-severe TBI patients.

Materials and Methods
Patients
This study was performed in a tertiary hospital which was a regional trauma center in Southwest China. Patients admitted to our hospital for TBI between March 2015 and December 2019 were eligible for this study. Most TBI patients hospitalized in our hospital were moderate-to-severe TBI (GCS ≤12) patients who would get suitable treatments and critical management in the intensive care unit (ICU). Patients who met the following criteria were excluded from this study: 1) GCS on admission >12; 2) Admitted to our hospital 6 hours after injury or transferred from other hospitals; 3) patients whose relevant data were not entirely recorded; and 4) patients who had a recent history of severe infection or surgery. After screening, 211 patients were finally included in this observational study. The inclusion flowchart of patients is shown as Figure 1. Our study got approvement from the ethics committee of West China hospital and accorded with the Helsinki Declaration. Informed consent forms of each patient were obtained from themselves or their legal representatives.
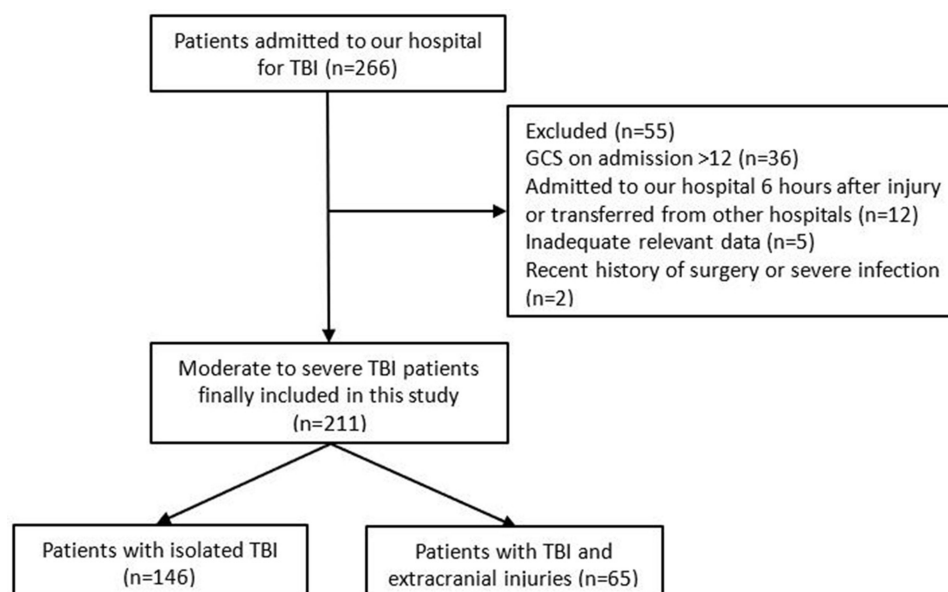
Figure 1 Flow diagram of included patients.
Abbreviations: TBI, traumatic brain injury; GCS, Glasgow Coma Scale.

Data Collection

Included variables were mainly collected from the records in electronic medical record system of our hospital. Injury mechanisms were obtained by talking with patients or their legal representatives on admission. Vital signs and GCS score on admission were evaluated by experienced emergency workers once patients were admitted to our hospital. Results of laboratory tests including serum PCT was acquired by analyzing the blood samples drawn on admission. The coagulopathy was confirmed based on international normalized ratio >1.6 or activated partial thromboplastin time >60 seconds. Intracranial injury types of each patient were recorded by checking the characteristics of computed tomography (CT) scan carried in our hospital. The AIS >1 of any extracranial body region was considered as the existence of extracranial injury. The primary outcome of this study was in-hospital mortality.

Statistical Analysis

Kolmogorov–Smirnov tests were performed to confirm the normality of included variables. Non-normally distributed variables and normally distributed variables were shown in the form of median (interquartile range) and mean±standard deviation, respectively. And categorical variables were presented as numbers (percentage). We compared the difference of non-normally distributed variables and normally distributed variables between two subgroups by using Mann–Whitney U-test and Student's t-test, respectively. Difference of categorical variables were analyzed by χ^2 test or Fisher test. Univariate logistic regression analysis was firstly utilized to explore the potential factors for mortality of included TBI patients. Then, potential significant factors in univariate regression were selected by conducting stepwise forward multivariate logistic regression. Significant risk factors in multivariate analysis were finally utilized to construct a prognostic model using logistic regression. We draw receiver operating characteristic (ROC) curves of single factors and the constructed prognostic model. Z-tests were conducted to compare the area under the ROC curve (AUC) difference of these factors and the model.

We considered that a two-sided p-value<0.05 was of statistical significance. SPSS 22.0 Windows software (SPSS, Inc, Chicago, IL) was used for all statistical analyses and figures drawing.

Results

Baseline Characteristics of Included Patients Grouping by Survival Outcome

A total of 211 TBI patients were included with mortality of 38.4% (Table 1). Age and sex ratio did not differ between survivors and non-survivors. Traffic accident (60.2%) and high falling injury (22.7%) ranked the first and the second among injury mechanisms. Vital signs on admission including systolic, diastolic blood pressure, and body temperature did not show significant differences between survivors and non-survivors. While non-survivors had significantly lower GCS (5 vs 7, p<0.001) and higher Abbreviated Injury Score (AIS) (5 vs 4, p<0.001) and Injury Severity Score (ISS) (25 vs 20, p<0.001). Results of laboratory tests showed that non-survivors had a lower level of platelet (80×10^9/L vs 113×10^9/L, p<0.001), cholesterol (2.25 mmol/L vs 2.87 mmol/L, p<0.001), and hemoglobin (81 g/L vs 90 g/L, p=0.010) than survivors. Whereas the blood level of glucose (12.88 mmol/L vs 8.66 mmol/L, p<0.001) and PCT (2.73 ng/mL vs 0.72 ng/mL, p<0.001) were significantly higher than survivors. Considering the intracranial radiological signs, we found that non-survivors had a higher incidence of subdural hematoma (33.3% vs 17.7%, p=0.010) and a lower incidence of epidural hematoma (3.7% vs 11.5%, p=0.036). Sixty-five patients suffered extracranial injury with an incidence of 30.8%. Compared with survivors, non-survivors had a shorter length of ICU stay (4 vs 18, p<0.001) and length of hospital stay (8 vs 30, p<0.001).

Prognostic Value of PCT and Other Index Alone for Predicting Mortality in TBI Patients with or without Extracranial Injury

Among the included 211 TBI patients, 146 patients were isolated TBI and 65 complicated with extracranial injuries. We evaluate the prognostic value of PCT in these two groups respectively. In isolated TBI patients, the AUC of single PCT, GCS, and AIS were 0.774, 0.751, and 0.743, respectively (Table 2; Figure 2A), while in TBI patients with extracranial injuries, the AUC of single PCT, GCS, AIS, ISS were only 0.553, 0.680, 0.608, and 0.590, respectively (Figure 2B).

Table 1 Baseline Characteristics of Included TBI Patients

Variables	Total patients (N=211)	Survivors (n=130, 61.6%)	Non-survivors (n=81, 38.4%)	*P*-value
Age (years)	44 (28–59)	44 (27–58)	44 (28–61)	0.542
Male	169 (80.1%)	105 (80.8%)	64 (79.0%)	0.756
Injury mechanism				0.121
Traffic accident	127 (60.2%)	76 (58.5%)	51 (63.0%)	
High falling	48 (22.7%)	32 (24.6%)	16 (19.8%)	
Stumbling	23 (10.9%)	11 (8.5%)	12 (14.8%)	
Others/Unknown	13 (6.2%)	11 (8.5%)	2 (2.5%)	
Vital signs in admission				
Systolic blood pressure (mmHg)	122 (108–138)	124 (110–139)	120 (107–139)	0.471
Diastolic blood pressure (mmHg)	75 (62–84)	75 (66–83)	75 (58–87)	0.487
Heart rate (bps)	100 (81–120)	96 (79–113)	103 (82–122)	0.044
Body temperature (°C)	36.8 (36.5–37.1)	36.8 (36.5–37.1)	36.8 (36.5–37.5)	0.560
GCS in admission	6 (4–7)	7 (5–9)	5 (3–6)	<0.001
AIS head	4 (4–5)	4 (4–5)	5 (4–5)	<0.001
ISS	25 (16–25)	20 (16–25)	25 (25–25)	<0.001
Laboratory tests				
White blood cell (×10^9/L)	15.14 (10.86–20.56)	14.67 (10.78–19.05)	15.79 (11.28–22.71)	0.194
Platelet (×10^9/L)	100 (66–155)	113 (77–163)	80 (45–135)	<0.001
Glucose (mmol/L)	9.72 (7.23–13.31)	8.66 (6.53–11.80)	12.88 (8.83–16.68)	<0.001
Albumin (g/L)	30.4±7.2	31.9±6.8	28.0±7.1	<0.001
Hemoglobin (g/L)	87 (77–106)	90 (79–110)	81 (72–99)	0.010
Cholesterol (mmol/L)	2.64 (1.92–3.45)	2.87 (2.21–3.76)	2.25 (1.62–2.97)	<0.001
PCT (ng/mL)	1.28 (0.39–4.38)	0.72 (0.29–2.52)	2.73 (0.69–13.66)	<0.001
Coagulopathy	86 (40.8%)	36 (27.7%)	50 (61.7%)	<0.001
Intracranial injury types				
Epidural hematoma	18 (8.5%)	15 (11.5%)	3 (3.7%)	0.036
Subdural hematoma	50 (23.7%)	23 (17.7%)	27 (33.3%)	0.01
Subarachnoid hemorrhage	126 (59.7%)	78 (60.0%)	48 (59.3%)	0.915
Intraventricular hemorrhage	9 (4.3%)	6 (4.6%)	3 (3.7%)	1.000
Diffused axonal injury	61 (28.9%)	34 (26.2%)	27 (33.3%)	0.265
Extracranial injury	65 (30.8%)	43 (33.1%)	22 (27.2%)	0.363
Surgical interventions				
Decompressive craniectomy	79 (37.4%)	44 (33.8%)	35 (43.2%)	0.173
Hematoma evacuation	91 (43.1%)	57 (43.8%)	34 (42%)	0.789
Length of ICU stay (day)	14 (4–27)	18 (11–32)	4 (2–18)	<0.001
Length of hospital stay (day)	23 (10–41)	30 (20–46)	8 (4–22)	<0.001

Abbreviations: TBI, traumatic brain injury; AIS, abbreviated injury score; ISS, injury severity score; GCS, Glasgow Coma Scale; PCT, procalcitonin.
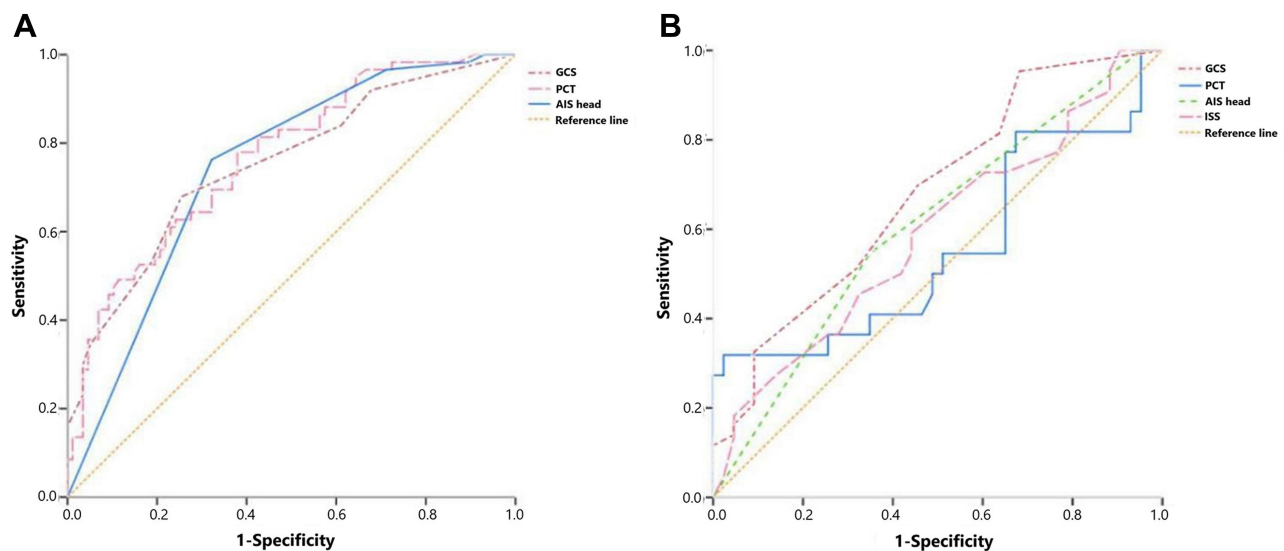
Table 2 Predictive Value of PCT and Other Trauma Scores in Patients with Isolated TBI or Patients with TBI and Extracranial Injuries

Patients with Isolated TBI				
Variables	AUC	95% CI	Sensitivity	Specificity
PCT	0.767	0.690–0.844	0.780	0.621
GCS	0.751	0.673–0.829	0.678	0.746
AIS	0.743	0.663–0.823	0.763	0.678
Patients with TBI and Extracranial Injuries				
Variables	AUC	95% CI	Sensitivity	Specificity
PCT	0.553	0.391–0.715	0.318	0.977
GCS	0.680	0.543–0.818	0.953	0.318
AIS	0.608	0.463–0.753	0.545	0.651
ISS	0.590	0.441–0.739	0.591	0.558

Abbreviations: PCT, procalcitonin; TBI, traumatic brain injury; AUC, area under the receiver operating characteristic curve; CI, confidence interval; GCS, Glasgow Coma Scale; AIS, abbreviated injury score; ISS, injury severity score.

Logistic Regression Analysis of Risk Factors for Mortality in Isolated TBI Patients

Because of the limited prognostic value of single PCT in TBI patients with extracranial injuries, we only performed logistic regression analysis in isolated TBI patients. Univariate logistic regression showed that GCS ($p<0.001$), AIS head ($p<0.001$), platelet ($p=0.008$), glucose ($p<0.001$), albumin ($p<0.001$), hemoglobin ($p=0.025$), cholesterol ($p<0.001$), PCT ($p=0.001$), and coagulopathy ($p<0.001$) were associated with mortality of included TBI patients (Table 3). However, after adjusting confounding effects, multivariate logistic regression indicated only GCS (OR=0.744, $p=0.008$), glucose (OR=1.236, $p<0.001$), cholesterol (OR=0.526, $p=0.002$), and PCT (OR=1.107, $p=0.022$) were independent risk factors of mortality.

Figure 2 (**A**) ROC curves of PCT and other trauma scores for predicting mortality in patients with isolated TBI. The AUC of PCT, GCS, and AIS head was 0.767 (95% CI=0.690–0.844), 0.751 (95% CI=0.673–0.829), and 0.743 (95% CI=0.663–0.823), respectively. (**B**) ROC curves of PCT and other trauma scores for predicting mortality in patients with TBI and extracranial injuries. The AUC of PCT, GCS, AIS head, and ISS was 0.553 (95% CI=0.391–0.715), 0.680 (95% CI=0.543–0.818), 0.608 (95% CI=0.463–0.753), and 0.590 (95% CI=0.441–0.739), respectively.

Table 3 Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Mortality in Isolated TBI Patients

Variables	Unadjusted Analysis			Adjusted Analysis		
	OR	95% CI	P-value	OR	95% CI	P value
Age	0.999	0.982–1.016	0.900			
Male	0.816	0.351–1.897	0.636			
Systolic blood pressure	0.997	0.984–1.009	0.586			
Diastolic blood pressure	0.985	0.966–1.005	0.132			
Heart rate	1.007	0.996–1.018	0.215			
Body temperature	1.084	0.887–1.325	0.430			
GCS in admission	0.638	0.526–0.774	**<0.001**	0.744	0.598–0.925	**0.008**
AIS head	3.767	2.098–6.765	**<0.001**			
White blood cell	1.039	0.988–1.093	0.139			
Platelet	0.993	0.987–0.998	**0.008**			
Glucose	1.278	1.158–1.411	**<0.001**	1.236	1.100–1.388	**<0.001**
Albumin	0.906	0.857–0.957	**<0.001**			
Hemoglobin	0.982	0.967–0.998	**0.025**			
Cholesterol	0.436	0.295–0.647	**<0.001**	0.526	0.352–0.785	**0.002**
PCT	1.139	1.054–1.232	**0.001**	1.107	1.015–1.208	**0.022**
Coagulopathy	4.415	2.178–8.950	**<0.001**			
Epidural hematoma	0.474	0.092–2.432	0.371			
Subdural hematoma	1.651	0.750–3.637	0.213			
Subarachnoid hemorrhage	0.900	0.464–1.746	0.754			
Intraventricular hemorrhage	0.358	0.039–3.284	0.363			
Diffused axonal injury	1.532	0.702–3.346	0.284			
Decompressive craniectomy	1.273	0.656–2.470	0.475			
Hematoma evacuation	0.883	0.455–1.711	0.712			

Note: Bold value indicates p<0.05
Abbreviations: TBI, traumatic brain injury; OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; AIS, abbreviated injury score; PCT, procalcitonin.

Prognostic Value of Logistic Model Incorporating PCT in Isolated TBI Patients

We utilized four significant factors in multivariate logistic regression to construct a prognostic model for isolated TBI patients.

The results of Table 4 showed the detailed AUC value, sensitivity, and specificity of PCT, glucose, GCS, and AIS (Figure 3). There were no statistical differences of AUC between these four factors. Whereas the AUC value of the four-factors prognostic model was 0.868, which was higher than that of PCT (Z=1.91, *p*<0.05), glucose (Z=1.96, *p*<0.05), or GCS alone (Z=2.34, *p*<0.05).

Discussion

Discovered three decades ago, PCT is a prepropeptide precursor of calcitonin, which is synthesized in thyroid C cells under physiological condition.[27,28] The significant increase of plasma PCT level under many kinds of inflammatory

Table 4 Prognostic Value of PCT and the Constructed Predictive Model in Patients with Isolated TBI

Variables	AUC	95% CI	Sensitivity	Specificity
PCT	0.767	0.690–0.844	0.780	0.621
Glucose	0.765	0.687–0.844	0.763	0.678
GCS	0.751	0.673–0.829	0.678	0.746
AIS	0.743	0.663–0.823	0.763	0.678
Predictive model	0.868	0.809–0.927	0.814	0.767

Abbreviations: PCT, procalcitonin; TBI, traumatic brain injury; AUC, area under the receiver operating characteristic curve; CI, confidence interval; GCS, Glasgow Coma Scale; AIS, abbreviated injury score.

stimulations, especially the bacterial infection, is mainly attributable to induced production from neuroendocrine cells in the lung or intestine.[29,30] Previous studies have illustrated that serum PCT concentration was associated with sepsis severity, development of systemic inflammatory response syndrome, and multiple organ dysfunction syndrome.[31–35] PCT is confirmed as not only a reliable diagnostic indicator of bacterial infection,[11,36–39] but also an effective predictor of prognosis in many kinds of brain injury patients including intracerebral hemorrhage, ischemic stroke, and aneurysmal subarachnoid hemorrhage.[18–22] Previous studies with a small sample size declared the positive correlation between serum PCT and sepsis development and mortality in neurotrauma patients.[23,26,40] Consistent with findings of these studies, we found that serum PCT of non-survivors was significantly higher than survivors in our study.

The possible mechanism involved in the elevated serum PCT after TBI is multifaceted. First, systemic inflammation caused by the initial injury and an invasive procedure could induce the production of PCT in TBI patients. Systemic
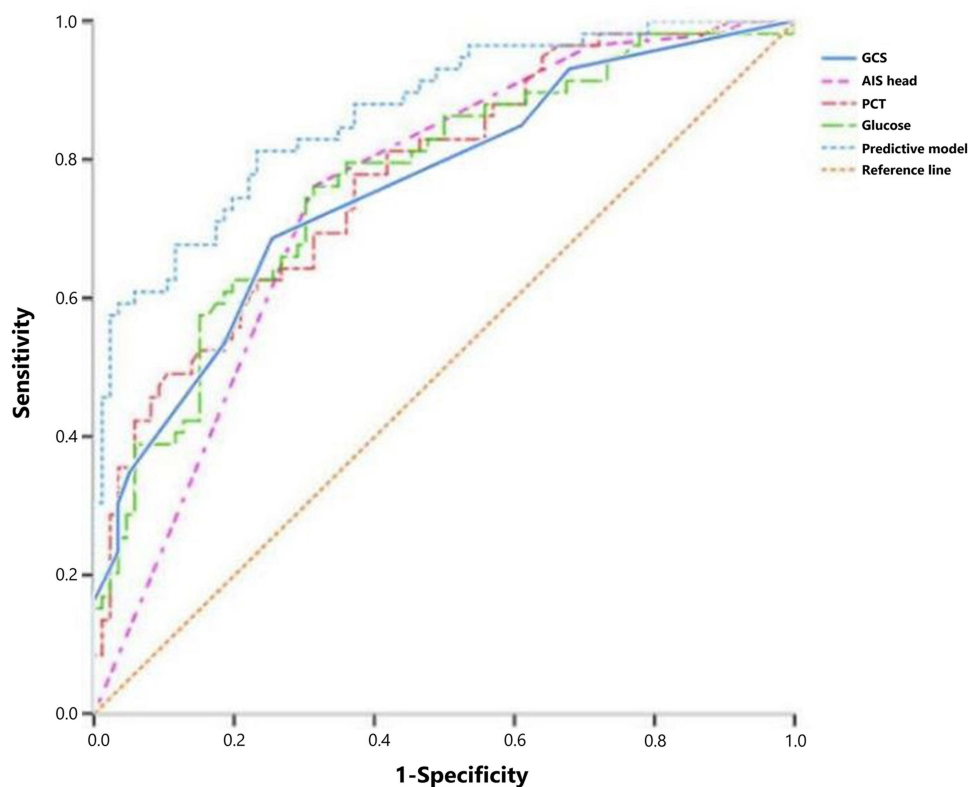
Figure 3 ROC curves of PCT and the constructed predictive model for predicting mortality in patients with isolated TBI. The AUC of PCT, glucose, GCS, and AIS head was 0.767 (95% CI=0.690–0.844), 0.765 (95% CI=0.687–0.844), 0.751 (95% CI=0.673–0.829), and 0.743 (95% CI=0.663–0.823), respectively. The AUC of the constructed predictive model was 0.868 (95% CI=0.809–0.927).

inflammatory response syndrome (SIRS) is a common complication in TBI patients with an incidence rate of 15.2% to 21%.[41,42] The SIRS early after traumatic injury is actually provoked by many factors including tissue damage, hypotension, hypoxia, cytokine release, and inflammation.[43] The PCT is considered as a classic acute-phase biomarker of the systemic inflammatory response.[44] Therefore, the initial elevated PCT after TBI could be considered as a reflection of developing systemic inflammation. Second, the local neural inflammation could also stimulate the synthesis of PCT in injured brain tissue. A previous study found that cerebrospinal fluid (CSF) procalcitonin concentration would increase after pediatric traumatic brain injury.[24] Due to the breakdown of blood–brain barrier, PCT in CSF could enter the peripheral circulation and lead to the elevated serum PCT. Some widely concerned pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), which take part in the process of secondary brain injury and disruption of neuronal regeneration, promote the production and release of PCT.[45–49] Another explanation for the elevated PCT in brain tissue is the upregulation of CALC-I gene (the gene encoding PCT) expression in the human brain tissue.[50] This mechanism was approved by the finding that increased expression of the CALC-I gene in brain tissue as a response to sepsis in animal models.[49] Some researchers believed that PCT was a member of a kind of vasodilating neuropeptides families which serves as an endogenous adaptive response to ischemic insult caused by cerebral hypoperfusion after TBI.[24,51]

The association between serum PCT and outcome in TBI patients might be mediated by local and systemic inflammation above-mentioned. As an acute phase protein PCT could indicate the level of SIRS, which has been confirmed associated with poor outcome in isolated TBI patients.[42] Previous studies have confirmed PCT as an independent predictor of multiple organ failure in the early post-traumatic phase in trauma patients with and without brain injury.[25,52] And the correlation between APACHE II, SOFA reflecting organ failure severity, and serum PCT before ICU discharge has been revealed by Spearman correlation analysis.[53] Therefore, a reasonable conjecture is that PCT is able to predict and evaluate the severity of multiple organ dysfunction syndrome (MODS), which is significantly associated with mortality following TBI.[54] In addition to the systemic inflammation, PCT might correlate with outcome of TBI patients by the mediation of local infection. Severe systemic inflammatory and imbalanced immune status caused by TBI could render patients susceptible to subsequent local infection.[55] It was estimated that 36% of patients treated in neuro-ICU would develop infectious complications.[56] Respiratory tract infection, urinary tract infection, bloodstream infection, and intracranial infection such as ventriculitis and meningitis were commonly detected in these patients.[57] As for TBI patients, the incidence of nosocomial infection was reported as high as 41%.[58] And infection development and severity are related to poor prognosis and delayed recovery in patients with neurotrauma.[58–63] Therefore, PCT could predict the outcome of TBI patients by indicating the possibilities of subsequent local infection under the influence of initial systemic inflammatory and immune status. Among all kinds of regional inflammation, the neuroinflammation may play a pivotal role in the pathophysiological process and neural regeneration of TBI. As mentioned above, elevated production of PCT is likely associated with the expression of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 in injured brain tissue and hypoxic-ischemic injury. The relationship between radiologic lesion burden, GCS score, and PCT was analyzed in a recent study.[64] Researchers considered quantitative analysis of acute phase biomarkers including PCT as an objective and supplemental assessment of neurologic status in TBI patients. A study similarly discovered that serum PCT was positively associated with severity and poor outcome of intracerebral hemorrhage patients by the mediation of increased volume of hematoma and perihematomal edema. Thus, more severe neural inflammation and injury severity indicated by elevated serum PCT is another cause leading to the poor outcome of TBI patients.[65,66] As a marker of inflammation and infection, PCT is readily available by drawing the blood sample. Some studies have conducted cost-effectiveness analysis of PCT and found it performed well in detecting infection and guiding antibiotic use with relatively lower expenditure.[67–69] The accessibility and fluctuation after injury of PCT makes it a potential prognostic marker of TBI.

Previous studies have explored the predictive value of single PCT on outcome and sepsis in TBI patients with several limitations. The AUC value of single PCT for predicting mortality in TBI patients was reported as ranging from 0.533 to 0.780 in previous studies,[23,26,70,71] whereas the AUC of PCT in our study was 0.774 for isolated TBI and 0.553 for those with extracranial injury. Therefore, it could be concluded that PCT was a reliable prognostic marker of isolated TBI patients but not TBI patients with extracranial injuries. Though Keshav Goyal et al[71] evaluated the prognostic value of

serially measured PCT levels on several time points for TBI patients, the sample size of this study was very small with obvious and improper statistical analysis that an excessive number of confounding variables included into multivariate regression. In addition, they did not evaluate the prognostic value of PCT in TBI with extracranial injury individually due to the limited number of these patients.

In our study, the significant difference between isolated TBI and those with extracranial injury might mean that extracranial injury could affect and weaken the relationship between brain injury and PCT level. Therefore, PCT may be a reliable prognostic marker aimed at isolated TBI but not those with extracranial injury. Finally, another noteworthy limitation mentioned in previous studies was that a single PCT value without combining other significant factors to construct a clinical score or model could not predict the clinical course of TBI patients accurately and comprehensively. Instead, one study found that combining PCT into National Institutes of Health Stroke Scale (NIHSS) could increase the prognostic value in ischemic stroke patients.[21] Another study also stated that modifying status epilepticus severity score using PCT could increase the prognostic value in status epilepticus patients.[18] Therefore, we conducted this study to explore the relationship between PCT, other clinical factors, and mortality by utilizing multivariate logistic regression analysis. As a result, PCT, conventional GCS, blood glucose, and cholesterol were independently associated with mortality in isolated moderate-to-severe TBI patients. Stress induced hyperglycemia have been verified many times as a potent risk factor of mortality in TBI patients.[72–75] The lower level of cholesterol in non-survivors is similar to findings of other studies indicating hypocholesterolemia is a risk factor of poor prognosis in various kinds of patients such as sepsis, intracerebral hemorrhage, and diffuse peritonitis.[76–78] And one previous study found, low serum levels of high-density lipoprotein cholesterol were positively associated with diffuse axonal injury which was an indication of poor prognosis in TBI patients.[79] The decreasing cholesterol level may be attributable to many factors including severe acute phase response, liver dysfunction, and hemodilution induced by blood loss. Our constructed model incorporating GCS, PCT, glucose, and cholesterol could evaluate a possible clinical course in isolated moderate-to-severe TBI patients more accurately than these factors alone.

Actually, plenty of studies have been designed and performed to develop novel and reliable prognostic tools for TBI. The two most concerned models among them are IMPACT and CRASH, which were developed to incorporate, age, GCS component, pupil reactivity and neuroimaging signs based on the large population size.[5,6] The AUCs of them both have reached above 0.8 with excellent discriminability and stability. The external validation for them in more specific kinds of patients is still in progress.[80,81] In addition to multimodal prognostic models, some biofluid markers including GFAP, UCHL-1, and NfL have also been explored and approved in evaluating prognosis of TBI patients.[4] These biomarkers involved in the pathophysiological process of TBI have been combined to a panel and could reflect brain injury severity and disease progression more accurately than one alone. While the panel has not been widely utilized all over the world, especially in the developing countries. Therefore, some regular examined laboratory indexes including PCT may be still valuable in evaluating the prognosis of TBI in the current clinical practice. Future studies collecting both the above-mentioned biofluid markers and PCT are worthwhile to conduct to compare their prognostic value with each other.

There were several limitations in our study. First, this study was conducted in a single center with a relatively limited sample size, especially the amount of TBI patients with extracranial injury. A further study including more participants is worthwhile to perform to validate the conclusions of our study. Second, the serum PCT level was assessed on admission. Though patients admitted to our hospital 6 hours after suffering injury were excluded, the association between PCT and outcome might still be confounded by the time interval from suffering injury to drawing a blood sample. Third, we did not evaluate previously developed multimodal prognostic calculators such as IMPACT, CRASH, and measure several widely approved biomarkers such as GFAP, S100 B, NfL, and Tau so we could not compare their prognostic value with PCT's. Fourth, only in-hospital mortality was recorded and other outcomes such as functional status and cognitive level after discharge were not evaluated in this study. Finally, the concentration of PCT in CSF which might reflect the degree of neural inflammation was not tested and, therefore, we could not analyze the relationship between serum PCT and CSF PCT.

Conclusion

PCT is useful in predicting mortality of isolated moderate-to-severe TBI patients but not TBI with extracranial injury. Our prognostic model composed of GCS, PCT, glucose, and cholesterol could guide clinicians to stratify risk level and strengthen management for isolated moderate-to-severe TBI patients.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

Our study obtained approval from the ethics committee of West China hospital (2021-1598) and accorded with the Helsinki Declaration. Informed consent forms of each patient were obtained from themselves or their legal representatives.

Author Contributions

Ruoran Wang and Yusi Hua should be considered co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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