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Naples Prognostic Score Predicts 6-Month Outcomes in Patients with Severe Traumatic Brain Injury: A Single-Center Retrospective Study

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ABSTRACT

AIM: To examine how Naples prognostic score (NPS) relates to 6-month outcomes in patients with severe traumatic brain injury (STBI).

MATERIAL and METHODS: We retrospectively analyzed the clinical data of 94 patients with STBI between September 2018 and September 2021. Galizia's method was used to calculate NPS, and patients were categorized as high (NPS>3) or low (NPS≤3) NPS according to their NPS scores based on receiver operating characteristic curve analysis. In addition, the controlling nutritional status score (CONUT) and prognostic nutrition index (PNI) were calculated. Based on the modified Rankin scale (mRS), the outcome for 6-months was evaluated. The mRS score for unfavorable outcomes was ≥3.

RESULTS: In the univariate analyses, patients in the unfavorable group had higher NPS scores ($p<0.001$). The multivariate analysis demonstrated that NPS was an independent predictor of poor outcomes after adjusting for potential confounding factors (adjusted odds ratio = 7.463, 95% confidence interval [CI]: 1.131–49.253, $p<0.05$). The area under the NPS curve for predicting poor outcomes was 0.755 (95% CI: 0.655–0.837, $p<0.001$), which was significantly higher than Glasgow coma score (GCS), CONUT, and PNI (NPS vs. GCS, $p=0.013$; NPS vs. CONUT, $p=0.029$; NPS vs. PNI, $p=0.015$).

CONCLUSION: NPS can be considered to be a novel and better independent predictor of poor outcomes in patients with STBI.

KEYWORDS: Naples prognostic score, Severe traumatic brain injury, Immune-nutritional status, Prognosis

ABBREVIATIONS: STBI: Severe traumatic brain injury, **NPS:** Naples prognostic score, **ALB:** Serum albumin, **TC:** Total cholesterol level; **NLR:** Neutrophil–lymphocyte ratio, **LMR:** Lymphocyte–monocyte ratio, **CONUT:** controlling nutritional status, **PNI:** Prognostic nutrition index, **mRS:** Modified Rankin scale, **GCS:** Glasgow coma scale, **SD:** Standard deviation, **CI:** Confidence interval, **AUC:** The area under the curve

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INTRODUCTION

Severe traumatic brain injury (STBI) exerts a huge burden on society and families due to high rates of mortality and associated complications. Previously conducted studies have indicated that a number of factors such as age, Glasgow coma score (GCS), injury severity, computed tomography findings, diabetes mellitus, intestinal dysfunction, and immune-nutritional status affect the prognosis of STBI (5,6,11,12,22). The host-related factors nutrition and immune status have attracted growing attention as predictors of clinical outcomes in a variety of diseases (9,15). Some studies have demonstrated that patients with STBI also suffered from immune-nutritional dysfunction and that the neuroinflammation caused by peripheral immune mediators, the negative nitrogen balance as well as the rapid protein breakdown in critically ill patients influence the functional impairment and subsequent poor prognosis (18,24). Therefore, identification of scoring systems that enable prediction of the prognosis of STBI and provide individualized treatment for improving immune-nutritional status are of utmost importance.

Several prognostic scoring systems have been reported to predict the outcome in patients with traumatic brain injury (TBI) (16,28). The controlling nutritional status score (CONUT) and prognostic nutrition index (PNI) were widely applied to clinical work because they combined inflammation and nutritional indicators. However, the noninclusion of neutrophils and monocyte in these systems limited their ability of evaluating immune status. A novel scoring system entitled the Naples prognostic score (NPS), which included the following four components: serum albumin (ALB), total cholesterol (TC) level, neutrophil–lymphocyte ratio (NLR), and lymphocyte–monocyte ratio (LMR) was developed. Furthermore, some studies (8,29,30) revealed that NPS could provide prognostic information in patients with various diseases. Nevertheless, the predictive value of NPS with regards to patients with STBI remains to be confirmed. Therefore, we decided to investigate the hypothesis that NPS could serve as a reliable index for predicting outcomes in patients with STBI. In this retrospective study, we aimed to examine the efficacy of NPS in predicting 6-months outcomes after STBI.

MATERIAL and METHODS

Patients

Clinical data for TBI patients treated in the Chongqing Medical University Second Affiliated Hospital's Department of Neurosurgery or intensive Care Unit from September 2018 to September 2021 were retrospectively analyzed. The inclusion criteria were as follows: 1) patients diagnosed with STBI; 2) age ≥ 18 years; 3) the time from injury to admission < 8 hours; 4) not being treated with any sedatives; 5) GCS (24 hours after admission) score < 8; 6) serum laboratory tests performed routinely in the first 24 hours following admission; 7) enteral nutrition support administered in a similar manner after admission; and 8) patients with infection treated with a similar anti-infection treatment. Exclusion criteria were as follows: 1) death within 24 hours after admission; 2) previous history of head trauma; 3) previous history of spontaneous cerebral hemorrhage, stroke, and autoimmune ailments; 4) pre-admission immunomodulatory therapy, which includes biological agents, azathioprine, corticosteroids, and methotrexate; 5) significant combined damages in the heart, liver, kidneys, spleen, and other critical organs.

Data Collection

Demographic data including age, sex, hypertension, diabetes, heart disease, and so on were collected from hospital databases and patient medical records. In addition, lifestyle risk factors, including smoking and drinking, and the incidence of cerebral hernia during hospitalization and surgical treatment were recorded. Medical complications, such as infection and deep venous thrombosis, were also noted. The GCS score of each patient was evaluated by professional or experienced neurosurgeons at admission. Serum albumin, TC, total lymphocyte count, neutrophil count, and monocyte count were determined using an automatic test system (Hitachi 7600 and BM 2000) on admission.

Methods

The following formulas were used to calculate NLR and LMR: neutrophil count ($\times 10^9$ L) / total lymphocyte count ($\times 10^9$ L), total lymphocyte count ($\times 10^9$ L) / monocyte count ($\times 10^9$ L). Galizia's method was used to calculate NPS (8). The receiver operating characteristic (ROC) curve of the 6-month survival period determined 3.5 as the best cutoff value of the NPS. The CONUT score, which consists of albumin, TC concentrations, and lymphocyte counts, was calculated in the same manner as described previously (16). The following formula was used to calculate PNI: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (/mm^3). Patients with STBI were characterized as high NPS group (NPS > 3, high-risk group) and low NPS group (NPS ≤ 3, low-risk group) based on the cutoff value. Telephone interviews were conducted to assess neurologic function in the sixth month following the incidence of STBI using the modified Rankin scale (mRS). Patients with unfavorable prognoses were defined as having an mRS score of ≥3.

Statistical Analysis

The softwares SPSS V.26 and MeDcalc19.0.7 were used to perform statistical analyses. The mean ± standard deviation (SD) or median (quartile range) was used to express continuous data, while classified data was expressed using frequencies and percentages (%). Categorical variables were analyzed using chi-square test or Fisher's exact test, and continuous variables were analyzed using Mann–Whitney U test or unpaired t-test. ROC curves were drawn in accordance with the Delong test to compare the predictive power of different grading systems. Spearman correlation was used to evaluate the correlation between NPS and mRS. We examined the relationship between variables and 6-month prognosis outcomes using univariate analysis. Multivariate logistic regressions were performed, and independent predictors were identified by setting variables that were significant in univariate analysis and clinically associated with prognosis (such as age) as covariates. Odds ratio (OR) and 95% confidence interval (CI)

were calculated. All P values were two-sided, with significance set to p<0.05.

RESULTS

Patient Characteristics

We initially assessed 179 TBI patients, but after excluding the unqualified samples 94 patients with various demographic characteristics were finally included in the study (Figure 1). Among the patients, 33 (35%) were injured in car accidents, 52 (55.3%) in falls, and 9 (9.6%) were injured in other ways. The average age was 53.2 years (range 18–93 years), and 80 among the 94 patients (85.1%) were males. The mean hospital stay was 39.5 days, and the average GCS was 6.5. A cerebral herniation was reported in 31 (33.1%) the patients shortly before or after admission. Of all STBI patients, 50 (53.2%) underwent surgery (Table I).

The Relationship Between NPS and mRS

Univariate and multivariate analyses were performed on 94 patients with STBI. In our study, 46 (48.9%) patients had good outcomes (mRS < 3) after 6 months of follow-up, whereas 59 (62.8%) patients had low NPS scores. Spearman correlation analysis demonstrated that the unfavorable group was associated with higher NPS (p<0.001), CONUT (p<0.01), NLR (p=0.207), neutrophil and monocyte counts (p=0.88, p=0.135), the morbidity due to pneumonia (p<0.01), rates of intracranial infection (p<0.01) and were inversely correlated with PNI (p<0.01), GCS score (p<0.01), ALB (p<0.05), TC (p<0.05), LMR (p<0.05), and lymphocyte count (p=0.172) (Table II). To obtain

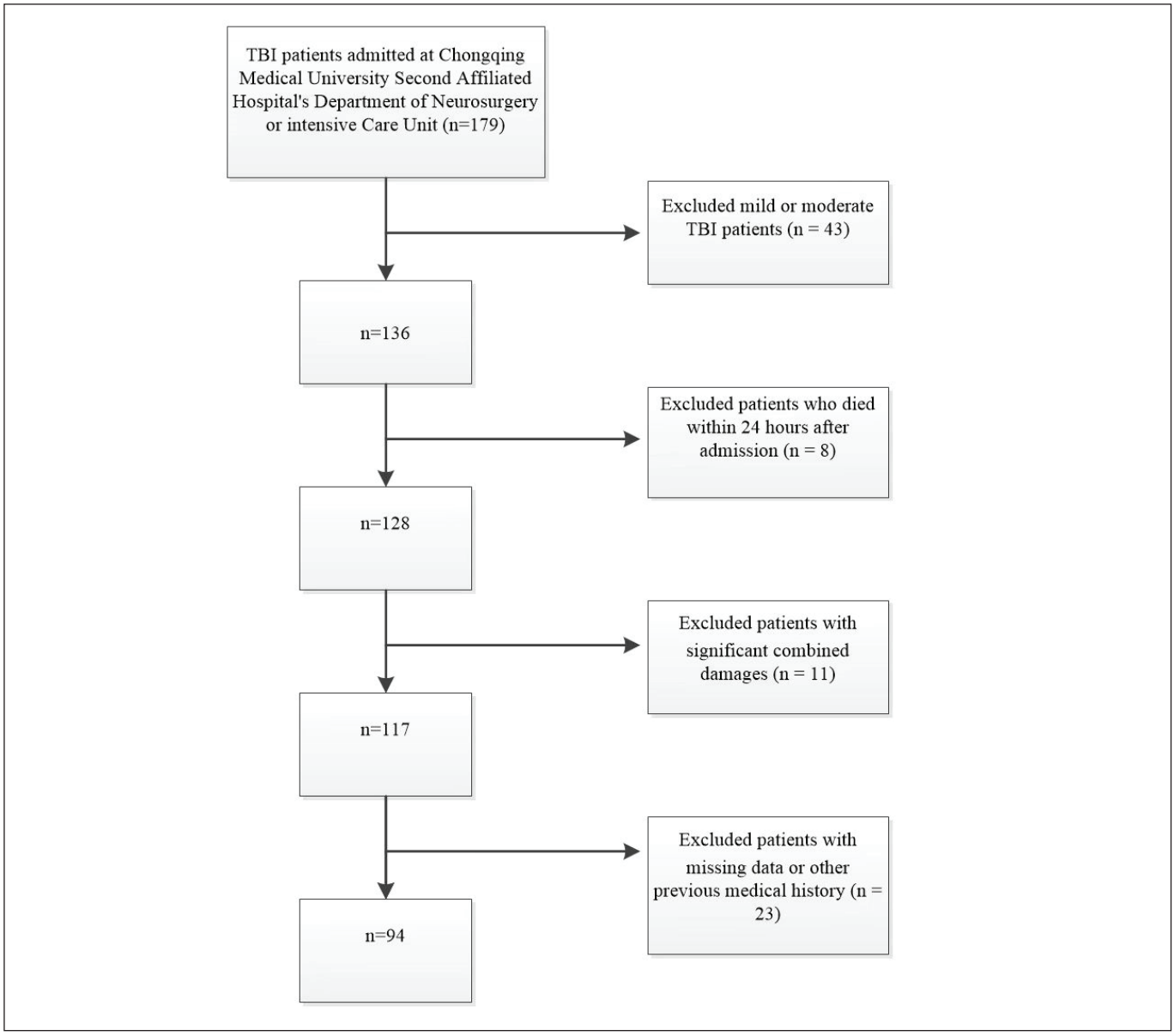

Figure 1: Flow chart of study population selected.

Table I: Characteristics of Patients with STBI

Characteristics		Value or No. of patient
Age (years)	Mean (SD)	53.2(16.4)
	Range	18-93
Gender	Male	80 (85.1)
	Female	14
Hospital Stay (days)	Mean (SD)	39.52 (28.9)
Smoking status	Never-smoker	45
	Smoker	49
Drinking status	Never-drinker	55
	Drinker	39
Hypertension	Absent	81
	Present	13
Diabetes mellitus	Absent	86
	Present	8 (8.5)
Cardiovascular disease	Absent	93
	Present	1
GCS score	Mean (SD)	6.54 (1.7)
Posttraumatic seizure	Absent	87
	Present	7
The type of injury	open injury	39
	closed injury	55
Cerebral herniation	No	63
	Yes	31
Surgery	No	44
	Yes	50
Pneumonia	No	28
	Yes	65
Intracranial infection	No	77
	Yes	17
Lower urinary tract infection	No	87
	Yes	7
Deep venous thrombosis	No	90
	Yes	4
ALB (mg/dL)	Mean (SD)	37.3 (7.0)
TC (mg/dL)	Mean (SD)	161.2 (47.4)
NLR	Mean (SD)	15.8 (10.5)
LMR	Mean (SD)	1.7 (1.9)
PNI	Mean (SD)	42.2 (8.1)
CONUT	Mean (SD)	4.35 (3.0)
NPS	Mean (SD)	3.2 (0.8)
NPS (%)	LOW (≤ 3)	59 (62.8)
	HIGH (> 3)	35 (37.2)
NPS	POINT	
	0	0
	1	10 (10.6)
	2	19 (20.2)
	3	30 (31.9)
	4	35 (37.2)

NPS: *Naples prognostic score,* ***ALB:*** *serum albumin,* ***TC:*** *total cholesterol level,* ***NLR:*** *neutrophil - lymphocyte ratio,* ***LMR:*** *lymphocyte-monocyte ratio;* ***CONUT:*** *controlling nutritional status;* ***PNI:*** *prognostic nutrition index;* ***GCS:*** *Glasgow coma scale;* ***SD:*** *standard deviation.*

a better perspective of the association between NPS and the 6-month outcomes, a multivariate analysis was conducted, and it was observed that NPS (adjusted OR = 7.463, 95% CI: 1.131–49.253, p<0.05) was still strongly correlated with mRS after adjusting for GCS score, age, pneumonia, and intracranial infection. Two additional models corroborated the relationship between CONUT (adjusted OR = 6.514, 95% CI: 1.140–37.237, p<0.05) and PNI (adjusted OR = 0.007, 95% CI: 0.110–0.449, p<0.05) with mRS (p<0.05) in the multivariate analysis (Table III). However, multivariate analysis did not demonstrate a strong association between individual components of NPS and mRS.

Comparison Between NPS and GCS and Between CONUT and PNI

The estimated area under the curve (AUC) and 95% CI were calculated at different time points for each prognostic scoring system, based on time-dependent ROC curves (Figure 2 and Table IV). The AUC of NPS for predicting unfavorable outcome was 0.755 (95%CI: 0.655–0.837, p<0.001), whereas that of GCS, CONUT, and PNI was 0.693 (95%CI: 0.589–0.894, p=0.002), 0.708 (95%CI: 0.606–0.798, p=0.001), and 0.690 (95%CI: 586–0.781, p=0.002), respectively. A significant superiority in NPS over GCS, CONUT, and PNI was detected using the Delong method (NPS vs. GCS, p=0.013; NPS vs. CONUT, p=0.029; NPS vs. PNI, p=0.015).

DISCUSSION

The present study first investigated the relationship between NPS and the outcome of 6-month STBI. Our findings indicated that patients with higher NPS scores at admission can possibly suffer from unfavorable outcomes 6 months after the brain injury. In addition, the results of time-independent ROC analysis revealed better prognostic reliability of NPS for mRS than other scoring systems, including GCS, CONUT, and PNI. Taken together, our study corroborated the hypothesis that NPS at admission could be a significant independent predictor of functional outcomes for patients with STBI.

Table II: In the Univariate Analysis of Participating Patients by 6-Month Prognosis Outcome

Characteristics	Total patients N=94	Favourable outcome (0-2) N=46	Unfavourable outcome (3-6) N=48	p-value
Age (years), mean (SD)	53.2 (16.4)	50.9 (14.4)	55.3 (18.2)	0.198[d]
Gender (male), n (%)	80 (85.1)	38 (82.6)	42 (87.5)	0.506[c]
Hospital Stay (days), mean (SD)	39.5 (28.9)	37.0 (3.9)	41.9 (4.5)	0.553[f]
GCS score, mean (SD)	6.5 (1.7)	7.2 (1.7)	5.9 (0.3)	**0.001[f]**
Smoking, n (%)	49 (52.1)	26 (56.5)	23 (47.9)	0.404[c]
Drinking, n (%)	39 (41.5)	21 (45.7)	18 (37.5)	0.423[c]
Hypertension, n (%)	13 (13.8)	6 (13)	7 (14.6)	0.829[c]
Diabetes mellitus, n (%)	8 (8.5)	3 (6.5)	5 (10.4)	0.715[a]
Posttraumatic seizure, n (%)	7 (7.4)	4 (8.7)	3 (6.3)	0.711[a]
Cardiovascular disease, n (%)	1 (1.1)	0	1 (2.1)	1[a]
Surgery, n (%)	50 (53.2)	22 (47.8)	28 (58.3)	0.307[c]
Pneumonia, n (%)	65 (69.1)	26 (56.5)	40 (83.3)	**0.001[c]**
Intracranial infection, n (%)	17 (18.1)	3 (6.5)	14 (29.2)	**0.004[c]**
Lower urinary tract infection, n (%)	7 (7.4)	2 (4.3)	5 (10.4)	0.436[a]
Deep venous thrombosis, n (%)	4 (4.3)	1 (2.2)	3 (6.3)	0.617[a]
ALB (mg/dL)	37.3 (7.0)	38.2 (6.5)	36.4 (7.5)	**0.038[f]**
TC (mg/dL)	161.2 (47.4)	171.6 (48.1)	151.4 (44.9)	**0.025[f]**
Neutrophil (109L)	12.0 (5.0)	11.7 (4.0)	12.3 (5.8)	0.880[f]
Lymphocyte (109L)	0.98 (0.6)	1.0 (0.5)	0.9 (0.6)	0.172[f]
Monocyte (109L)	0.7 (0.4)	0.67 (0.3)	0.82 (0.48)	0.135[f]
NLR	15.8 (10.5)	13.6 (7.3)	17.9 (12.6)	0.207[f]
LMR	1.7 (1.9)	1.9 (2.2)	1.5 (1.7)	**0.032[f]**
PNI	42.2 (8.1)	43.3 (7.4)	41.1 (8.6)	**0.001[f]**
CONUT	4.3 (0.3)	3.9 (2.9)	4.8 (2.9)	**0.003[f]**
NPS (%)				**0.021[e]**
0	0	0	0	
1	10 (10.6)	10 (21.7)	0	
2	19 (20.2)	12 (26.1)	7 (14.6)	
3	30 (31.9)	16 (34.8)	14 (29.2)	
4	35 (37.2)	8 (17.9)	27 (56.3)	
NPS (%)				<0.001[c]
LOW (≤ 3)	59 (62.8)	38 (82.1)	21 (43.7)	
HIGH (> 3)	35 (37.2)	8 (17.9)	27 (56.3)	

NPS: *Naples prognostic score,* ***ALB:*** *Serum albumin,* ***TC:*** *Total cholesterol level,* ***NLR:*** *Neutrophil - lymphocyte ratio,* ***LMR:*** *Lymphocyte-monocyte ratio,* ***CONUT:*** *Controlling nutritional status;* ***PNI:*** *Prognostic nutrition index,* ***GCS:*** *Glasgow coma scale.*
[a] Fisher's exact test. [b] Continuous calibration of x2 test. [c] X2 test. [e] Rank sum test. [d] T-test. [f] U-test.

Table III: Multivariate Analysis of the Involvement of Different Variables in Stbi Patients with Poor Functional Outcomes at 6 Months

			Model 1		
	Age	**GCS**	**Pneumonia**	**Intracranial infection**	**NPS**
β	0.06	-0.588	0.136	2.324	2.01
OR	1.062	0.555	1.146	10.221	7.463
95% CI	1.020-1.107	0.380-0.811	0.358-3.669	1.887-55.36	1.131-49.253
p	**0.004**	**0.002**	0.819	**0.007**	**0.037**

			Model 2		
	Age	**GCS**	**Pneumonia**	**Intracranial infection**	**CONUT**
β	0.056	-0.521	0.243	2.35	1.874
OR	1.058	0.594	1.276	10.482	6.514
95% CI	1.07-1.1	0.410-0.861	0.406-4.003	1.998-54.997	1.14-37.237
p	**0.005**	**0.006**	0.677	**0.005**	**0.035**

			Model 3		
	Age	**GCS**	**Pneumonia**	**Intracranial infection**	**PNI**
β	0.047	-0.525	0.040	2.135	-2.660
OR	1.048	0.592	1.041	8.460	0.070
95% CI	1.009-1.688	0.400-0.875	0.329-3.286	1.688-42.391	0.110-0.449
p	**0.014**	**0.009**	0.946	**0.009**	**0.005**

NPS: *Naples prognostic score,* ***CONUT:*** *Controlling nutritional status,* ***PNI:*** *Prognostic nutrition index,* ***GCS:*** *Glasgow coma scale,* ***OR:*** *Odds ratios,* ***95%CI:*** *95% confidence interval.*

Table IV: The ROC Curve Comparison Between CONUT, PNI and NPS

	NPS	**CONUT**	**PNI**
AUC	0.755	0.708	0.690
Youden index	0.389	0.345	0.327
p	**<0.001**	**0.001**	**0.002**

NPS: *Naples prognostic score,* ***CONUT:*** *Controlling nutritional status,* ***PNI:*** *Prognostic nutrition index,* ***AUC:*** *The area under the curve.*

Host-related factors, injury type and extent, and treatment influence the clinical outcomes of STBI patients (2). Immune-nutritional status has been recognized as one of the most critical factors related to the host (1). Various serum indicators have been used to assess immune-nutritional status (3, 23). However, the precision of a single indicator is limited under the influence of multiple nonpathological factors. Therefore, various prognostic scoring systems including PNI, CONUT, NPS, and so on have been developed.

A recently conducted research has indicated that neuroinflammation and the immune system were closely linked to wound healing during the early stages, and to the recovery of neurological impairment at advanced stages (7). Meisel (17) reported that the infiltration of a large number of T lymphocytes at damaged sites may be associated with a favorable outcome due to release of growth factors and regulating function of the lymphocytes, which is in agreement with our findings. T lymphocytes were not the only white blood cells that contribute to the immune process , as neutrophils, which are inflammatory cells, are recruited to the damaged site quickly and these release toxic molecules that promote secondary damage (14,19). Monocytes are also involved in pathogenic activity during the chronic phase after TBI, and are associated with edema (7). All the viewpoints outlined above corroborate with our findings that elevated neutrophil and monocyte counts were related to poor clinical outcomes.

LMR and NLR, which are combinations of the aforementioned lymphocytes, neutrophils, and monocytes, provided a better prognosis for TBI than their individual values. Higher NLR levels have been shown to be associated with deleterious clinical outcomes (including high mortality rate) in patients with STBI (4,31). Furthermore, an association between LMR and the neurological outcome of patients following acute

ischemic stroke has also been reported (10). Thus, elevated NLR and lower LMR observed in the unfavorable group in our study were as expected.

Apart from above immunological indicators, NPS also includes albumin (ALB) and TC. ALB represents nutritional status and is a superior indicator to assess nutrition in patients with TBI (3). Studies have reported that lowered ALB concentration indicates an impaired ability to resist trauma, resulting in detrimental consequences (27). Tokunaga et al. considered reduced ALB concentration to represent systemic inflammation (26). We observed a significant difference in serum albumin levels between the favorable and unfavorable groups, which was in agreement with the previous reports. As another nutritional indicator complement to ALB, TC was of importance as well (20). The concentration of cholesterol was determined to be a key factor affecting the ability of myelin and axolemma to withstand strain during injuries (13), which could explain the lower levels of TC detected in the unfavorable groups in our investigation.

One study had identified PNI as a reliable prognostic indicator in cancer patients with near-terminal stages, while according to few other studies, CONUT score was an effective tool for predicting TBI outcomes (16,21,28). We calculated both CONUT and PNI, and the multivariate analysis revealed that CONUT and PNI were also independent predictors of mRS. However, comparison of the area under the ROC curve demonstrated that NPS was more efficacious in predicting poor outcomes as CONUT and PNI by. A possible underlying reason may be that NPS contains a broader range of indicators than CONUT or PNI separately. Also, GCS, the most common scale to evaluate TBI severities and outcomes (25), failed to demonstrate better predictive power than NPS. In part, this may be due to the fact that GCS is a subjective score, not a quantitative one.

Our findings indicated that NPS can independently be used to predict the prognosis of STBI patients and was also demonstrated to be more powerful than GCS, CONUT, and PNI in predicting poor outcomes. Our findings indicate a link between immune-nutritional status and prognosis of patients with STBI. Immune status management and adequate nutritional support seem to be pivotal treatments for improving the prognosis of patients suffering from an STBI. Clinicians can identify patients who are at high risk of malnutrition and immune disorders based on their NPS score at admission. The STBI patients at higher risk can then receive appropriate attention and treatment as soon as possible. In light of the foregoing research findings, it can be concluded that patients with STBI could benefit from NPS as a treatment guide.

However, some potential limitations still exist in our study. First of all, subject selection bias is unavoidable in this retrospective observational study conducted in a single center, with relatively few patients. Also, only a single set of serum data was collected on admission, but the posttraumatic immune response is usually long-term, chronic, and dynamic. Therefore, more relevant basic research and prospective studies with larger samples are necessary.

CONCLUSION

Higher NPS is closely correlated with poorer outcomes in patients suffering from STBI. In addition, NPS has a greater predictive value and is more objective and comprehensive than other indicators. With NPS, clinicians can identify individuals at risk of malnutrition or immune disorders at an early stage and offer timely nutritional and immunological intervention to result in better outcomes for patients.

Ethics Approval

Chongqing Medical University's Second Affiliated Hospital Ethics Committee has approved this study on August 18, 2022 (No. 2022. kelunshen139).

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Declarations

The manuscript complies with all instructions to the authors. The authorship requirements have been met and the final manuscript was approved by all authors. This manuscript has not been published elsewhere and is not under consideration by another journal.

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AUTHORSHIP CONTRIBUTION

Study conception and design: CC, ZX
Data collection: CC, HY, WS
Analysis and interpretation of results: CC, YZ, WS
Draft manuscript preparation: CC, MS, WS
Critical revision of the article: CC, MS, YZ, RL, YT, HY, WS, ZX
Other (study supervision, fundings, materials, etc...): ZX
All authors (CC, MS, YZ, RL, YT, HY, WS, ZX) reviewed the results and approved the final version of the manuscript.

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