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Dynamic changes in neuron-specific enolase level to glasgow coma scale score ratio predict long-term neurological function of diffuse axonal injury patients

Weiliang Chen[1], Jiayi Wu[2], Shengwen Li[3], Chunyu Yao[1], Rui Chen[1], Wen Su[1] and Guanjun Wang[1*]

Abstract

Background Patients with diffuse axonal injury (DAI) are often plagued by sequelae, and the current indicators for predicting long-term neurological function are not accurate enough. Our previous studies have found that serum Neuron-specific enolase (NSE) level to Glasgow Coma Scale (GCS) score ratio(NGR) at admission could be used as an independent predictor of DAI.

Objective To explore the accuracy of dynamic changes of NGR in predicting long-term neurological function in patients with DAI.

Methods Patients with DAI were included based on clinical MRI as the diagnostic standard, and divided into two groups with favorable and unfavorable outcome according to the 6-month Extended Glasgow Outcome Scale (GOSE) as the prognosis indicator. The differences in clinical parameters between the two groups of patients were compared by Pearson correlation analysis. The trend of dynamic changes in NSE, GCS, and NGR at 1st, 3rd, 5th, 7th and 14th days after injury were shown by line graphs. The predictive efficacy of various parameters for long-term neurological function were further analyzed by receiver operator characteristic (ROC) curves.

Results Among the 102 DAI patients, 75 (73.5%) were classified to favorable outcome group (GOSE5-8) and 27 (26.5%) to unfavorable outcome (GOSE1-4). The NSE, NGR and Marshall CT grade at the first day after injury in the favorable outcome group were significantly lower than those in the unfavorable outcome group ($p=0.005$, $p<0.001$, $p=0.002$), but the GCS score was significantly higher than that of the latter ($p=0.006$). There was a negative correlation between NGR at 1st, 3rd, 5th, 7th, and 14th days post-TBI (r1=-0.557, r3=-0.746, r5=-0.761, r7=-0.727, r14=-0.694), and the 6-month GOSE. DAI patients with a favorable outcome exhibited a gradual decline in NGR. The area under the ROC curves (AUC) of NGR at 1st, 3rd and 5th days post-TBI were 0.751 (95% CI, 0.646–0.856, $p<0.001$), 0.913 (95% CI, 0.859–0.967, $p<0.001$), 0.934 (95% CI, 0.886–0.982, $p<0.001$), which were the largest among the three parameters.

*Correspondence:
Guanjun Wang
hainingwwwhk@163.com

Full list of author information is available at the end of the article

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Conclusions The dynamic changes of NGR may be an accurate predictor of long-term neurological function in patients with DAI.

Clinical trial registration Trial Registration Number ChiCTR2100044352, registration date was March 17, 2021.

Keywords Diffuse axonal injury, Neuron specific enolase, Glasgow coma scale, Dynamic change, Neurological function

Introduction

DAI is caused by acceleration-deceleration or rotational forces on brain tissues, resulting in axonal shear injuries and delayed axonal disconnection, categorized as a special type of TBI [1, 2]. DAI may lead to long-term neurological dysfunction, 20–38% of DAI patients were followed up with unfavorable outcome [3–5].

If DAI can be diagnosed early after TBI and the long-term neurological function of these patients can be accurately predicted, appropriate treatment measures and early targeted rehabilitation programs can be given to DAI patients with a high probability of unfavorable outcome, which will be of great help in improving their prognosis [6–8]. Therefore, many scholars were committed to exploring prognosis assessment schemes for DAI. Chabok. et al. [9] found that serum NSE and S100BB levels increased within 3 days after DAI were associated with poor outcome. The severity of TBI and the grading of DAI also affected the prognosis [10]. Early fever and extensive DAI on magnetic resonance imaging (MRI) were associated with worse long-term outcomes in children with severe TBI [11]. Grassi. et al. [12] applied diffusion tensor imaging (DTI) to dynamically assess the integrity of the brain white matter in DAI patients and found that changes in the microstructure of the white matter were associated with cognitive dysfunction. In Palmieri. et al. [13] review article, they mentioned that the main clinical factors affecting DAI prognosis were early GCS, blood pressure, peripheral oxygen saturation, glycemia and time to consciousness recovery.

The patient's condition changes over time, and it is not accurate enough to predict the long-term neurological function of DAI patients using only admission or a certain time point parameters [12, 13]. We need to explore convenient collected, objective, and dynamically predictive indicators. Our previous studies have found that NGR at admission could be used as an independent predictor of DAI [7], so we further hypothesized that the dynamic changes in NGR can more accurately predict the long-term neurological function of DAI patients and provide support for disease assessment and treatment strategy.

Methods

Participants

Patients with DAI diagnosed by MRI within 30 days after injury were screened in this retrospective observational study between July 2021 and June 2023. Long-term neurological function of DAI patients were assessed by GOSE at 6 months after injury. This data collection site was approved by the local Institutional Review Board, and written informed consent was obtained from all participants or their representatives.

The inclusion criteria were the following: age between 18 and 70 years, time from TBI to emergency department within 6 h, diagnosed as DAI by clinical MRI scan within 30 days after injury. The exclusion criteria were the following: craniotomy within 14 days after injury, unable to complete serum NSE collection and testing on the 1st, 3rd, 5th, 7th, and 14th days post-TBI(68/153, 44.4%), pre-hospital sedation and intubation(27/153, 17.6%), progressive brain illness (Parkinson disease, dementia, seizure disorder, multiple sclerosis, brain tumor)(9/153, 5.9%), secondary brain injury(infarction, hemorrhage and intracranial infection)(24/153, 15.7%), history of brain surgery or stroke without full recovery(6/153, 3.9%), severe peripheral organ complications have not been reversed(7/153, 4.6%), TBI combined with severe circulatory failure(12/153, 7.8%).

Reactions and quantification of NSE were performed with Beckman DXI800(Beckman Coulter, CA, USA), using a commercially available chemiluminescent immunoassay kit (Sichuan Orienter Biotechnology CO., Ltd. Chengdu, China).

Parameters

Demographic and clinical characteristics were collected upon arrival to emergency department, including age, sex, causes of trauma(road traffic accident, fall, and others), admission GCS score, pupillary light reflex (none, unilateral or bilateral, flashlight method), Marshall computed tomography(CT) grade (evaluated on a scale from 1 to 6) from the first head CT scan, mean arterial blood pressure (MAP), hypotension and hypoxia, duration of coma, timing of MRI, number of DAI Lesions, length of in-hospital stay, serum NSE levels at the 1st, 3rd, 5th, 7th, and 14th days post-TBI. Pain and sedative drugs were stopped before GCS scoring during hospitalization.

Definitions

The clinical MRI was performed with a 1.5T scanner (Siemens Symphony, ATim). DAI were defined as TBI patients with lesions in gray-white matter junction of the cerebrum, corpus callosum, or brain stem with T2-weighted imaging (T2WI), T2-weighted fluid attenuated inversion recovery (T2 FLAIR) and diffusion-weighted imaging (DWI) in MRI [14, 15]. These lesions were defined as having hypointense focus presented on T2WI (hemorrhagic DAI), or hyperintense focus presented on DWI, T2 FLAIR and T2WI (non-hemorrhagic DAI) [15, 16]. The MRI and CT images were independently analyzed by two experienced neuroradiologists, who had access to patient clinical information but were blinded to the serum NSE levels.

Outcome assessment

Neurological function status assessment at 6 months post-injury was performed by a structured telephone survey of patients or caregivers. GOSE was used to quantify 6-month outcome as favorable neurological outcome (GOSE 5–8; no or moderate disability) or unfavorable neurological outcome (GOSE 1–4; severe disability or death). The imputed 6-month GOSE average from the primary analysis in our study was assigned to those missing GOSE [17] (favorable outcome group 4/75, unfavorable outcome group group 2/27).

Table 1 Demographic and clinical characteristics of DAI patients with favorable and unfavorable outcome group

Variables	Unfavorable outcome ($n=27$)	favorable outcome ($n=75$)	*p* value
Male, n (%)	19(70.4)	53(70.7)	0.977
Age (years), median (IQR)	55 (47–63)	53(42–59)	0.210
Cause of trauma, n (%)			
Road traffic accident	11(40.7)	37(49.3)	0.443
Fall	14(51.9)	31(41.3)	0.345
Others	2(7.4)	7(9.3)	0.762
Pupillary light reflex, n (%)			
None pupillary light reflex	7(25.9)	2(2.7)	< 0.001*
Unilateral pupillary light reflex	6(22.2)	6(8)	0.049*
Bilateral pupillary light reflex	14(51.9)	67(89.3)	< 0.001*
GCS1, median (IQR)	8(4.5–10.5)	10(8–12)	0.006*
Marshall CT score, median (IQR)	4(3–5)	3(2–4)	0.002*
Timing of MRI (IQR)	16(12–21)	14(8–19)	0.064
Number of DAI Lesions (IQR)	8(6-8.5)	6(5–8)	0.057
Length of in-hospital stay (IQR)	21(18.5–30.5)	17(14–22)	0.001*
NSE1, median (IQR)	34.1 (28.3–39.3)	23.4 (17.3–31.8)	0.005*
NGR1, median (IQR)	4.5 (3-6.6)	2.7(1.8–3.6)	< 0.001*

MRI, magnetic resonance imaging; NSE1, serum neuron-specific enolase level on the 1st day post-TBI; GCS1, Glasgow Coma Scale on the 1st day post-TBI, NGR1, serum NSE level to admission GCS score ratio on the 1st day post-TBI; GOSE, Extended Glasgow Outcome Scale, favorable outcome = GOSE5–8; unfavorable outcome = GOSE1–4, IQR = (25th percentile–75th percentile). *statistically significant difference between the two groups

Statistical analysis

All statistical analyses were performed using GraphPad Prism 9.5 (GraphPad Software, San Diego, CA, USA). A value of $p < 0.05$ with a two-tailed test was considered statistically significant. Categorical data are presented as frequency or percentage and compared by Fisher exact test. Continuous data are presented as the median and interquartile range (IQR) and were compared by the Mann-Whitney U test. Pearson correlation analysis was employed to show the association of the dynamic changes of various clinical parameters and GOSE, and presented in the form of a forest plot. The ROC curves were performed to assess the diagnostic accuracy of parameters at different time points in predicting the neurological function status of DAI patients at 6 months.

Results

Enrollment and characteristics of patients

255 patients with TBI met all the inclusion criteria were enrolled during the study period. 153 patients were excluded due to the exclusion criteria, and a total of 102 patients were analyzed. Among them, 75 DAI patients were classified into the favorable outcome group 6 months after injury, and 27 patients were classified into the unfavorable outcome group. By comparing the clinical parameters between the two groups, it was found that there was no significant statistical difference in the five aspects of cause of trauma, sex, age, timing of MRI and number of DAI Lesions between the two groups of patients. The patients in the favorable outcome group had significantly higher frequency of intact bilateral pupillary light reflex. The serum NSE level, NGR and Marshall CT grade on the first day after injury in the favorable outcome group were significantly lower than those in the unfavorable outcome group ($p = 0.005$, $p < 0.001$, $p = 0.002$), but the GCS score was significantly higher than that of the latter ($p = 0.006$). The length of in-hospital stay in the favorable outcome group was significantly shorter than that in the unfavorable outcome group ($p = 0.001$) (Table 1).

Correlation between dynamic changes in clinical parameters and GOSE

Pearson correlation analysis was employed to define the association of dynamic changes in clinical parameters with 6-month GOSE (Fig. 1). There was a negative correlation between Marshall CT score(r=-0.474), serum NSE and NGR levels at 1st, 3rd, 5th, 7th, and 14th days post-TBI (NSE: r1=-0.435, r3=-0.658, r5=-0.603, r7=-0.565, r14=-0.335; NGR: r1=-0.557, r3=-0.746, r5=-0.761, r7=-0.727, r14=-0.694), and the 6-month GOSE

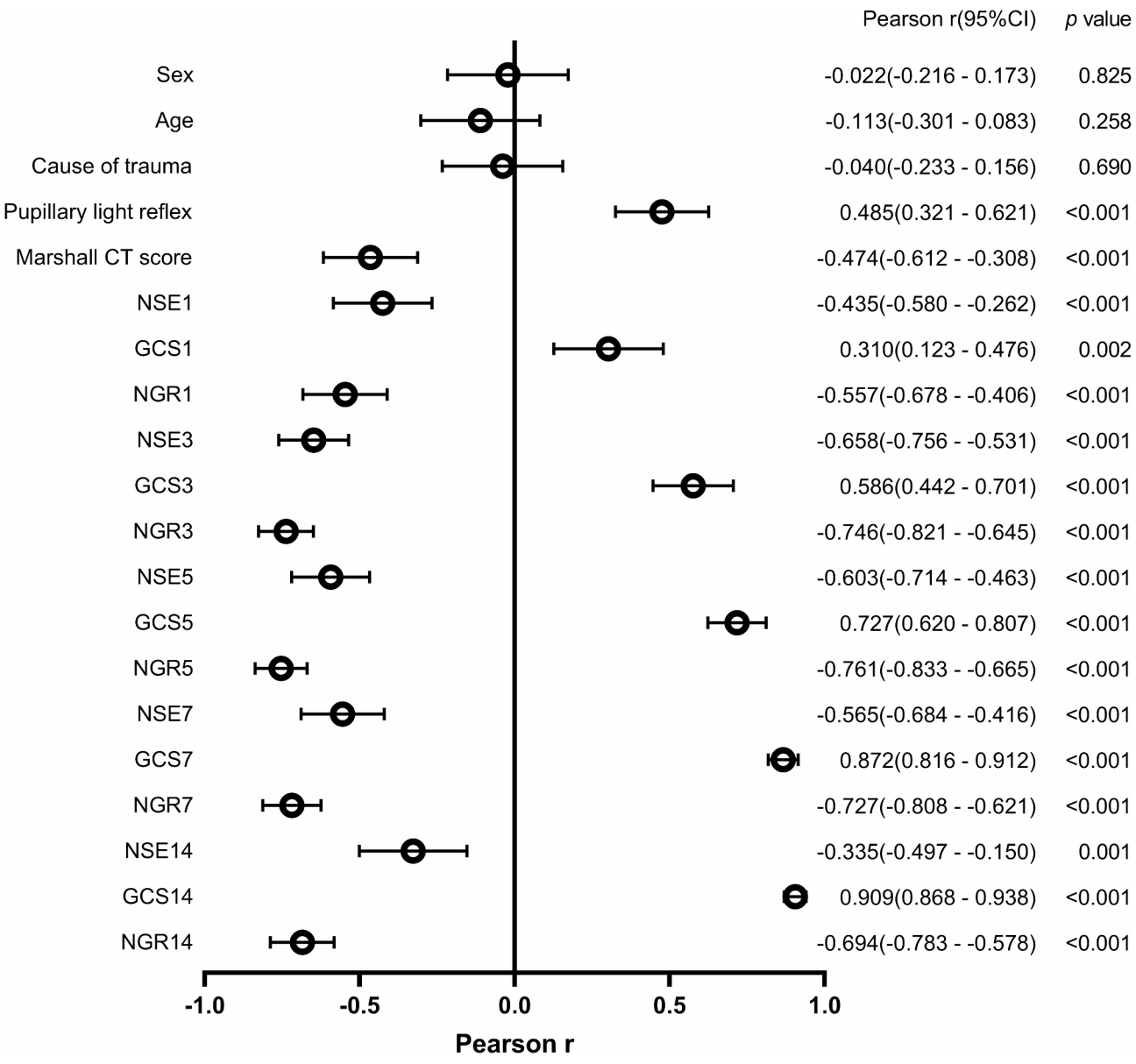

Fig. 1 Correlation between dynamic changes of clinical parameters and 6-month GOSE. NSE1, serum neuron-specific enolase level at the 1st day post-TBI; GCS1, Glasgow Coma Scale at the 1st day post-TBI, NGR1, serum NSE level to admission GCS score ratio at the 1st day post-TBI

in patients with DAI. Additionally, there was a positive correlation between GOSE and pupillary light reflex, as well as GCS at 1st, 3rd, 5th, 7th, and 14th days post-TBI ($r = 0.485$, GCS: r1 = 0.310, r3 = 0.586, r5 = 0.727, r7 = 0.872, r14 = 0.909). However, there was no significant correlation between the cause of trauma ($p = 0.690$), age ($p = 0.258$), sex ($p = 0.825$), and the 6-month GOSE.

Comparison of the dynamic changes of parameters between favorable and unfavorable outcome group

Figure 2 presents line graphs illustrating the dynamic changes in serum NSE levels, GCS, and NGR in DAI patients at 1st, 3rd, 5th, 7th, and 14th days post-TBI. Serum NSE levels (Fig. 2A): Patients with a favorable outcome showed a consistent downward trend, while those with an unfavorable outcome experienced a rapid increase in the three days post-TBI, reaching a peak and then gradually decreasing. GCS (Fig. 2B): Patients with a favorable outcome demonstrated a continuous increase in GCS scores. In contrast, patients with an unfavorable outcome showed a decreasing trend within the five days post-TBI, followed by a slow increase, with the peak value significantly deviating from the normal range. NGR (Fig. 2C): Patients with a favorable outcome exhibited a gradual decline in NGR levels. On the other hand, patients with an unfavorable outcome experienced

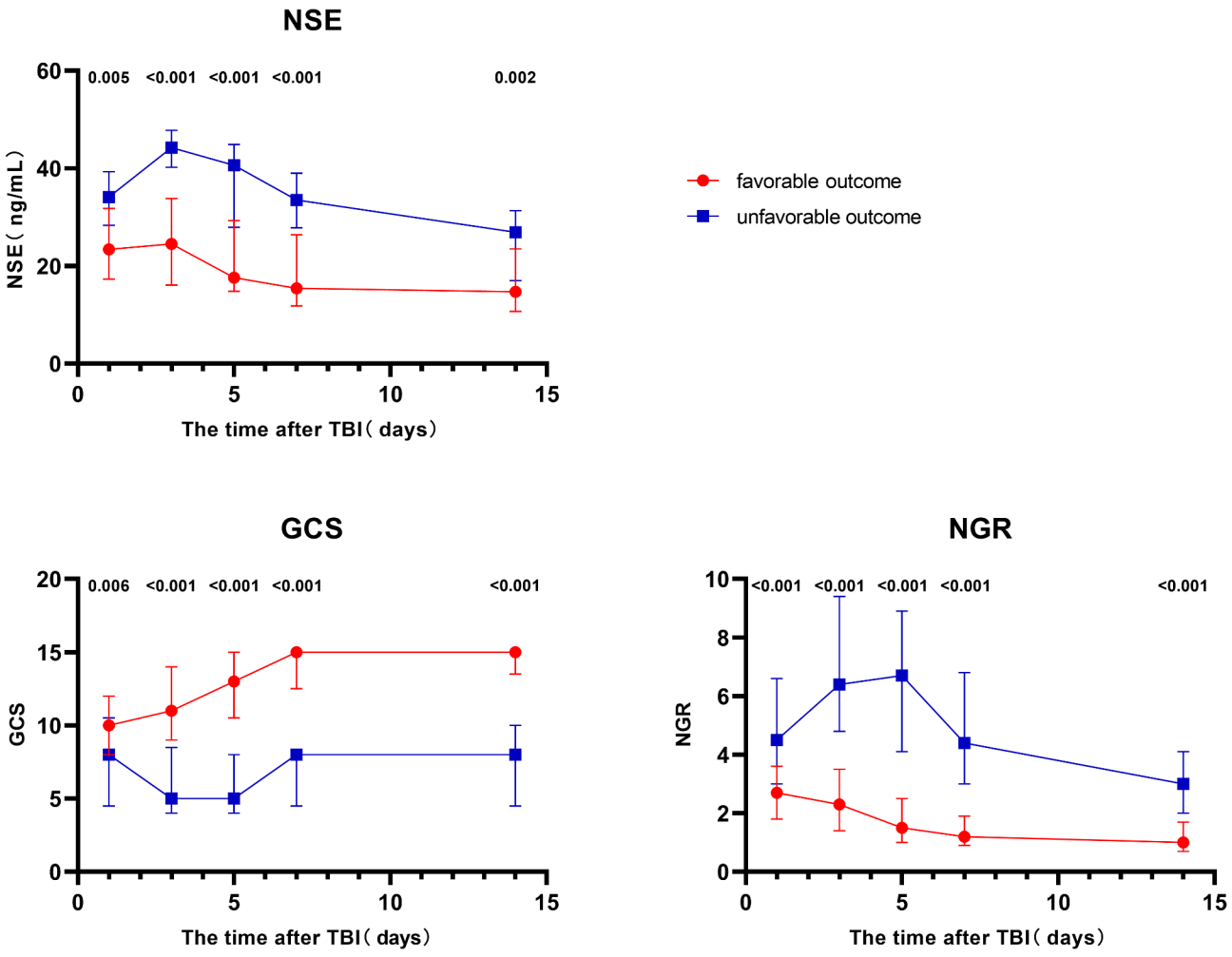

Fig. 2 Dynamic changes in NSE, GCS, and NGR in DAI patients at 1st, 3rd, 5th, 7th, and 14th days post-TBI. The numbers represent Mann-Whitney U test p-values comparing favorable and unfavorable outcomes at each time point. NSE, neuron-specific enolase; GCS, Glasgow Coma Scale, NGR, serum NSE level to admission GCS score ratio. The data was entered as median (25th percentile–75th percentile)

a continuous increase in NGR levels within the five days post-TBI, reaching a peak and then slowly decreasing. Moreover, the overall NGR levels remain higher in the unfavorable outcome group compared to the favorable outcome group, with significant statistical differences (Supplementary material).

Predictive power of parameters for long-term neurological function

The predictive power of various parameters at different time points for long-term prognosis after injury was compared using the AUCs, as shown in Fig. 3.

The AUC of NGR at 1st day post-TBI was 0.751 (95% CI, 0.646–0.856, $p < 0.001$), which was the largest among the three parameters (GCS, 0.677, NSE, 0.679) (Fig. 3A). The AUC of NGR at 3rd day post-TBI was 0.913 (95% CI, 0.859–0.967, $p < 0.001$), was larger than NSE and GCS (0.821, 0.849) (Fig. 3B). The AUC of NGR at 5th day post-TBI was 0.934 (95% CI, 0.886–0.982, $p < 0.001$), was still larger than NSE and GCS(0.806, 0.925) (Fig. 3C). The AUC of GCS at 7th day post-TBI was 0.986 (95% CI, 0.967-1.000, $p < 0.001$), while the AUC of NGR was 0.928 and NSE was 0.775 (Fig. 3D). The AUC of GCS at 14th day post-TBI was 0.994 (95% CI, 0.984-1.000, $p < 0.001$), which was the largest among the three parameters (NGR, 0.906, NSE, 0.699) (Fig. 3E).

Discussion

This retrospective study showed that the proportion of patients with an unfavorable outcome (GOSE 1–4) at 6 months after injury in DAI patients was 26.5% (27/102). The accuracy of clinical parameters in predicting prognosis varied significantly at different time points. At 1st, 3rd, and 5th days post-TBI, NGR had the highest predictive efficacy, while at 7th and 14th days post-TBI, GCS had the highest predictive efficacy. These findings suggest that clinicians need to use different parameters flexibly when assessing patients' long-term neurological function

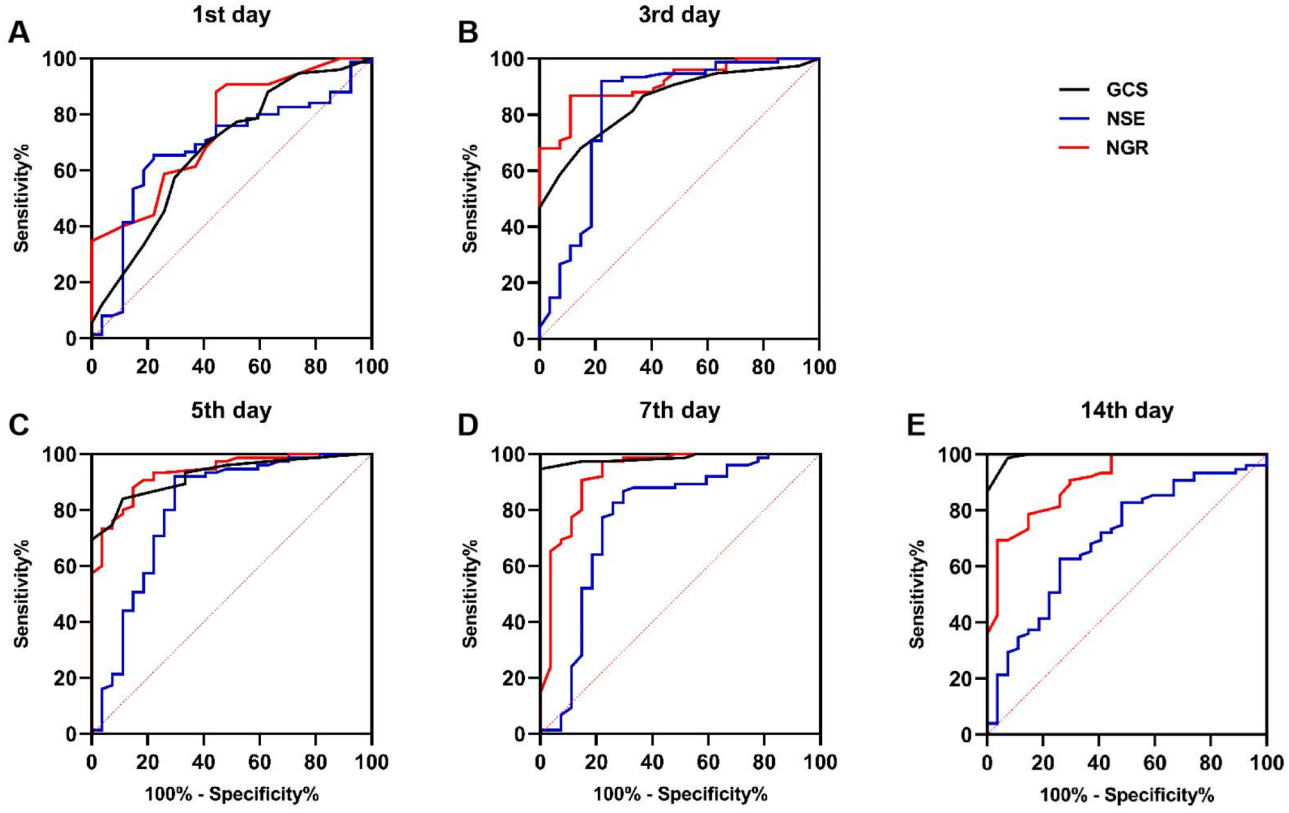

Fig. 3 Comparative analysis of the predictive power of parameters at different time points for long-term prognosis after injury. The parameter with the largest AUCs at 1st, 3rd, and 5th days post-TBI were NGR (0.751, 0.913, 0.9343), while at 7th and 14th days post-TBI, the parameter with the largest AUCs were GCS (0.986, 0.994). AUC, area under the curve; NSE, neuron-specific enolase; GCS, Glasgow Coma Scale; NGR, serum NSE level to admission GCS score ratio

at different stages of treatment, in order to optimize treatment strategies.

Long-term neurologic function in DAI patients

DAI is usually caused by external injury involving shearing force on brain tissues, and it manifests in the form of focal axonal shear injuries and axonal breakage [1, 2, 17]. More than 50 million people are suffering from TBI each year worldwide, among them, moderate to severe TBI patients with DAI are more likely to have long-term sequelae or serious neurological deficits, even death [18–21].

Chen. et al. [22] followed up 79 DAI patients for 6 months and used the GOSE score to assess the patients' long-term neurologic function, finding that 68.4% (54/79) of the patients could be classified as favorable outcome (GOSE 5–8). Eijck. et al. [23] collected clinical and radiological data from 185 DAI patients aged over 16 years. The main outcome was the long-term follow-up GOSE score. The study found that 51% of the patients had a favorable outcome, defined as a GOSE score of 6–8. Xie. et al. [6] used the GOS score to assess the prognosis of 93 DAI patients, and found that 38.7% of the patients had an unfavorable outcome (Glasgow Outcome Scale, GOS1-3). Matsukawa. et al. [24] retrospectively analyzed 78 DAI patients who were consecutively admitted over a period of 6 years, using GOSE as an assessment indicator 1 year after brain injury, and found that the presence of genu of corpus callosum lesions suggested that DAI patients may still have disabilities 1 year after TBI. Yue. et al. [25] observed 108 TBI patients in a TRACK-TBI pilot study, using GOSE at 6 months post-injury as a prognostic assessment indicator, and found that the presence of DAI and MRI contusion in patients with negative initial head CT was significantly associated with poor clinical outcomes at 6 months. Currently, most scholars used GOSE at 6 months post-injury as an indicator for assessing the long-term neurological function of DAI patients, and about 20-38% of DAI patients were classified as unfavorable outcome (GOSE 1–4). The rate of unfavorable outcome at 6 months post-injury in our study was 26.5%, which is basically consistent with the above studies.

Predictors of long-term neurological function in DAI patients

DAI patients typically experience varying degrees of coma, with durations ranging from a few minutes to several days or longer [6, 13], and the initial cranial CT scan may be negative, making prognosis assessment challenging [25]. Eijck. et al. [23] conducted a follow-up analysis of the long-term neurological function of 134 DAI patients and found that age, consciousness recovery within 7 days, pupillary light reflex, and DAI grade were independent factors affecting the long-term functional prognosis of DAI patients. Our previous study also found that the more sensitive the pupillary light reflex, the higher the admission GCS and the longer the education, the better the long-term cognitive function of DAI patients [22].

In addition to clinical parameters, many scholars were actively exploring the predictive effects of biomarkers on the long-term neurological function of DAI. Patients with DAI with high NSE levels might have poor prognosis, and if NSE was persistently high expressed, they were at a high risk of death [26]. Chabok. et al. [9] used enzyme-linked immunosorbent assay to detect protein S100BB and NSE levels in 28 severe DAI patients at 6 h, 24 h, 48 h, and 72 h after injury, and used survival rate at discharge and GOS scores at 3 months and 2 years as clinical outcome variables. The results showed that increased serum NSE and S100BB concentrations within 3 days after DAI were associated with poor prognosis. Glial fibrillar acidic protein(GFAP) and ubiquitin carboxy-terminal hydrolase L1(UCH-L1) have been shown to discriminate patients regarding the presence or absence of brain lesions on initial CT scan [27]. Following DAI, disruption of axoplasmic transport leads to accumulation of β-APP in axons, bringing its concentration to detectable levels [28]. As the main cytoskeletal component of nerve cells, neurofilament light chain(NfL) and spectrin play important roles in maintaining axonal caliber and neuron morphology. Increased levels of these biomarkers result from axonal cell damage [29]. Unfortunately, these biomarkers were either difficult to collect in cerebrospinal fluid or were not widely used in hospitals in China, which limited their application as prognostic indicators for DAI in clinical practice.

In this study, through Pearson correlation analysis, we found that: there was a negative correlation between Marshall CT score, serum NSE and NGR levels at 1st, 3rd, 5th, 7th, and 14th days post-TBI and the 6-month GOSE in patients with DAI. Additionally, there was a positive correlation between GOSE and pupillary light reflex, as well as GCS at 1st, 3rd, 5th, 7th, and 14th days post-TBI. These results were consistent with the above papers and our previous research findings: NGR was a parameter that combines serum NSE levels and GCS scores, which objectively reflected the severity of DAI patients from the two aspects of biomarkers and clinical physical examination, and was a simple, objective and accurate early DAI predictor [7].

Efficacy of dynamic changes in parameters in predicting long-term neurological function

Grassi. et al. [12] used diffusion tensor imaging (DTI) to scan the white matter of 20 DAI patients at 2, 6 and 12 months post-injury, and found that microstructural changes in the white matter were associated with cognitive function. In addition, the dynamic changes of glycemia, GCS, NSE and AQP4 could also predict the therapeutic effect of DAI [13]. Sohrevardi. et al. [30] conducted a cross-sectional study on 20 DAI patients, 20 multiple trauma patients without brain injury, and 20 healthy subjects, and measured the levels of interleukin 8 (IL-8), transforming growth factor beta1 (TGF beta1) and Nitric oxide (NO) in the blood at days 1st, 2nd, 3rd, and 7th after injury. The results showed that the serum TGF beta1 level increased at admission and reached its peak at the 7th day. The GOS score at the 7th day of admission in the DAI group was significantly positively correlated with the serum IL-8 level (r=-0.68, p = 0.002), and the GCS at the 7th day of admission was significantly correlated with the IL-8 concentration (r=-0.55, p = 0.026). Regardless of clinical parameters or various blood indicators, they are all dynamically changing during the treatment process of patients. The above studies had clarified that the dynamic changes of parameters could more accurately predict the long-term neurological function of DAI patients. In the 6-month favorable outcome group of DAI patients, NSE and NGR levels showed a continuous decline, and GCS scores showed a continuous increase. In contrast, in the unfavorable outcome group of DAI patients, NSE and NGR levels increased within 5 days after injury, and GCS scores decreased. There were significant differences between the two groups. The ROC curves showed that the AUCs of NGR were the largest within 5 days post-TBI, indicating that it had the highest predictive efficacy for the long-term neurological function of DAI patients. However, after 7 days, the AUCs of GCS were the largest.

Limitations

There are several limitations in our present study. First, the sample size is not large enough to evaluate the predictive value of NGR for the long-term neurological function of DAI patients. A significant proportion of eligible patients (60.0%) were excluded due to strict inclusion and exclusion criteria, which may limit the generalizability of our findings. Future studies with larger sample sizes and more inclusive criteria are needed to validate our results. Second, the pathological process after DAI is relatively complex, and there are many differential metabolites in

the blood [31, 32], but only the serum NSE levels were employed to predict the 6-month GOSE. Plasma NfL, GFAP and UCH-L1 will be considered for inclusion in predictive models in expanded studies after they are widely used in routine clinical practice in China. Third, the time points at which the parameters were collected were not sufficient, and the follow-up period for DAI patients was not long enough, which may have caused bias in the results.

Conclusions

Our study demonstrated that the continuous decline of NGR was closely associated with favorable outcomes in DAI patients, and that NGR had high accuracy in predicting 6-month GOSE within 5 days post-injury, suggesting its potential as an effective predictor of long-term neurological function. However, future research should address the following directions: (1) Expanding sample sizes and adopting multi-center designs to validate the generalizability of NGR's predictive value across diverse populations; (2) Incorporating additional biomarkers (e.g., plasma NfL, GFAP, and UCH-L1) into dynamic predictive models to enhance prognostic accuracy; (3) Conducting longitudinal studies with extended follow-up periods and denser time-point sampling to refine the temporal relationship between parameter trajectories and functional outcomes; (4) Exploring the integration of NGR with clinical parameters (e.g., GCS at later stages) to develop a multi-modal prognostic tool for personalized treatment strategies. These efforts will advance our understanding of DAI progression and optimize clinical decision-making for improved patient outcomes.

Abbreviations

TBI	traumatic brain injury
DAI	diffuse axonal injury
GCS	Glasgow Coma Scale
NSE	Neuron-specific enolase
NGR	NSE level to GCS score ratio
GOSE	Extended Glasgow Outcome Scale
ROC	receiver operator characteristic
AUC	area under the ROC curves
CI	confidence interval
MRI	magnetic resonance imaging
CT	computed tomography
DWI	diffusion-weighted imaging
IQR	interquartile range
GOS	Glasgow Outcome Scale
GFAP	Glial fibrillar acidic protein
UCH-L1	Ubiquitin carboxy-terminal hydrolase L1
NfL	neurofilament light chain
IL-8	Interleukin 8
TGF beta1	transforming growth factor beta1
NO	Nitric oxide

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04116-5.

Supplementary Material 1

Author contributions

W.C.: conceptualization, investigation, data collection, data curation, review and editing. J.W. and S.L.: conceptualization, investigation, resources, data curation, and editing. G.W.: conceptualization, supervision, project administration and writing-review. C.Y. and R.C.: conceptualization, investigation, resources, data curation, writing-review and project administration. W.S.: conceptualization, investigation, resources, data curation.

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Data availability

Data is provided within supplementary information files.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, approved by the Ethics Committee of Haining people's Hospital and written informed consent was obtained from all participants or their representatives, registered at the Chinese Clinical Trial Registry (ChiCTR2100044352).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Neurosurgery, Haining People's Hospital, Haining, Zhejiang, China
[2]Department of Clinical Laboratory, Haining People's Hospital, Haining, Zhejiang, China
[3]Department of Orthopaedics, Haining People's Hospital, Haining, Zhejiang, China

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