Submitted: 14 January, 2025 Accepted: 28 February, 2025 Published: 08 July, 2025 DOI:10.22514/sv.2025.099

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ORIGINAL RESEARCH

A study of the relationship between serum SIRT6 levels and neurological impairment and prognosis after early traumatic brain injury

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Abstract

Background: The objective of this research was to explore the correlation between serum sirtuin 6 (SIRT6) levels and neurological dysfunction, as well as the prognosis following early traumatic brain injury (TBI). **Methods**: As a retrospective analysis, the study involved 103 severe TBI patients admitted to our hospital, while 103 additional non-traumatic brain injury (non-TBI) patients from the same timeframe served as the control group. After one month post-injury, patients in the trauma cohort were categorized into two groups based on the Glasgow prognostic score (GOS): a group with favorable prognosis (62 cases) and a group with unfavorable prognosis (41 cases). **Results**: Patients in the TBI group had substantially lower serum SIRT6 levels than those in the non-TBI group ($t = 9.335$, $p < 0.001$). Following an early TBI, SIRT6 levels were positively correlated ($r = 0.566$, $p < 0.001$) with GOS scores and negatively correlated ($r = -0.557$, $p < 0.001$) with the National Institutes of Health Stroke Scale (NIHSS) scores, according to Spearman's correlation analysis. Patients in the poor prognosis group had lower Glasgow Coma Score (GCS), SIRT6 and GOS scores at admission, and higher NIHSS scores and Rotterdam computed tomography (CT) scores than those in the good prognosis group at 1 month post-injury ($p < 0.05$). The area under the curve (AUC) of serum SIRT6 was 0.942 (95% confidence interval (CI): 0.878–0.979). NIHSS score (odds ratio (OR) = 1.964, $p = 0.016$), Rotterdam CT score (OR = 57.995, $p = 0.013$), GCS score (OR = 0.300, $p = 0.015$), and serum SIRT6 level (OR = 0.025, $p = 0.006$) were significant determinant factors for poor prognosis in patients with early TBI. **Conclusions**: Serum SIRT6 was significantly lower in patients with early TBI and was associated with neurological impairment as well as poor prognosis.

Keywords

Traumatic brain injury; Sirtuin 6; Neurological impairment; Prognosis

1. Introduction

Traumatic brain injury (TBI) is a prevalent neurological condition frequently encountered in the fields of emergency medicine and neurosurgery. It is typically the result of external forces impacting the head, leading to significant disability and mortality rates [1]. Although some TBI patients are successfully rescued, they are often left with different degrees of neurological impairments, resulting in cognitive and emotional dysfunction. These injuries not only disrupt the daily routines and work capacity of the patients but also have the potential to escalate the societal financial burden [2].

Sirtuins, also known as SIRTs, are a group of histone deacetylases that rely on Nicotinamide adenine dinucleotide (NAD+) for their activity. They play crucial roles in numerous biological functions including cellular metabolism, gene regulation, and the cell cycle by modulating the acetylation status of a diverse range of targets [3]. In recent years, the role of SIRTs in neurological diseases has gradually gained attention. Several studies have shown [4, 5] that SIRTs can participate in the development and damage repair process of the nervous system by regulating neuronal survival, apoptosis, and synaptic plasticity. Zhang *et al.* [6] found that the increased expression of SIRT6 could boost the nuclear factor erythroid2-related factor 2 (NRF2) signaling pathway, lessen oxidative stress, alleviate tissue damage and neurological impairments, suggesting its promising role as a therapeutic target for ischemic stroke. Although it can be hypothesized from existing studies that SIRT6 may play an important role in neurological disorders, the relationship between serum SIRT6 levels and neurological impairment and prognosis after early traumatic brain injury (TBI) is unclear. In view of this, this study employed a retrospective cohort study method to analyze the relationship between serum SIRT6

levels and neurological impairment and prognosis in patients with early TBI. We hope to provide new ideas for the clinical diagnosis and treatment of TBI patients and contribute to the improvement of their clinical outcomes.

2. Materials and methods

2.1 Patients

As a retrospective analysis, 103 patients with TBI admitted to our hospital from May 2021 to October 2023 were selected as study subjects. Inclusion criteria: (1) TBI was diagnosed by clinical cranial CT or MRI examination; (2) admissions occurred within 24 hours post-injury. The patients with TBI were selected for the study. Exclusion criteria: (1) physiologic disruption of brain function caused by nontraumatic factors such as other somatic diseases or intracranial diseases; (2) previous neurological dysfunction; (3) those with neurological and muscular diseases; (4) those with combined malignant tumours and coagulation disorders; (5) those lost to follow up after discharge; (6) those with cardiac, hepatic, and renal insufficiency at the time of admission. Another 103 cases of non-traumatic brain injury (non-TBI) patients were selected as the control group in the same period. Inclusion criteria for the control group: (1) the patient was admitted for ischemic stroke, hypoglycemia, and intracranial infection; (2) Glasgow Coma Score (GCS) $\geq$8 at the time of admission; (3) age $>$18 years. Exclusion criteria: (1) those with injuries due to trauma; (2) those requiring extracorporeal circulation support; (3) those with symptoms of brain death at the time of admission; and (4) those with combined malignant tumours and coagulation disorders.

2.2 Data collection

Patients (May 2021 to October 2023) were selected from the hospital's electronic medical record database and were screened according to the set inclusion-exclusion criteria. Detailed clinical data were collected on the patients finally included in the study, including gender, age, body mass index, Glasgow Coma Score (GCS) on admission [7], and routine blood results (including white blood cell count (WBC), platelet count (PLT), neutrophils/lymphocytes (NLR) and SIRT6). Serum SIRT6 levels were measured using an enzyme-linked immunosorbent assay kit (#MBS3808982, MyBioSource, San Diego, CA, USA).

Typically, blood tests are performed on patients with traumatic brain injury at the time of admission to the hospital, at specific times after the injury (*e.g.*, 24 h, 48 h, 72 h, *etc.*), and at various stages during treatment. Blood samples from all these time points were used as a source of retrospectively collected samples for this study (blood samples are usually kept by the hospital laboratory). Blood samples at the time of admission were selected for testing in this study.

2.3 Assessment of neurological impairment

Early traumatic brain injury (ETBI) is a relative time concept that refers to the period of time from when the patient is injured to until 72 hours post-injury. (1) After being admitted, the patients underwent cranial CT scans using a Siemens dual-source CT scanner from Germany. The Rotterdam CT score [8] was calculated based on the CT findings of the patients: a score of 0, 1 or 2 points was assigned for normal, compressed, and disappeared basal cisterns, respectively; a midline shift $<$5 mm was given 1 point, while a shift $\geq$5 mm was given 0 points; epidural hematoma was assigned 1 point; ventricular or subarachnoid hemorrhage was also scored as 1 point. The total score was determined by adding up the points for all the criteria, with an additional point added to the sum. The total score ranges from 1 to 6 points, with larger scores indicating more severe craniocerebral injury. (2) The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate the neurological function of the patients [9], and the higher the score, the more serious the neurological impairment.

2.4 Assessment of prognosis

Patients who had experienced TBI were reevaluated one month after the injury using the Glasgow Outcome Scale (GOS) for prognostic evaluation [10]: those with a GOS score of $<$4 were categorised as a poor prognosis group, and those with a GOS score of $\geq$4 were categorised as a good prognosis group.

2.5 Statistical analyses

The data of this study were analyzed statistically using SPSS26.0 (IBM Corp., SPSS Statistics, Armonk, NY, USA). Count data were compared using chi square (χ^2) test or Fisher's exact probability method. Measurements were tested by the Shapiro-Wilk test, and those conforming to normal distribution were expressed as mean $\pm$ standard deviation, and compared using the *t*-test. Measures not normally distributed were described as M (Q1, Q3) and compared using the Mann-Whitney U test. Non-parametric Spearman's rank correlation was used for correlation analysis. The prognosis of the patients was dichotomized and ROC (Receiver Operating Characteristic) curves were plotted using Medcalc software (version 15.0, MedCalc Software, Ostend, Belgium) with serum SIRT6 level as a predictor variable. Using the ROC, the predictive utility of blood SIRT6 levels for a bad prognosis in individuals with early TBI was examined. The predictive efficacy was indicated by an area under the curve (AUC) of less than 0.7, predictive efficacy between 0.7 and 0.9, and strong predictive efficacy beyond 0.9. Using a multivariate logistic regression model, risk variables influencing the prognosis of patients with early TBI were examined. A difference was deemed statistically significant if it was $p < 0.05$.

3. Results

3.1 Comparison of general information of patients in TBI group and non-TBI group

The differences in age, gender, and body mass index distribution between patients in the TBI group and the non-TBI group were not statistically significant ($p > 0.05$, Table 1). When compared to the non-TBI group, the TBI group's NIHSS score was substantially higher ($p < 0.05$), and its admission GCS

TABLE 1. Comparison of general information of patients in TBI group and non-TBI group.

Parameter	TBI group (n = 103)	non-TBI group (n = 103)	t/χ^2	p
Male (n (%))	58 (56.31)	63 (61.17)	0.501	0.479
Age (mean ± SD)	60.68 ± 5.23	61.69 ± 5.77	1.321	0.188
Body mass index (kg/m^2, mean ± SD)	23.50 ± 1.29	23.40 ± 1.45	0.541	0.589
NIHSS score (mean ± SD)	19.54 ± 2.42	13.17 ± 1.74	21.693	<0.001
GCS score at admission (mean ± SD)	10.92 ± 1.65	12.65 ± 1.24	8.491	<0.001

TBI: traumatic brain injury; SD: standard deviation; NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Score.

score was significantly lower ($p < 0.05$, Table 1).

3.2 Relationship between serum SIRT6 level and neurological impairment after early traumatic brain injury

Patients in the TBI group had substantially lower serum SIRT6 levels than those in the non-TBI group ($t = 9.335$, $p < 0.05$, Fig. 1A). Spearman correlation analysis showed that SIRT6 level in the TBI group was negatively correlated with NIHSS score after early traumatic brain injury ($r = -0.557$, $p < 0.001$, Fig. 1B) and favorably connected with GOS score ($r = 0.566$, $p < 0.001$, Fig. 1C).

3.3 Comparison of clinical data between poor prognosis group and good prognosis group

All TBI patients underwent GCS assessment after injury, and a total of 41 patients had a poor prognosis, with a poor prognosis incidence rate of 39.81%. In contrast to the patients in the favorable prognosis group, those in the unfavorable prognosis group exhibited notably lower GCS scores upon admission, alongside significantly higher NIHSS scores, as well as elevated levels of Rotterdam CT scores ($p < 0.05$, Table 2).

3.4 Relationship of serum SIRT6 level on prognosis of TBI patients

Patients in the poor prognosis group had substantially lower serum SIRT6 levels than those in the good prognosis group ($p < 0.05$, Fig. 2A). As ROC analysis, the AUC of serum SIRT6 level for predicting poor prognosis in patients with early traumatic brain injury was 0.942 (95% CI: 0.878–0.979), suggesting a high predictive efficacy of SIRT6. The corresponding sensitivity and specificity were 92.68% and 95.16%, respectively (Fig. 2B).

3.5 Multivariate analysis of poor prognosis in patients with early TBI

In the logistic regression analysis model, the Rotterdam CT score, SIRT6, NIHSS score and GCS score upon admission were utilized as independent factors, and the prognosis of the patients in the trauma group was recorded as the dependent variable. As per Table 3, it was observed that the NIHSS score and Rotterdam CT score emerged as significant risk factors ($p < 0.05$, Table 3 and Fig. 3), while the GCS score and SIRT6 levels upon admission were identified as protective factors against an unfavorable outcome in early TBI patients ($p < 0.05$, Table 3 and Fig. 3).

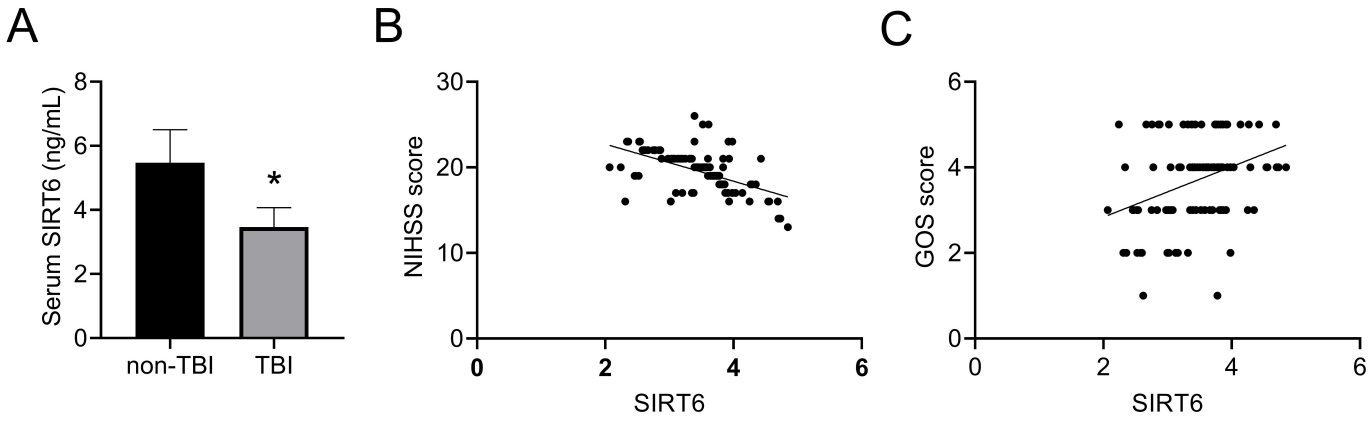

FIGURE 1. Relationship between serum SIRT6 levels and neurological impairment after early traumatic brain injury. (A) Comparison between serum SIRT6 levels in non-traumatic brain injury and traumatic brain injury groups. (B) Correlation between SIRT6 and NIHSS scores. (C) Correlation between SIRT6 and GOS scores. *$p < 0.05$. SIRT6: sirtuin 6; TBI: traumatic brain injury; NIHSS: National Institutes of Health Stroke Scale; GOS: Glasgow prognostic score.

TABLE 2. Comparison of clinical data between the poor prognosis group and the good prognosis group.

Parameter	Poor prognosis group (n = 41)	Good prognosis group (n = 62)	t/χ^2	p
Male (n (%))	25 (60.98)	33 (53.23)	0.602	0.438
Age (yr)	59.78 ± 5.16	61.27 ± 5.24	1.418	0.159
Body mass index (kg/m^2, mean ± SD)	23.35 ± 1.34	23.60 ± 1.26	0.9570	0.341
GCS score at admission (mean ± SD)	9.90 ± 1.37	11.60 ± 1.47	5.888	<0.001
Dull pupillary reflex to light (n (%))	11 (26.83)	12 (19.35)	0.795	0.373
Diffuse brain damage (n (%))	14 (34.15)	13 (20.97)	2.216	0.137
Surgical treatment (n (%))	31 (75.61)	40 (64.52)	1.418	0.234
WBC (×10^9/L, mean ± SD)	12.64 ± 2.59	12.01 ± 2.25	1.286	0.201
PLT (×10^9/L, mean ± SD)	251.48 ± 24.25	244.36 ± 19.37	1.652	0.102
NLR (mean ± SD)	4.11 ± 0.49	3.90 ± 0.62	1.877	0.0639
NIHSS score (mean ± SD)	21.05 ± 2.19	18.55 ± 2.04	5.916	0.008
Rotterdam CT score (mean ± SD)	5.10 ± 0.62	3.38 ± 0.79	11.720	<0.001

SD: standard deviation; GCS: Glasgow Coma Score; WBC: white blood cell count; PLT: platelet count; NLR: neutrophils/lymphocytes; NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography.

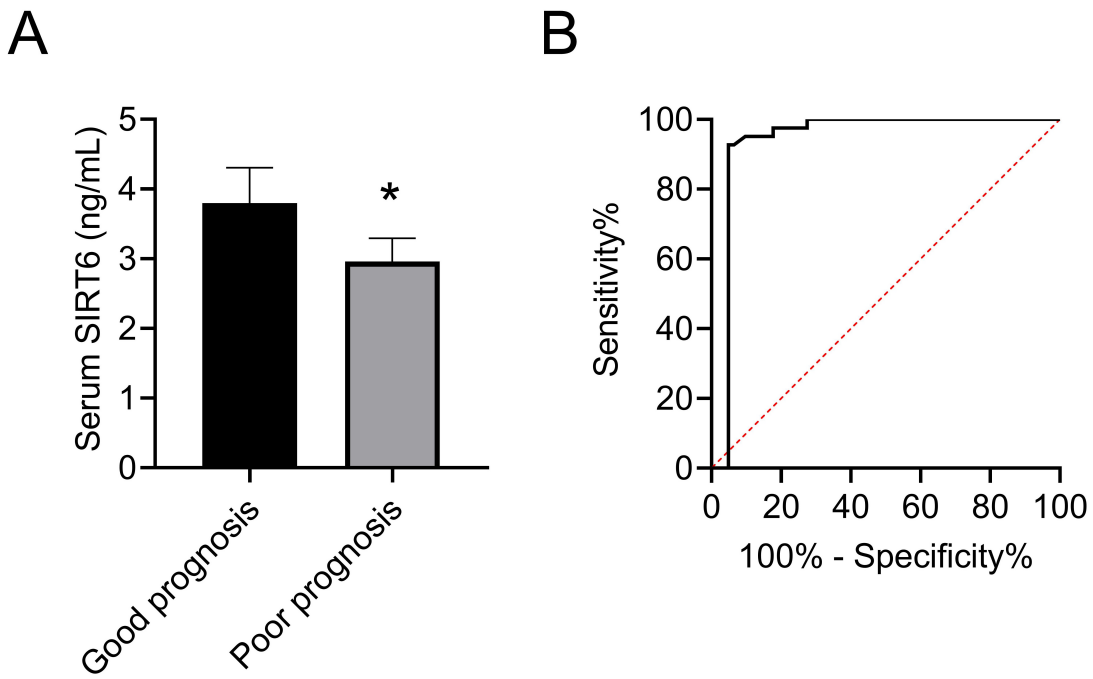

FIGURE 2. Relationship of serum SIRT6 level on prognosis of TBI patients. (A) Comparison between serum SIRT6 levels in poor and good prognosis groups. (B) ROC curve of serum SIRT6 level predicting poor prognosis in patients with early traumatic brain injury. *$p < 0.05$. SIRT6: sirtuin 6.

TABLE 3. Multivariate analysis of poor prognosis in patients with early TBI.

Variables	β	S.E.	Wald	OR	95% CI	p
GCS score at admission	−1.202	0.495	5.908	0.300	0.114–0.792	0.015
SIRT6	−3.703	1.347	7.555	0.025	0.002–0.346	0.006
NIHSS score	0.675	0.280	5.817	1.964	1.135–3.398	0.016
Rotterdam CT score	4.060	1.636	6.156	57.995	2.347–1433.330	0.013

GCS: Glasgow Coma Score; SIRT6: sirtuin 6; NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography; β: regression coefficient; S.E.: standard error; OR: odds ratio; CI: confidence interval.

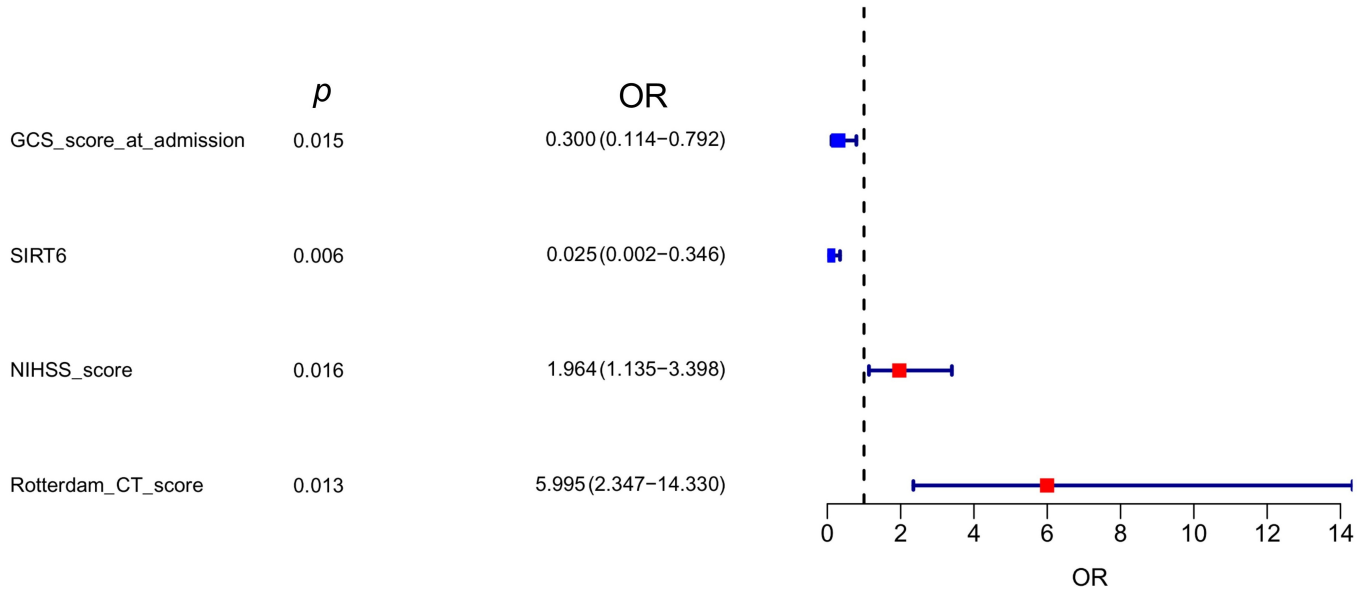

FIGURE 3. Forest plot from multivariate logistic regression analysis. GCS: Glasgow Coma Score; SIRT6: sirtuin 6; NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography; OR: odds ratio.

4. Discussion

TBI is usually caused by an external physical force acting on the head, resulting in damage to brain tissue [11]. The injury often leads to profound neurological deficits, such as compromised consciousness, impaired cognitive abilities, and diminished motor skills [12]. Patients with severe TBI may also experience prolonged coma, severe neurological deficits or even death. In the past, the treatment of patients with early TBI often paid more attention to the resuscitation of life and neglected the recovery of neurological function. This may have led to some patients being left with different degrees of neurological and limb dysfunction after being successfully resuscitated, seriously affecting the quality of life [13]. Therefore, it is of great clinical significance to screen effective biomarkers to be used as evaluation indexes of neurological function impairment and prognosis in patients with early TBI. According to the study's findings, individuals with TBI had considerably lower serum SIRT6 levels than those without TBI, indicating a possible correlation between the two. A group of proteins known as sirtuins, which rely on nicotinamide adenine dinucleotide for their function, play diverse biological roles. The mammalian sirtuin family comprises seven unique proteins with different subcellular distributions, tissue preferences, and molecular targets [14]. SIRT6 is one among them; it is widely expressed *in vivo* and regulates several biological processes, including autophagy, inflammation, and oxidative stress. Following a traumatic brain injury (TBI), the neurological function is significantly impacted by both brain tissue damage and the subsequent inflammatory response. A reduction in the levels of SIRT6, a crucial neuroprotective factor, could suggest a severe impairment in the patient's neurological function, leading to hindered neuronal survival and axonal growth [15]. Smirnov *et al.* [16] highlighted the crucial role of SIRT6 in regulating mitochondrial function within the brain. They emphasized the neuroprotective effects of SIRT6, noting its ability to mitigate DNA damage accumulation and protect against ischemic brain injury. This underscores the strong association between SIRT6 and brain injury prevention. Therefore, serum SIRT6 is expected to be an important predictor of prognosis in patients with TBI.

The NIHSS scoring system is widely utilized in clinical practice to evaluate the extent of central nervous system impairment in stroke patients, wherein elevated scores are indicative of greater severity of nerve damage [17]. The GOS score is often used as an important indicator of efficacy assessment in treatment studies for various types of brain diseases or injuries [18]. Previous studies have indicated a direct relationship between the levels of SIRT6 transcripts and short-term neurological damage, which is associated with short-term prognosis [19]. In the present study, it was found by Spearman correlation analysis that SIRT6 levels were negatively correlated with NIHSS scores and positively correlated with GOS scores after early TBI, suggesting that serum SIRT6 may be associated with the degree of neurological impairment and prognosis of patients with TBI. Moreover, through the utilization of ROC analysis, it was determined that the AUC relating to serum SIRT6 levels in forecasting the unfavorable outcomes of early TBI patients was 0.942. This indicates that serum SIRT6 levels possess a degree of predictive capability for identifying poor prognoses in early TBI patients.

In the nervous system, SIRT6 has an important effect on neuronal survival and synaptic plasticity, since it can promote neuronal survival and axon growth, as well as inhibit neuronal apoptosis and necrosis, thus favoring the recovery of neurological function [20]. Therefore, patients with higher serum SIRT6 levels tend to have a relatively better prognosis as well. Liberale *et al.* [21] discovered a notable correlation between serum SIRT6 levels and the 90-day mortality of individuals with acute ischemic stroke. They observed that lower levels of SIRT6 were linked to an increased risk of mortality in these patients. This suggests that SIRT6 could serve as both a promising prognostic indicator and a target for therapeutic in-

terventions in individuals suffering from acute ischemic stroke. In this study, Logistic regression analysis also revealed SIRT6 to be an independent predictive factor for prognosis of TBI patients. As a result, SIRT6 level may be a useful biomarker for estimating TBI patients' early prognosis.

By studying early serum SIRT6 levels, the present study can provide a theoretical basis for early intervention and fill the gap of existing studies in this critical time window. For example, clarifying the relationship between SIRT6 and neurological impairment at an early stage may prompt clinicians to take targeted measures at an early stage. Predicting patient prognosis by monitoring SIRT6 levels is a perspective that is less addressed in existing studies. Because this study was a retrospective analysis, its sample size was limited, and its data gathering methods might have been insufficient. In order to deepen the exploration of the relationship between SIRT6 and the prognosis of TBI patients, it will be crucial to enlarge the sample size and extend the duration of follow-up in forthcoming studies. Furthermore, it is now unclear if serum SIRT6 is the most appropriate evaluation index because this study only examined the patients' levels at the time of admission. In disease surveillance, serum markers must be dynamically characterized. Moreover, given the strict inclusion and exclusion criteria and the study's reliance on pre-existing archived samples, there may be a potential selection bias. Moreover, the clearance rate of SIRT6 *in vivo* is indicated by its elimination half-life. When designing this study, the main emphasis was on establishing the relationship between alterations in SIRT6 concentrations and clinical parameters, with limited consideration given to the kinetic characteristics of SIRT6. In the future investigations, it will be essential to align the assay time point with the elimination half-life to ensure the optimal detection of SIRT6 levels that most accurately represent the underlying condition. Furthermore, we selected patients with non-traumatic brain injury in the same period as the control group to compare with TBI patients in terms of serum SIRT6 levels, as well as neurological function impairment and prognosis, with a view to better explore the specific influencing factors and pathophysiological mechanisms of traumatic brain injury. To ensure the scientific validity of the results, the clinical significance of the differences in serum SIRT6 levels, neurological impairment and prognosis with TBI patients can be explored more deeply in the future with respect to the characteristics of different types of nontraumatic brain injuries in the control group.

5. Conclusions

In conclusion, serum SIRT6 levels were correlated with the degree of neurologic impairment and the prognosis of patients with early TBI, and were significantly lower in these patients. Monitoring serum SIRT6 levels may be a potential biomarker for prognostic assessment in TBI patients.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

DPZ, YQC—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. DPZ, WWH, BYM, ZKL, XJZ—supervised the data collection; analyzed the data; interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Changzhou Cancer Hospital (Approval no. 2024(SR)NO.026). Written informed consents were obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Deping Zou, Weiwei Han, Banyou Ma, Zhuoka Luo, Xiajie Zhou, Yiqun Chao. A study of the relationship between serum SIRT6 levels and neurological impairment and prognosis after early traumatic brain injury. Signa Vitae. 2025; 21(7): 75-81. doi: 10.22514/sv.2025.099.