Published Online: 2025 September 16 **Research Article**

Clinical Value of PEWS Combined with Serum Neuron-Specific Enolase in the Assessment of Severity and Prognosis of Children with Viral Encephalitis

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Received: 23 January, 2025; **Revised:** 23 May, 2025; **Accepted:** 25 May, 2025

Abstract

Background: Viral encephalitis (VE) is an infectious disease of the nervous system caused by infection with the herpes simplex virus and other neurotropic viruses. The disease leads to disorders of consciousness and signs of meningeal irritation, and it has a high mortality rate if untreated. Even survivors often suffer from severe neurological complications.

Objectives: The aim of this study was to investigate the assessment of serum neuron-specific enolase (NSE) on the severity of VE in children and to evaluate the potential benefits of integrating the pediatric early warning score (PEWS) with serum NSE.

Methods: A total of 117 children diagnosed with VE were prospectively included. The children were classified into mild-moderate (n = 62) and severe (n = 55) groups. The prognosis of children at discharge was assessed using the Glasgow Outcome Scale (GOS). Serum NSE levels were determined using an enzyme-linked immunoassay. The PEWS test was administered to the children upon admission. Serum NSE cut-off values were calculated using receiver operating characteristic (ROC) analysis. The PEWS and serum NSE were compared between children in the good prognosis (n = 85) and poor prognosis (n = 32) groups. A clinical model for predicting poor prognosis in children with VE was constructed using multifactorial logistic regression analysis.

Results: Serum NSE levels were significantly higher in the Severe group than in the mild-moderate group. Serum NSE levels greater than 80.4 ng/mL effectively distinguished children with severe VE. The PEWS was significantly lower, while serum NSE levels were higher in the poor prognosis group compared to the good prognosis group. The combination of PEWS and serum NSE provided predictive insights into poor outcomes for children with VE.

Conclusions: Increased serum NSE levels are associated with the clinical severity of VE in patients. The PEWS and NSE level assessments can predict the prognosis of VE patients, especially in severe cases.

Keywords: Pediatric Early Warning Score, Neuron-Specific Enolase, Viral Encephalitis, Prognosis

1. Background

Viral encephalitis (VE) is an infectious disease of the nervous system caused by infection with the herpes simplex virus and other neurotropic viruses (1). It is prevalent in children and immunocompromised individuals, with clinical features including fever, headache, and other symptoms. The incidence rate of VE on a global scale is 10.5 cases per 100,000 annually (2). This disease results in consciousness disorders and meningeal irritation symptoms, and if left untreated, it has a high fatality rate, with survivors frequently experiencing severe neurological problems (3). The VE is typically diagnosed through clinical symptoms and signs, supported by analyses such as cerebrospinal fluid examination, MRI, electroencephalography, and CT (4). Consequently, there is a need to actively identify simple

How to Cite: Yan H, Yan R, Song Y, Meng X. Clinical Value of PEWS Combined with Serum Neuron-Specific Enolase in the Assessment of Severity and Prognosis of Children with Viral Encephalitis. Jundishapur J Microbiol. 2025; 18 (9): e159701. https://doi.org/10.5812/jjm-159701.

and practical markers and methods to diagnose VE and predict children's prognosis.

The pediatric early warning score (PEWS) is a scoring method that assesses the respiratory, circulatory, and conscious conditions of children in a relatively simple manner (5) to predict risk and early identify children at risk of cardiopulmonary failure. The PEWS is used in a diverse array of diseases, serving as an important tool for evaluating risk and predicting children's prognoses. For example, PEWS provides an insightful perspective on improving the quality of care in pediatric cancer patients to prevent deterioration deaths (6). Baseline PEWS is a reliable determinant of mortality in pediatric critical trauma (7). However, no study has reported PEWS in children with VE.

Neuron-specific enolase (NSE) is an enzyme found mainly in neurons and neuroendocrine cells, but it is also distributed in peripheral nerves, non-neural tissues, and serum. The NSE was initially recognized as a tumor marker, and its elevated serum levels are associated with the diagnosis and prognosis of tumors, including non-small cell lung cancer (8), melanoma (9), and small cell carcinoma of the bladder (10). In recent years, most studies have found that NSE levels are elevated in neurological disorders such as brain injury (11), acute cerebral infarction (12), and craniocerebral trauma (13), which can reflect the degree of neurological damage, recovery, or death. Elevated serum NSE is associated with more severe clinical symptoms such as fever and sustained convulsion in pediatric acute encephalitis syndrome (14). In cases of VE in children, pathogens might damage neurons by penetrating and directly invading them. This damage results in NSE leaking into the extracellular space and body fluids, leading to elevated serum NSE levels.

2. Objectives

The purpose of this research was to determine if there is a correlation between serum NSE and VE severity, and to create a clinical model that predicts poor prognosis in these children using PEWS and serum NSE.

3. Methods

3.1. Patients

One hundred and seventeen children with VE admitted to The Second People's Hospital of Liaocheng (No. 202004LC25) from October 2022 to March 2024 were selected.

3.1.1 Inclusion Criteria

1. All children met the diagnostic criteria for VE as outlined in the Zhufutang Textbook of Pediatrics (9th edition, 2022): (A) fever, headache, projectile vomiting, convulsions or seizures, drowsiness, and disturbance of consciousness; (B) focal or diffuse abnormalities on electroencephalogram; (C) normal or elevated cerebrospinal fluid pressure on lumbar puncture prior to antibiotic therapy, with a mild/moderate increase in leukocytes.

2. Children were aged 1 to 12 years before antibiotic treatment.

3. Children were diagnosed for the first time and had not received any treatment prior to hospitalization.

4. The family members of the children had signed an informed consent form.

3.1.2. Exclusion Criteria

1. Children with cardiac insufficiency and hepatic and renal dysfunction.

2. Children with purulent meningitis, bacterial meningitis, tuberculous meningitis, and other conditions that may affect the results of this study.

3. Children with other acute and chronic inflammatory diseases and autoimmune diseases.

4. Children with congenital anomalies.

5. Children who abandoned treatment, were transferred, or discharged from the hospital.

One of the following conditions was regarded as severe (15): Frequent convulsions (≥ 3 times in 24 hours) or persistent convulsions; brainstem symptoms such as respiratory failure; disturbance of consciousness, delirium, agitation, involuntary movements, and urinary system disorders. Failure to meet the criteria for severe disease was considered mild to moderate. The study included 50 male and 67 female patients, with an average age of 6.17 ± 1.08 years. Another 35 hospitalized children without neurological injury during the same period were selected as the control group, including 20 males and 15 females, aged 5.85 ± 1.48 years. The healthy

children had no infectious diseases, neurological diseases, renal diseases, or autoimmune diseases, and there was no significant difference between the two cohorts in terms of age and gender. The families or guardians of the children gave informed consent to the study and signed a written consent form, and the study was approved by the Ethics Committee of The Second People's Hospital of Liaocheng (No. 202004LC25).

3.2. Clinical Data Collection

Age, gender, and clinical symptoms (fever, vomiting, headache, disturbance of consciousness, convulsion, limb movement disorders, and psychiatric disorders) were obtained from the medical record system. Cerebrospinal fluid white blood cell count, blood sodium, blood potassium, C-reactive protein (CRP), and procalcitonin (PCT) levels were obtained from laboratory tests. Hyponatremia was defined as a serum sodium concentration of less than 135 mmol/L; hypokalemia was defined as a serum potassium concentration of less than 3.5 mmol/L (16).

3.3. Pediatric Early Warning Score

Children were assessed by PEWS within 6 hours of admission to the hospital. PEWS (17) scores consciousness (0 = normal; 1 = lethargy; 2 = agitated irritability; 3 = lethargy or coma), respiratory system (0 = normal; 1 = increase in respiratory rate by more than 10 breaths/min from the normal range, with an inspiratory flow of ≥ 3 L/min; 2 = increase in respiratory rate by ≥ 20 breaths/min from the normal range, with an inspiratory flow of 6 L/min; 3 = respiratory rate decreased by 5 times/min compared with the normal range, with an inspiratory flow of 8 L/min), and circulatory system (0 = normal; 1 = whitish skin color, capillary filling time of 3 s; 2 = greyish skin color, capillary filling time of 4 s, and increase in heart rate by ≥ 20 beats/min compared with the normal range; 3 = grey skin color, capillary filling time of 5 s, heart rate increased ≥ 30 beats/min from the normal range). The PEWS ranges from 0 to 9, with higher scores signifying more severe conditions. The PEWS was closely monitored during their hospital stay for those requiring close observation to ensure they received the necessary care.

3.4. Video Electroencephalogram Monitoring

Video electroencephalogram (VEEG) was used to assess brain function. A BEPLUSLTM EEG machine manufactured by EBNeuro (Italy) was used, with scalp electrodes placed and bipolar leads traced. The evaluation was performed on the day after the child was admitted to the hospital. The results of VEEG were classified as mild (background rhythm abnormality or structural abnormality), moderate (increase in slow-wave activity with pathological waveforms such as spike waves, sharp waves, and triphasic waves), and severe (extensive slow-wave activity or the presence of burst suppression pattern and widespread low voltage) (18).

3.5. Measurement of Serum Neuron-Specific Enolase

On the day following admission, 5 mL of fasting venous blood was collected from patients in the case group into vacuum tubes without EDTA K2 anticoagulant, while serum samples were separated from the leftover blood of children in the control group. All blood samples collected were stored at room temperature for 1 hour and then centrifuged for 10 minutes (1600 g, 4°C). Serum was stored frozen at -80°C until analyzed. The serum was analyzed using the Human NSE ELISA Kit (Elabscience Biotechnology, TX, USA). The NSE was measured three times using a spectrophotometer at 450 nm, with 630 nm as the calibration wavelength. Parameter fitting was performed using the ELISACalc software. Based on the OD value of the sample, the fitted concentration was derived from the standard curve and multiplied by the dilution to obtain the measured concentration of the sample. The intra-assay variation coefficient was less than 10%. Normal NSE values for children are 7.2 - 12 ng/mL.

3.6. Prognostic Assessment

The Children's Glasgow Outcome Scale (CGOS) was used to assess the prognosis of children at discharge (19): Grade 1 = death; grade 2 = vegetative state; grade 3 = severe disability that prevents self-care in daily life and requires care; grade 4 = mild disability that enables independence in daily life; grade 5 = recovery that enables normal activities and self-care in daily life. In the

CGOS system, grades 1 to 4 are considered poor prognosis, while grade 5 is considered good prognosis.

3.7. Statistical Analyses

All statistical analyses were independently reviewed by a certified biostatistician to ensure methodological validity. Statistical analyses were performed using SPSS 20.0 software. Shapiro-Wilk tests were used to determine the normality of the data. For normal distribution, the measurement data were shown as mean ± standard deviation (SD), and Student's *t*-test was used for between-group comparisons; for skewed distribution, continuous variables were shown as median (IQR), and the Mann-Whitney U-test was used for between-group comparisons. Count data were expressed as frequency (n) and rate (%), and the chi-square test or Fisher's exact test was used.

The role of serum NSE in differentiating disease severity was evaluated by plotting the receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC) using the software package 4.0.5 in R (v4.0.5). The clinical model for predicting the poor prognosis of children with VE was constructed using multifactorial logistic regression analyses, with the factors with statistical significance ($P < 0.05$) in univariate analysis included as independent variables. The predictive value of different clinical models was evaluated by ROC and AUC, and the accuracy, sensitivity, and specificity were obtained by calculating the maximum Youden Index. Differences between ROC curves were compared using MedCalc 19.2.1 software (MedCalc, Mariakerke, Belgium). All visualizations were created using GraphPad Prism 8 (GraphPad, San Diego, CA), with two-tailed tests applied, and $P < 0.05$ was considered statistically significant.

4. Results

4.1. Pediatric Early Warning Score and Serum Neuron-Specific Enolase Levels in Children with Viral Encephalitis

A total of 117 children with VE, ranging from 3 to 10 years of age, were included in this study, and none of them experienced a death event during hospitalization. On admission, 62 had mild-moderate symptoms and 55 had severe symptoms. Serum NSE levels were significantly higher in children with VE than in control children (127.89 [66.86, 175.30] vs. 8.47 [2.09, 9.71], $P < 0.001$). Notably, serum NSE levels were significantly higher in the severe group than in the mild-moderate group (155.30 [58.42, 191.52] vs. 79.98 [66.36, 130.43]; $P < 0.001$, Figure 1). Figure 2 illustrates that serum NSE levels differentiated children based on disease severity (AUC = 0.77, $P < 0.001$), and it was possible to distinguish children with severe VE when serum NSE levels were greater than 80.4 ng/mL.

4.2. Prognosis and Clinical Characteristics of Children with Viral Encephalitis

Of the 62 children with mild-moderate symptoms, 9 had a poor prognosis, and of the 55 severe children, 23 had a poor prognosis, with a significant difference between the two groups ($P < 0.001$, not shown in the table). This suggests that the severity of clinical symptoms on admission is associated with prognosis. The clinical characteristics of children with poor prognosis (n = 32) and good prognosis (n = 85) were compared, as shown in Table 1. At clinical baseline, the percentages of disturbance of consciousness (21.88% vs. 8.23%, $P = 0.043$) and convulsions (62.50% vs. 35.29%, $P = 0.008$) were significantly higher in the poor prognosis group than in the good prognosis group. No significant differences in age, gender, hyperthermia, vomiting, headache, duration of convulsions, motor, and mental disorders were observed between the two groups ($P > 0.05$).

On the VEEG results, about half of the patients had mild abnormalities (48.72%, 57/117); there was a significant difference in the extent of brain injury between the two groups ($P < 0.001$), with a higher percentage of severe abnormalities in the poor prognosis group (37.50%). In terms of laboratory parameters, CRP levels were significantly higher in the poor prognosis group (7.50 ± 3.20 vs. 5.60 ± 2.47, $P = 0.001$). Notably, there were significant differences in PEWS and serum NSE levels between the two groups, with PEWS significantly lower in the poor prognosis group than in the good prognosis group (3 [2, 4] vs. 1 [1, 3], $P < 0.001$), and serum NSE levels significantly higher in the poor prognosis group than in the good prognosis group (149.38 [85.20, 217.46] vs. 122.75 [56.96, 157.3], $P < 0.001$).

4.3. A Clinical Model for Poor Prognosis in Children with Viral Encephalitis Based on Pediatric Early Warning Score and

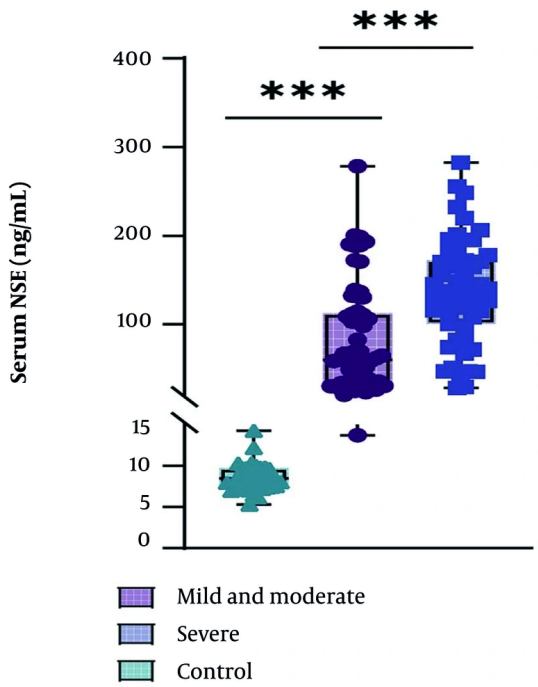

Figure 1. Serum neuron-specific enolase (NSE) levels in children with mild-moderate symptoms and severe symptoms (*** $P < 0.001$).

Serum Neuron-Specific Enolase

Next, three predictive models were constructed using stepwise forward logistic regression: The base model (model 1, variables with $P < 0.05$ in the univariate analysis were included in the analysis, and additionally, hyponatremia was included as a variable), model 2, and model 3 (variables shown in the table). As shown in Table 2, all three models were significant ($P < 0.001$), and the inclusion of PEWS (model 2) increased the ability of CRP to predict the risk of poor prognosis in children with VE, with an increase in OR from 1.48 to 1.56 times. Additionally, the model's predictive value was improved by including serum NSE, though it did not enhance the prediction ability of CRP and PEWS, and model 3 had a higher AUC than models 2 and 1 (Figure 3). As shown in Table 3, the accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of model 3 were all increased.

5. Discussion

The VE is an inflammatory encephalopathy caused by various viral infections, which can induce immune brain damage, with lesions affecting the brain parenchyma and consequently disrupting the blood-brain barrier (20). Serum NSE is a prime marker for brain injury, indicating the extent of damage in the nervous system. In children with VE and brain barrier damage, serum NSE crosses the blood-brain barrier into body fluids and serves as a blood marker for brain damage. The results of the present study showed that serum NSE levels were elevated in children with severe VE and those with a poor prognosis. Serum NSE combined with PEWS improved the assessment validity of predictive models for poor prognosis in children with VE.

The NSE is strongly associated with brain injury and neuroinflammation. In a meta-analysis, serum NSE was shown to have moderate discriminatory power with respect to prognosis in patients with craniocerebral injuries, but the optimal discriminatory threshold and the optimal time of sampling remain uncertain due to

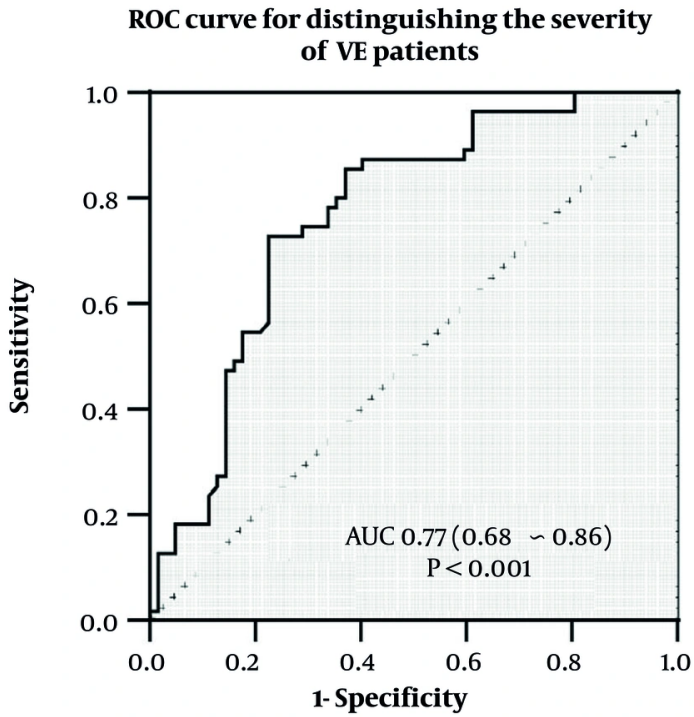

Figure 2. Receiver operating characteristic (ROC) curves to assess the potency of serum neuron-specific enolase (NSE) levels to differentiate between patients with different degrees of viral encephalitis (VE) (Abbreviation: AUC, area under the ROC curve).

significant differences between studies (21). In this study, we first determined the cut-off value of serum NSE for children with severe and mild-moderate VE as 80.4 ng/mL. The discrimination of severe conditions is mainly based on brain injury-related features, such as frequent convulsions, persistent convulsions, disturbance of consciousness, and involuntary movements (22).

The present study showed that serum NSE was higher in children with VE than in healthy controls, suggesting that disruption of blood-brain barrier integrity in children with VE affects the serum compartment. Serum NSE is an effective indicator of brain injury in children with VE, particularly those with a poor prognosis. Serum NSE is higher in patients with severe acute craniocerebral injury, and serum NSE is lower in these patients with a good prognosis (23). In cases of acute bacterial meningitis, brain metabolism is often impacted, and patients with elevated lactate: Pyruvate ratios tend to have significantly increased NSE levels, indicating that the brain tissue is deteriorating (24). The main pathological changes in VE are edema, softening, or necrosis of brain tissue, which can lead directly to severe neurological damage.

The PEWS is scored based on consciousness, cardiovascular system, and respiratory system. The PEWS facilitates rapid screening of severe children who may be at risk of deterioration and guides clinical triage and treatment. The results of this study showed that the PEWS of patients in the poor prognosis group was higher than that of the good prognosis group, which is consistent with a previous study (7). Therefore, the present study attempted to construct a prediction model for poor clinical outcomes in children with VE using PEWS in combination with serum NSE based on the characteristics of clinical variability.

We found that the proportion of disturbance of consciousness and convulsions occurring after admission was significantly higher in the poor prognosis group than in the good prognosis group. This

Table 1. Comparison of Clinical Baseline, Pediatric Early Warning Score and SERUM Neuron-Specific Enolase Levels in Children with Different Prognoses [a, b, c]

Variables	Poor Prognosis (N = 32)	Good Prognosis (N = 85)	P-Value [d]
Gender			0.892
Male	14 (43.75)	36 (42.35)	
Female	18 (56.25)	49 (57.64)	
Age (y)	6.46 ± 1.14	6.06 ± 1.04	0.071
Fever (> 39°C)	18 (56.25)	32 (37.65)	0.07
Vomiting	7 (21.88)	20 (23.53)	0.85
Headache	12 (37.50)	29 (34.11)	0.732
Disturbance of consciousness	7 (21.88)	7 (8.23)	0.043
Convulsion	20 (62.5)	30 (35.29)	0.008
Convulsion time (min)			
< 5	11 (84.62, 11.13)	26 (96.30, 26.29)	0.189
> 5, < 30	2 (15.38, 2.13)	1 (3.70, 1.27)	
Movement disorder	6 (18.75)	12 (14.11)	0.57
Mental disorder	1 (3.13)	0 (0.00)	0.274
VEEG			< 0.001
Mild abnormality	7 (21.88)	50 (58.82)	
Moderate abnormality	13 (40.62)	25 (29.41)	
Severe abnormality	12 (37.50)	10 (11.76)	
Hyponatremia	11 (34.38)	15 (17.65)	0.052
Hypokalemia	4 (12.50)	9 (10.59)	0.749
White blood cell count ($\times 10^9$/L)	12.13 ± 2.47	11.85 ± 2.14	0.558
CRP (mg/dL)	7.50 ± 3.20	5.60 ± 2.47	0.001
PCT (μg/L)	6.25 ± 2.3	4.36	0.47
PEWS	3 [2, 4]	1 [1, 3]	< 0.001
NSE (ng/mL)	129.38 [65.20, 197.46]	102.75 [36.96, 137.3]	< 0.001

Abbreviations: VEEG, video electroencephalogram; CRP, C-reactive protein; PCT, procalcitonin; PEWS, pediatric early warning score; NSE, neuron-specific enolase.

[a] Values are expressed as No. (%), mean ± standard deviation (SD), or median [IQR].

[b] Categorical values were compared using the chi-square test or Fisher's exact test.

[c] Student's *t*-test or Mann-Whitney test was used to assess the difference between the two groups of continuous values.

[d] P-value < 0.05 was statistically significant.

indirectly suggests that the degree of brain injury seems to be more pronounced in children in the poor prognosis group. In addition, the VEEG results also verified this situation, and the proportion of patients with abnormal EEG in the poor prognosis group was significantly higher than that in the good prognosis group.

In children with VE, brain damage and neuron destruction lead to neuronal necrosis and apoptosis when the brain tissue experiences hypoxia or infection in the central nervous system. Neural axon damage causes axonal cortical fibers to germinate and form abnormal excitatory circuits between neurons, leading to epileptic-like activity. CNS infections can cause neurotransmitter imbalance, an imbalance between inhibitory transmitter synthesis and excitatory transmitter production, leading to abnormalities in synaptic ionic pathways, causing abnormal firing of neurons in the cerebral cortex (25). Additionally, patients with VE are often accompanied by fever, vomiting, and diarrhea, which may lead to the loss of water and electrolytes in the body, especially sodium. Hyponatremia is associated with abnormal antidiuretic hormone secretion in patients with VE (26). The involvement of the hypothalamus in inflammation leads to irregular hormone release.

In this study, the proportion of children with hyponatremia was slightly higher in the poor prognosis group than in the good prognosis group, although no significant difference was observed. However, this also

Table 2. Multifactorial Stepwise Forward Logistic Regression to Construct a Clinical Model for Predicting Poor Prognosis in Children with Viral Encephalitis [a]

Variables	Model 1 [b]			Model 2 [c]			Model 3 [d]		
	β	P	OR (95% CI)	β	P	OR (95% CI)	β	P	OR (95% CI)
Intercept	-3.79	< 0.001	0.09 (0.06 - 0.25)	-3.99	< 0.001	0.06 (0.01 - 0.15)	-4.91	< 0.001	0.03 (0.01 - 0.09)
Disturbance of consciousness									
0	-	-	1.00 (reference)	-	-	1.00 (reference)	-	-	1.00 (reference)
1	0.16	0.859	1.17 (0.20 - 6.79)	0.09	0.916	1.10 (0.19 - 6.18)	0.5	0.906	1.05 (0.23 - 5.71)
Disturbance of consciousness									
0	-	-	1.00 (reference)	-	-	1.00 (reference)	-	-	1.00 (reference)
1	0.74	0.469	2.09 (0.28 - 15.42)	1.07	0.296	3.22 (0.36 - 29.03)	0.98	0.249	2.66 (0.50 - 3.64)
Hyponatremia									
0	-	-	1.00 (reference)	-	-	1.00 (reference)	-	-	1.00 (reference)
1	0.57	0.422	1.77 (0.44 - 7.14)	0.32	0.666	1.38 (0.32 - 5.88)	0.14	0.818	1.15 (0.36 - 3.64)
VEEG									
1	-	-	1.00 (reference)	-	-	1.00 (reference)	-	-	-
2	0.07	0.166	1.07 (0.78 - 6.47)	0.7	0.31	0.78 (0.58 - 5.52)	0.23	0.425	0.80 (0.60 - 6.12)
3	-0.66	0.0.062	0.94 (0.90 - 8.27)	- 0.76	0.192	0.88 (0.75 - 6.27)	- 0.95	0.105	0.88 (0.72 - 5.98)
CRP	0.39	0.04	1.48 (1.14 - 1.93)	0.31	0.035	1.56 (1.04 - 1.92)	0.43	0.023	1.48 (1.06 - 2.07)
PEWS	-	-	-	0.09	0.044	1.40 (1.01 - 1.52)	0.02	0.066	1.82 (0.98 - 2.82)
Serum NSE	-	-	-	-	-	-	0.01	0.001	1.05 (1.01 - 1.02)

Abbreviations: OR, odd ratio; VEEG, video electroencephalogram; CRP, C-reactive protein; PEWS, pediatric early warning score; NSE, neuron-specific enolase.

[a] Values are expressed as 95% confidence interval (CI).

[b] Clinical factors (disturbance of consciousness, disturbance of consciousness, hyponatremia, VEEG, and CRP).

[c] Incorporation of PEWS score based on base model.

[d] Incorporation of serum NSE based on model 2.

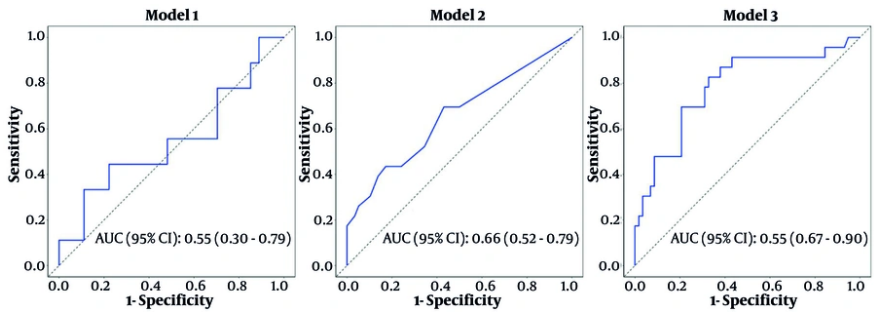

Figure 3. Model-based receiver operating characteristic (ROC) curves to assess the predictive value of the model (abbreviation: 95% CI, 95% confidence interval).

suggests that children with poor prognosis have a slightly higher level of inflammatory response, which in turn affects the prognostic profile. This is also indicated by the higher levels of blood CRP in children with a poor prognosis.

The prognosis of VE in children is closely related to the severity of the disease, and 85.48% of the 62 mild-moderate children in this study had a good prognosis. Additionally, long-term regression of VE has been shown to be associated with genetic polymorphisms (27). However, these tests are difficult to predict the prognosis of children. Therefore, in this study, PEWS combined with serum NSE was used to construct a model for clinical prediction of short-term poor

Table 3. Specificity, Sensitivity and False-Positive and False-Negative Rates for Optimal Thresholds of Receiver Operating Characteristic Curves [a]

Models	Cut-off	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV
Model 1 [b]	0.232	0.55 (0.30 - 0.79)	0.50 (0.33 - 0.67)	0.52 (0.33 - 0.71)	0.44 (0.12 - 0.77)	0.74 (0.54 - 0.93)	0.24 (0.03 - 0.44)
Model 2 [c]	0.26	0.66 (0.52 - 0.79)	0.60 (0.49 - 0.71)	0.57 (0.44 - 0.70)	0.70 (0.51 - 0.88)	0.82 (0.71 - 0.94)	0.39 (0.24 - 0.54)
Model 3 [d]	0.217	0.78 (0.67 - 0.90)	0.72 (0.60 - 0.81)	0.67 (0.55 - 0.79)	0.83 (0.67 - 0.98)	0.91 (0.82 - 0.99)	0.50 (0.34 - 0.66)

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; PPV, positive predictive value; NPV, negative predictive value.

[a] Values are expressed as 95% confidence interval (CI).

[b] Clinical factors (disturbance of consciousness, disturbance of consciousness, hyponatremia, VEEG, and CRP).

[c] Incorporation of pediatric early warning score (PEWS) based on base model.

[d] Incorporation of serum neuron-specific enolase (NSE) based on model 2.

prognosis in children with VE. In this research, no children with VE experienced death or entered a vegetative state following treatment, and the majority of adverse events resulted in mild disability (84.38%, 27 out of 32).

To investigate the assessment value of PEWS combined with serum NSE, we first constructed model 1 for poor prognosis using only the factors that were significantly different between the two groups of children in terms of clinical characteristics. The data demonstrated that the model offered some predictive value, yet its predictive capability was slightly lessened. The inclusion of PEWS alone improved the predictive value of the model, especially the prediction performance of CRP for poor prognosis of VE. The PEWS combined with serum NSE further improved the predictive efficacy of the model.

Several limitations must be considered in this study. Brain injury has been shown in only a small number of patients. Obviously, a single serum NSE measurement offers limited insights. Ideally, multiple time points of sampling would be necessary to better understand the exact relationship between NSE and the severity of VE. This study also centers on the child's condition upon discharge as the endpoint, though it's important to explore the children's long-term prognosis. Thus, creating a comprehensive rehabilitation plan and providing home care instructions, along with conducting a thorough assessment of children, is essential. Additionally, the results of this study are applicable to this study cohort and should be cautiously extrapolated to other regional populations or to patients with other diseases.

5.1. Conclusions

High serum NSE levels are indicative of VE exacerbation. In VE patients, especially in children with severe VE, early PEWS assessment and elevated NSE levels can predict adverse prognostic events.

Footnotes

Authors' Contribution: H. L. Y. designed the research study. H. L. Y. and R. X. Y. performed the research. Y. F. S. and X. P. M. provided help and advice. R. X. Y. and Y. F. S. analyzed the data. H. L. Y. wrote the manuscript. X. P. M. reviewed and edited the manuscript. All authors read, approved the final manuscript, and contributed to editorial changes in the manuscript,

Conflict of Interests Statement: The authors declare no conflict of interest.

Data Availability: The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical Approval: The present study was approved by the Ethics Committee of The Second People's Hospital of Liaocheng (No. 202004LC25). All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Funding/Support: The present study received no funding/support.

Informed Consent: Written informed consent was obtained from each subject.

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