Retrospective Study

Predictive Value of Preoperative Antioxidant Levels in Postherpetic Neuralgia: A Retrospective Study

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Disclaimer: This retrospective study adhered to the World Medical Association Declaration of Helsinki. Data are presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. This study was approved by the Ethics Committee of the First Affiliated Hospital of Jiaxing University,1882 Zhonghuan South RD, Jiaxing, China (2024-KY-077). Written informed consent was obtained from all patients before the study procedures. There was no external funding in the preparation of this article.

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Background: Herpes zoster (HZ) presents as painful blisters caused by the reactivation of the varicella-zoster virus. Postherpetic neuralgia (PHN) is a challenging complication of HZ. Oxidative stress, implicated in various skin diseases, may play a role in PHN, motivating the investigation of blood antioxidants as potential predictors of the complication. Only a limited amount of research has explored the connection between serum antioxidants and HZ outcomes.

Objectives: To examine the impact of specific serum antioxidants on the development of PHN.

Study Design: A retrospective, observational study.

Setting: The study was carried out in the Pain Department of the First Hospital Affiliated to Jiaxing College in Jiaxing, China.

Methods: A total of 305 patients were included in the study, with 149 classified into the PHN group and 156 into the non-PHN group. Demographic information such as gender, age, disease duration, hospitalization, affected site, number of segments involved, complications, and treatment details were gathered. Moreover, common hematological data, including patients' levels of albumin (ALB), total bilirubin (TBIL), uric acid (UA), homocysteine (Hcy), and C-reactive protein (CRP) upon admission were recorded. Factors influencing prognosis were analyzed through both univariate and multivariate logistic regression analyses. Furthermore, a receiver operating characteristic (ROC) curve was constructed to evaluate the predictive potential of ALB and TBIL for prognosis.

Results: In the univariate analysis, age (odds ratio [OR] = 2.386, $P = 0.000$), disease duration (OR = 2.182, $P = 0.001$) and levels of albumin (OR = 0.284, $P = 0.000$), and TBIL (OR= 0.224, $P = 0.000$) were found to be correlated with PHN. Multifactorial logistic regression analysis revealed that an age exceeding 60 years (OR = 1.979, $P = 0.012$), ALB levels ≥ 44 g/L (OR = 0.278, $P = 0.000$), and TBIL levels ≥ 9.2 μmol/L (OR = 0.302, $P = 0.000$) were independent factors associated with PHN. The ROC curve demonstrated high predictive values for PHN with ALB and TBIL.

Conclusions: This study highlights the significant association between serum antioxidants, specifically ALB and TBIL, and the prognosis of PHN in patients with HZ.

Limitations: The nonrandomized, single-center, and retrospective design are major limitations of this study.

Key words: albumin, total bilirubin, oxidative stress, antioxidants, postherpetic neuralgia, predictive value

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Herpes zoster (HZ) is a skin condition marked by painful blisters, triggered by the reactivation of the latent varicella-zoster virus within the ganglia (1). The annual incidence of HZ is approximately 4 to 4.5 cases per 1000 individuals (2). Increasing age and immunosuppression are the primary risk factors of HZ (3,4). Postherpetic neuralgia (PHN) refers to pain of varying intensity that persists for at least 3 months after blister resolution. This pain is characterized by intense mechanical nociceptive hypersensitivity, significantly impacting patients' quality of life. The prevalence of PHN has shown an upward trend in recent years (5-7).

Oxidative stress is a pathological state of dysregulated intracellular redox balance. This imbalance results in the generation of significant quantities of reactive oxygen radicals and other oxidative molecules, initiating cellular damage and inflammatory responses. Oxidative stress has been linked to numerous skin diseases, a phenomenon attributed to the imbalance between reactive oxygen species (ROS) and antioxidants (8,9). Increases in ROS are also associated with reduced cellular immune responses (10). Antioxidants comprise a group of compounds that prevent oxidative reactions by decreasing the generation of free radicals, thus shielding cells and tissues from oxidative harm. Several studies have established the significant function of antioxidants in addressing inflammatory reactions and nerve impairment induced by oxidative stress. Furthermore, several natural plant extracts and medications have demonstrated noteworthy antioxidant properties, suggesting their potential efficacy in mitigating the cellular damage that oxidative stress triggers (11,12). Li Jing and colleagues have discovered that in a clinical setting, a specific herb with the ability to prevent oxidative stress may be used with other medications to cure PHN (13).

Increased oxidative stress weakens the effectiveness of the immune system and increases the risk of viral infections in older people. A significant amount of evidence supports the involvement of oxidative stress in the onset and advancement of autoimmune conditions like leukemia, psoriasis, pemphigus vulgaris (PV), and lupus (14-17). Neuropathic pain is also associated with oxidative stress and reduced antioxidant capacity (18).

Cases of HZ are often accompanied by neuropathic pain, yet their underlying causes are not fully understood. HZ has been reported to occur alongside an altered oxidative state, which ensues when the level of antioxidants in the circulation decreases, thus disrupting the balance of the redox system (19-21). However, there is a lack of research exploring the correlation between antioxidants and PHN. Therefore, the objective of this study was to examine the predictive significance of typical blood antioxidants, such as albumin (ALB), total bilirubin (TBIL), uric acid (UA), and homocysteine (Hcy), in relation to PHN.

Methods

Study Population

The retrospective study included all patients diagnosed with HZ who were admitted to the First Affiliated Hospital of Jiaxing University, located in Zhejiang, China, between January 2024 and April 2024. Approval was obtained from the Medical Ethics Committee of the First Affiliated Hospital of Jiaxing University (JiaXing, Zhejiang Province, China, approval number: 2024-KY-077). After the application of inclusion and exclusion criteria, a total of 305 patients were ultimately selected for the study. The patient selection procedure is depicted in Fig. 1.

Inclusion and Exclusion Criteria

Patients eligible for the study were included if they: 1) met the diagnostic criteria for HZ; 2) had HZ for a duration of less than 3 months; 3) were from 19 to 94 old; and 4) experienced moderate to severe pain with a numerical rating scale (NRS) score > 3.

Patients were excluded if they: 1) had diabetes mellitus; 2) were undergoing chemotherapy; 3) had other complications related to neuropathic pain disorders; 4) refused to provide clinical data and information; 5) discontinued treatment or had incomplete clinical data; or 6) had accompanying organic liver and kidney pathologies. The exclusion criteria resulted in the elimination of 86 patients.

Demographic Data

Demographic data on observational indicators were collected for each patient, including gender, age, duration of disease, affected segments, number of affected segments, length of hospitalization, complications, and treatment. Relevant biochemical test data collected at admission included patients' levels of ALB, UA, TBIL, Hcy, and CRP. Ganglionic involvement was classified into cervical, thoracic, lumbar, sacral, and trigeminal ganglia categories, as well as multisegmental involvement. Comorbidities such as hypertension and coronary artery disease were also noted. Treatment

options comprised pulsed radiofrequency (PRF), nerve blocks (NB), or a combination of both.

Follow-Up

After being discharged from the hospital, patients were monitored monthly for 3 months. Following this period, the patients were categorized into 2 groups: PHN and non-PHN. PHN was characterized as indicating a poor prognosis.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corporation), with all data subjected to normality testing via the Shapiro-Wilk test and examination of histograms. Non-normally distributed continuous data were expressed as medians and interquartile ranges (IQRs), while categorical data were displayed as numerals and percentages (%). Group comparisons were conducted using analysis of variance (ANOVA). The Mann-Whitney U test was applied for non-normally distributed continuous data, while the chi-square test was performed for categorical data. Demographic and biochemical test data were included in univariate analyses, and independent variables were included in multivariate logistic regression analyses (with a significance level set at $P < 0.05$).

The odds ratio (OR) value is used in regression analysis to indicate the dominance ratio of the variables, and the P-value responds to the significance of the OR value of the results. Multivariate logistic regression analysis was used to analyze independent factors affecting PHN in HZ patients with OR values that were significantly different in the univariate analysis. The predictive value of ALB and TBIL in determining the likelihood of PHN occurrence in HZ patients was evaluated using receiver operating characteristic (ROC) curve analysis, with the calculation of the area under the curve (AUC). A significance level of $P < 0.05$ was considered statistically significant.

Results

Baseline Data for Groups

This study comprised 305 patients diagnosed with HZ. Among them, 149 patients (48.85%) belonged to the PHN group, while 156 (51.15%) were placed in the non-PHN group. There were no statistically significant differences observed between the 2 groups in gender, number of segments, involved segments, length of hospitalization, complications, or treatment ($P > 0.05$).

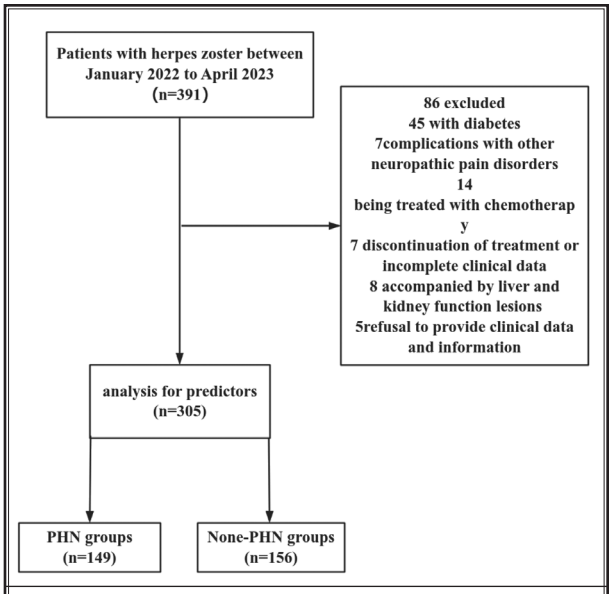

Fig. 1. *Flow of patients through this retrospective study. Ultimately, 305 HZ patients were included.*
PHN: postherpetic neuralgia.

However, significant differences in age and disease duration were observed between the 2 groups ($P < 0.05$). Further details are presented in Table 1.

Biochemical Data Analysis

Between the groups, no significant differences were observed in the levels of UA, Hcy, or CRP in the patients' blood ($P > 0.05$). However, levels of ALB and TBIL appeared to be significantly lower in the PHN group than in the non-PHN group ($P < 0.05$). Details are shown in Table 2.

Univariate Analysis

The dependent variable in this study was the occurrence of PHN, categorized as 0 for non-PHN and one for PHN. Independent variables consisted of median ALB, TBIL, UA, Hcy, and CRP values among both PHN and non-PHN patients, which were 44 g/L, 9.2 μmol/L, 279.5 μmol/L, 9.3 μmol/L, and one, respectively. Patients were categorized into above-median and below-median groups based on the median of those continuous variables.

In the univariate analysis, age (OR = 2.386, $P = 0.000$), disease duration (OR = 2.182, $P = 0.001$), and levels of ALB (OR = 0.284, $P = 0.000$) and TBIL (OR = 0.224, $P = 0.000$) were identified as factors associated with PHN. However, gender, number of segments, involved

segments, length of hospitalization, complications, treatment, UA, Hcy, and CRP did not show significant associations with PHN ($P > 0.05$). Additional details can be found in Table 3.

Multivariate Logistic Regression Analysis

Multivariate logistic regression analyses were performed, using the occurrence of PHN as the dependent variable. Independent variables included in the analysis were those identified with a significance level of $P < 0.05$ from the univariate analyses. The results showed that an age > 60 years (OR = 1.979, 95% CI: 1.162 - 3.370, $P = 0.012$), ALB levels ≥ 44 g/L (OR = 0.278, 95% CI: 0.167 - 0.464, $P = 0.000$), and TBIL levels ≥ 9.2 μmol/L (OR = 0.302, 95% CI: 0.181 - 0.503, $P = 0.000$) were independent factors influencing PHN. More detailed findings can be found in Table 4.

Table 1. *Respective demographic or characteristic data of both PHN and non-PHN groups.*

Demographic or Characteristic	Non-PHN (n = 156)	PHN (n = 149)	x^2	*P*
Gender			0.553	0.457
Female	93 (59.6)	95 (63.8)		
Male	63 (40.4)	54 (36.2)		
Age (years)			13.305	0.000
<60	78 (50.0)	44 (29.5)		
>60	78 (50.0)	105 (70.5)		
Course of Disease (Days)			10.823	0.001
<7	77 (49.4)	46 (30.9)		
>7	79 (50.6)	103 (69.1)		
Number of Segments			2.495	0.287
<3	18 (11.5)	24 (16.1)		
3	110 (70.5)	106 (71.1)		
>3	28 (18.0)	19 (12.8)		
Involved Segment			70181	0.208
cervical ganglia	22 (14.1)	19 (12.8)		
thoracic ganglia	106 (67.9)	92 (61.7)		
lumbar ganglia	15 (9.6)	11 (7.4)		
sacral ganglia	2 (1.3)	2 (1.3)		
trigeminal ganglia	3 (1.9)	8 (5.4)		
multiple-site	8 (5.1)	17 (11.4)		
Length of Hospitalization (Days)			0.355	0.552
<3	79 (50.6)	80 (54.1)		
>3	77 (49.4)	68 (45.9)		
Complication			2.844	0.092
No	134 (85.9)	117 (78.5)		
Yes	22 (14.1)	32 (21.5)		
Treatment			4.252	0.119
PRF	81 (51.9)	67 (45.0)		
NB	33 (21.2)	47 (31.5)		
PRF+NB	42 (26.9)	35 (23.5)		

Results are expressed as percentages. *P*-values were compared by x^2 test as appropriate.

Abbreviations: PHN: postherpetic neuralgia; PRF: pulsed radiofrequency; NB: nerve block.

ROC Curves

In the analysis, PHN was considered as the state variable. The AUC values for ALB and TBIL levels were calculated using ROC curve analysis. The results indicated that ALB levels showed a strong predictive value for PHN (AUC = 0.722, $P = 0.000$), with a critical value of 43.05, a sensitivity of 82.1%, and a specificity of 43.6%. Similarly, TBIL levels displayed a high predictive value for PHN (AUC = 0.714, $P < 0.001$), with a critical value of 9.55, a sensitivity of 62.2%, and a specificity of 28.2%. Results are shown in Table 5 and Figs. 2 and 3.

Discussion

PHN is prevalent among senior citizens, with increasing incidence as patients advance in age (22,23). Aging implies a dual impact: the body's immune system and nervous system become more fragile and susceptible to pain. Moreover, older individuals often have a diminished capacity to manage chronic pain, making it challenging for them to cope with the persistent discomfort characteristic of PHN. After the demographic data from 305 patients with HZ were analyzed, the study revealed that age emerged as a risk factor for PHN. Older patients were more prone to developing PHN, particularly those aged over 60 years, whose in-

Table 2. *Levels of antioxidants in blood serum in both groups of patients.*

Blood-Related Data	Non-PHN (n = 156)	PHN (n = 149)	Z	*P*
ALB (g/L)	44.8 (3.5)	42.6 (4.5)	-6.694	0.000
TBL (μmol/L)	11 (5.8)	8 (3.8)	-6.161	0.000
UA (μmol/L)	283.25 (87.4)	274.7 (93.6)	-1.083	0.279
Hcy (μmol/L)	9.5 (4.4)	9 (4.4)	-1.170	0.242
CRP (mg/L)	1 (2)	1 (2.2)	-1.046	0.296

Results are expressed as medians (interquartile range [IQR]). *P*-values were compared by Mann-Whitney U test as appropriate.
Abbreviations: PHN: postherpetic neuralgia; ALB: albumin; TBL: total bilirubin; UA: uric acid; Hcy: homocysteine; CRP: C-reactive protein.

Table 3. *Univariate analysis of PHN in patients with HZ.*

	Odds Ratio (95% CI)	*P*
Gender		0.457
Women	1	
Men	0.839 (0.528-1.332)	
Age (Years)		0.000
< 60	1	
> 60	2.386 (1.489-3.824)	
Course of Disease (Days)		0.001
< 7	1	
> 7	2.182 (1.366-3.486)	
Number of Segments		
< 3	1	
3	0.723 (0.371-1.408)	0.340
> 3	0.509 (0.219-1.184)	0.117
Involved Segment		
cervical ganglia	1	
thoracic ganglia	1.005 (0.512-1.973)	0.989
lumbar ganglia	0.849 (0.315-2.288)	0.746
sacral ganglia	1.158 (0.148-9.029)	0.889
trigeminal ganglia	3.088 (0.716-13.322)	0.131
multiple-site	2.461 (0.869-6.966)	0.090
Length of Hospitalization (Days)		0.552
≤ 3	1	
> 3	0.872 (0.556-1.368)	
Complication		0.094
No	1	
Yes	1.666 (0.917-3.026)	
Treatment		
PRF	1	
NB	1.722 (0.993-2.985)	0.053
PRF+NB	1.007 (0.579-1.752)	0.979
ALB (g/L)		0.000
< 44	1	
≥ 44	0.224 (0.139-0.363)	
TBL (μmol/L)		0.000
< 9.2	1	
≥ 9.2	0.284 (0.177-0.455)	
UA (μmol/L)		0.391
< 279.5	1	
≥ 279.5	0.821 (0.524-1.288)	
Hcy (μmol/L)		0.157
< 9.3	1	
≥ 9.3	0.722 (0.460-1.133)	

Table 3 cont. *Univariate analysis of PHN in patients with HZ.*

	Odds Ratio (95% CI)	*P*
CRP (mg/L)		0.962
< 1	1	
≥ 1	0.989 (0.631-1.550)	

Abbreviations: PHN: postherpetic neuralgia; HZ: herpes zoster; PRF: pulsed radiofrequency; NB: nerve block; ALB: albumin; TBL: total bilirubin; UA: uric acid; Hcy: homocysteine; CRP: C-reactive protein.

Table 4. *Multivariable logistic regression of PHN in patients with HZ.*

	Odds Ratio (95% CI)	*P*
Age (Years)		0.012
≤ 60	1	
> 60	1.979 (1.162-3.370)	
Course of Disease (Days)		0.089
≤ 7	1	
> 7	1.585 (0.932-2.696)	
ALB (g/L)		0.000
< 44	1	
≥ 44	0.278 (0.167-0.464)	
TBL (μmol/L)		0.000
< 9.2	1	
≥ 9.2	0.302 (0.181-0.503)	

Abbreviations: PHN: postherpetic neuralgia; HZ: herpes zoster; ALB: albumin; TBL: total bilirubin.

Table 5. *ROC curve distribution of ALB for PHN in patients with HZ.*

	AUC	95% CI	*P*
ALB (g/L)	0.722	0.664-0.779	0.000
TBL (μmol/L)	0.704	0.646-0.762	0.000

Abbreviations: ROC: receiver operating characteristic; AUC: area under curve; CI: confidence interval; PHN: postherpetic neuralgia; HZ: herpes zoster; ALB: albumin; TBL: total bilirubin.

cidence of PHN was 1.979 times that of patients under 60 years old.

Recent research has reported that herpetic pain is linked to the presence of reactive oxygen species (ROS), which are implicated in sensory nerve impairment. Prolonged accumulation of ROS and reactive nitrogen species (RNS) in the dorsal root ganglia may contribute to neuronal injury, resulting in inflammatory nociceptive hypersensitivity and neuropathic pain, affecting both central and peripheral nerves (19,20).

The therapeutic potential of antioxidants in many disorders has drawn growing attention. Research has also revealed that decreased levels of common

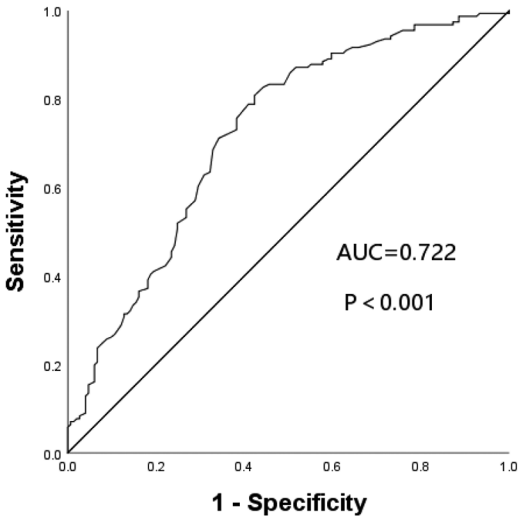

Fig. 2. *ROC curve distribution of ALB for PHN in patients with HZ.*
ROC: receiver operating characteristic; AUC: area under curve; PHN: postherpetic neuralgia; HZ: herpes zoster;ALB: albumin.

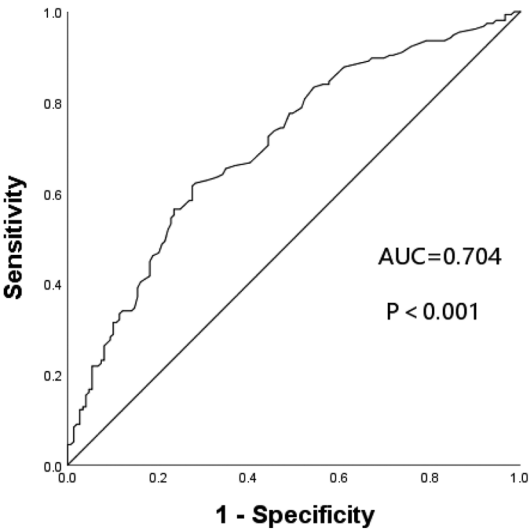

Fig. 3. *ROC curve distribution of TBL for PHN in patients with HZ.*
ROC: receiver operating characteristic; AUC: area under curve; PHN: postherpetic neuralgia; HZ: herpes zoster; TBL: Total bilirubin.

antioxidants such as TBIL, UA, and ALB in the bloodstream are linked to several disorders. Hui Zhang and colleagues discovered that patients with lower levels of serum UA had an increased risk of developing peripheral neuropathy in type 2 diabetes mellitus (24). Moreover, Yang's team observed that migraine sufferers had decreased serum levels of UA, TBIL, and ALB, indicating a diminished antioxidant status (25). Tuba Oskay and co-authors observed significantly lower levels of serum UA, TBIL, and ALB in patients with HZ than in healthy individuals, while levels of Hcy and CRP were significantly higher in HZ patients than in healthy controls (21). These findings suggest a potential association between uncontrolled reactivation of the varicella-zoster virus and reduced antioxidant levels. It can thus be postulated that these biomarkers may also play a significant role in PHN.

The present study included the prevalent indicators of blood antioxidant capacity and identified ALB and TBIL as risk factors in the onset of PHN among HZ patients. Human serum ALB serves various functions, including the maintenance of plasma osmolality and the transportation of hormones, vitamins, mineral oligomers, and drugs. Serum ALB also acts as a pivotal antioxidant in the bloodstream and protects cells from damage caused by oxidative stress by trapping free radicals, binding metal ions, and scavenging oxides. These antioxidant mechanisms help serum ALB maintain cellular health and prevent oxidative stress-induced diseases (26,27). Studies have shown that serum ALB is a reliable biomarker for predicting outcomes in several medical areas, including emergency medicine, cardiovascular illness, infections, renal diseases, cancer, and autoimmune rheumatic ailments (28). This protein stimulates the growth and specialization of T and B cells, ultimately enhancing immune cell function. Serum ALB has a role in controlling the inflammatory response, preventing an excessive inflammatory reaction, and safeguarding the body against inflammatory harm. Decreased levels of ALB in the body have a negative impact on the immune system and its ability to fight inflammation, leading to a higher susceptibility to viral infections and prolonged neuro-inflammation. This phenomenon explains why individuals with low ALB levels continue to have neuropathic pain for 3 months after recovering from herpes. The present study has found that individuals with HZ who have low levels of serum ALB are more susceptible to developing PHN, a finding that aligns with comparable observations made in studies conducted in other medical fields.

TBIL is a tetrapyrrole compound with antioxidant activity. There is growing evidence suggesting that TBIL is a powerful antioxidant and can protect cells from damage (29,30). Although TBIL can be harmful in large amounts, it functions as a potent antioxidant in serum when present within its normal physiological range. Alterations in the expression and activity of enzymes involved in bilirubin synthesis are often observed in aging-related neurological and neurodegenerative diseases, as are changes in blood bilirubin levels (31). Recent research has indicated that TBIL serves as a potential predictor for the aforementioned ailments, with low bilirubin levels within the physiological range posing a risk factor for numerous diseases.

Based on the ROC curve, it was found that ALB and TBIL had a high predictive value for the development of PHN, with optimal cut-off values of 43.05 g/L and 9.55 mol/L, respectively. Reduced preoperative levels of TBIL and ALB indicate a compromised antioxidant status in the patient, thereby increasing the risk of neurological injury caused by oxidative stress and ultimately resulting in an unfavorable prognosis. Patients should be followed up while their levels of ALB and TBIL are tracked. If those decrease progressively, then prophylactic intervention should be provided.

Limitations

The current study presents some limitations. Firstly, its retrospective nature may introduce varying degrees of retrospective bias. Therefore, future research should include a broader array of indicators and a larger sample size and validate the findings through prospective studies. Secondly, because of the a single-center setting of this study, the absence of external validation stands out as a primary limitation. In addition, the study population comprised Chinese individuals, potentially limiting the generalizability of the findings to other regions. Thus, there is a need for larger, multicenter, prospective studies with refined prediction models in the future.

Conclusion

In conclusion, the study indicated that age and the levels of ALB and TBIL within a patient's blood serum may be considered as independent risk factors for PHN. Furthermore, individuals with HZ displaying lower levels of ALB and TBIL appear to be predisposed to developing PHN. Due to their affordability and simplicity of measurement, serum ALB and TBIL could serve as practical tools for evaluating the risk for PHN in individuals with HZ.

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