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Risk assessment of severe adult tetanus using the NLR and AST level and construction of a nomogram prediction model

Yuyan Wang, Liyuan Zhang *

Department of Infectious Diseases, The Second Affiliated Hospital of Hainan Medical University, Haikou 570311, Hainan Province, China

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ABSTRACT

Objective: We sought to examine high-risk factors for severe tetanus, construct a nomogram model, and predict the risk probability of severe tetanus in adult patients to provide a theoretical basis for clinical intervention. **Methods**: A retrospective analysis was employed in this study, which enrolled 65 adult patients with tetanus diagnosed at the Second Affiliated Hospital of Hainan Medical University from January 2017 to September 2022. Study participants were divided into severe and mild groups based on the Ablett classification. The general data and laboratory markers of both groups were compared, and logistic regression analysis was used to screen for independent risk factors for severe tetanus. A nomogram prediction model was constructed, and receiver operating characteristic (ROC), calibration curve, and decision curve analysis (DCA) were constructed and used to assess discrimination, calibration, and net benefit. **Results:** Of the 65 adults patients with tetanus, 28 were placed in the severe group and 37 were placed in the mild group. Univariate logistic regression analysis showed that there were statistically significant differences in the incubation period, time from disease onset to treatment, white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), platelet count (PLT), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lactate dehydrogenase level (LDH), myoglobin level (Mb), and aspartate aminotransferase (AST) level between the two groups ($P < 0.05$). while the differences in age; sex; and creatine kinase, creatine kinase isoenzyme, and alanine aminotransferase levels were not statistically significant ($P > 0.05$). Multivariate analysis showed that NLR (odds ratio [OR] = 4.998, 95 % confidence interval [CI] = 1.154–21.649, $P = 0.031$), AST (OR = 1.074, 95 % CI = 1.007–1.146, $P = 0.031$), PLT (OR = 1.055, 95 % CI = 1.006–1.106, $P = 0.027$), and incubation period (OR = 0.597, 95 % CI = 0.423–0.843, $P = 0.003$) are independent risk factor for severe tetanus. A Nomogram for predicting Severe Tetanus (N-ST) prediction model was constructed based on variables in the multivariate analysis with $P < 0.05$. The ROC curve showed that the optimal cutoff point was 108.044 points. At this point, the sensitivity was 86.5 %, the specificity was 89.3 %, the area under the ROC curve was 0.936, and model discrimination was good. The calibration curve overlapped with the ideal curve, and the DCA curve showed that the model can provide clinical benefits. **Conclusion:** NLR, AST, PLT, and incubation period are predictors of severe tetanus. The constructed N-ST model can provide a new, convenient, and rapid method to predict the risk probability of severe tetanus in adults and guide early clinical intervention.

* Corresponding author. Department of Infectious Diseases, The Second Affiliated Hospital of Hainan Medical University, 368 Yehai Avenue, Longhua District, Haikou 570311, Hainan Province, China.
E-mail address: 569255496@qq.com (L. Zhang).

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1. Introduction

Tetanus is an acute infectious disease caused by *Clostridium tetani*. The toxin tetanospasmin produced by this bacterium is known to be one of the most toxic substances in the world. Tetanus has significant pathogenicity and a high mortality rate [1]. Laryngospasm, asphyxiation, lung infection, and organ failure can occur in severe cases, and the mortality rate can reach 65–70 % in centers without appropriate intensive care facilities [2]. During treatment, high-dose sedatives must be administered, and prompt tracheotomy is performed; however, this causes sputum accumulation and lung infection. Therefore, such treatments are not recommended for mild cases, showing that treatment approaches for severe and mild tetanus should have some differences. Currently, the Ablett classification

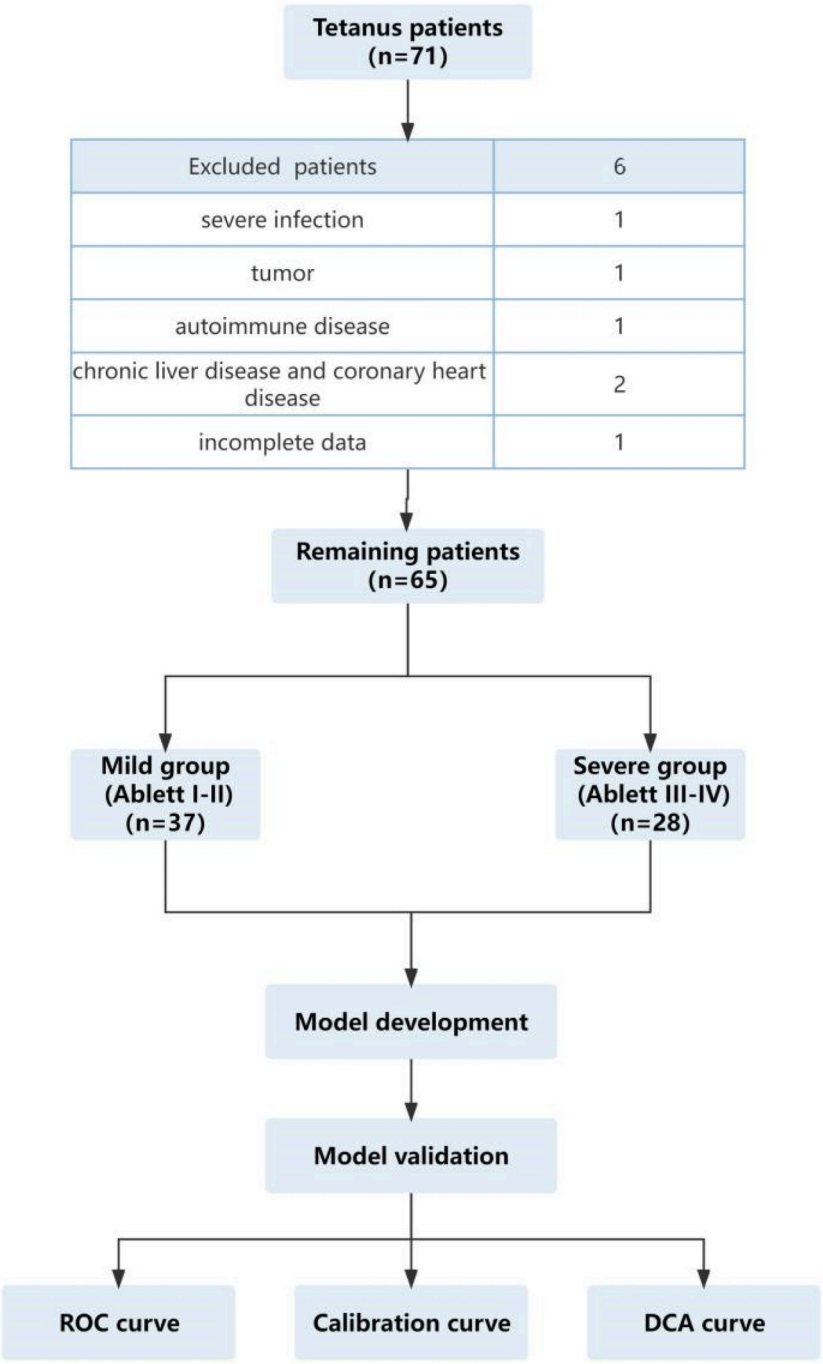

Fig. 1. Flow diagram of study population selection.

is used to evaluate the patient's condition and is a qualitative judgment method. The use of this qualitative method often causes delayed treatment and some limitations in clinical work. Therefore, the use of objective markers and the early prediction of disease severity is vital to providing suitable treatment. The neutrophil-to lymphocyte ratio (NLR) can reflect dynamic changes in neutrophils and lymphocytes in the human body and is a novel inflammatory marker that represents the degree of inflammation and immune status of the body. In recent years, NLR has shown good prediction effects in infectious disease, tumors, and immune diseases [3]. One study showed that patients with severe spasms tend to have more severe conditions, and their myocardial enzyme levels are higher when muscle spasm severity is greater [4]. Therefore, inflammatory markers and myocardial zymography results can be used as quantitative markers to determine the severity of tetanus in patients. Nomogram prediction models are widely used in disease diagnosis, outcome, and prognosis prediction [5], but there are no reports of studies using such models to predict severe adult tetanus. In this study, a retrospective analysis was carried out to search for laboratory markers associated with severe tetanus, determine high-risk factors, and construct a nomogram prediction model for early screening of patients with severe tetanus to provide a theoretical basis for treatment regimen selection.

2. Participants and METHODS

2.1. Study participants

Seventy-one adult patients with tetanus diagnosed at the Second Affiliated Hospital of Hainan Medical University from January 2017 to September 2022 were considered for this study. The definition of patients with tetanus was extracted from the nomenclature of the *International Classification of Disease, Tenth Revision (ICD-10)*. The diagnosis of tetanus was mainly based on clinical manifestations, including one of the following two manifestations: (1) the presence of clenched teeth or a wry smile, and (2) painful muscle cramps [2]. History of trauma was not necessary for diagnosis [6]. The exclusion criteria were as follows: (1) presence of other severe infections, malignant tumors, autoimmune diseases, liver cirrhosis, chronic renal failure, or coronary heart disease; (2) age <18 years; and (3) incomplete data in the medical records. Sixty-five patients were finally included (Fig. 1). The study participants were divided into the severe group (Ablett grades III and IV) and a mild group (Ablett grades I and II) based on the Ablett classification [7]. The Ablett classification of tetanus severity defines four grades as follows: grade I (mild to moderate trismus, generalized spasticity, no respiratory compromise, no spasms, little or no dysphagia); grade II (moderate trismus, marked rigidity, mild to moderate but short spasms, moderate respiratory compromise with an increased respiratory rate [>30 breaths per minute], mild dysphagia); grade III (severe trismus, generalized spasticity, reflex prolonged spasms, increased respiratory rate [>40 breaths per minute], apneic spells, severe dysphagia, tachycardia [>120 beats per minute]); and grade IV (clinical features of grade 3 tetanus, violent autonomic disturbances involving the cardiovascular system, severe hypertension and tachycardia alternating with relative hypotension and bradycardia [either of which might be persistent]). Ethical approval was obtained from the Human Research Ethics Committee of the Second Affiliated Hospital of Hainan Medical University, China (LW2021188), and the Committee waived informed consent.

2.2. Study methods

The general data of patients (age, sex, incubation period, time from disease onset to treatment, the degree of trismus, muscle spasms, respiratory rate, and heart rate) and blood routine, hepatic function, and myocardial zymography results immediately after admission were collected. NLR, platelet count, and the platelet-to-lymphocyte ratio (PLR) were calculated based on the blood routine results.

2.3. Statistical methods

R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform statistical analysis, and general data and laboratory markers were compared between the severe group and mild group. Quantitative data are expressed as $x \pm s$, and intergroup comparisons were carried out by independent-samples *t*-test. Qualitative data are expressed as the number and percentage of patients, and intergroup differences were tested using chi-squared test without continuity correction. Logistic regression analysis was used to screen for independent risk factors for severe tetanus. The rms R package was used to construct a nomogram prediction model, and the ROC curve, calibration curve, and DCA curve were successively plotted and used to assess the discrimination, calibration, and net benefit of the model in order to measure its predictive capacity. $P < 0.05$ was considered statistically significant.

3. Results

3.1. General data

Among the 65 adult tetanus patients, 28 were placed in the severe group and 37 were placed in the mild group. In total, there were 45 men and 20 women, and the mean age was 59.04 ± 14.85 years. Sixty-three patients had a definite history of trauma (including 31 with puncture wounds by iron product, 8 with puncture wounds by wood products, 7 with falls, 4 with surgical wound infections, and 13 with other causes of trauma) and 2 patients did not have a definite history of trauma. Patients with a history of trauma did not promptly receive tetanus antitoxin or tetanus immunoglobulin prophylaxis. On the day of admission, local blocking with tetanus antitoxin was performed regardless of whether the wound had healed, followed by wound incision and debridement. All of the patients

had lockjaw as the initial symptom, and muscle spasms were present on the day of admission. After admission, the patients were given tetanus antitoxin, anti-infective medication, sedation, nutrition support, and other basic treatments. Eleven patients underwent tracheotomy. In our study, two patients died in the hospital, five patients voluntarily ended treatment and left the hospital, and their deaths were confirmed by phone during follow-up. All of these patients were in the severe group. The remaining 58 patients showed no obvious sequelae after follow-up. Table 1 shows a comparison of general data between the severe and mild groups.

3.2. Univariate logistic regression analysis

There were no statistically significant differences in age; sex; or creatine kinase, creatine kinase isoenzyme, and ALT levels between the severe group and mild group ($P > 0.05$). The severe group had higher white blood cell count, neutrophil count, PLT, NLR, PLR, LDH, myoglobin, and AST values compared to the mild group, while the incubation period, time from disease onset to treatment, and lymphocyte count of the severe group were lower than those of the mild group, and these differences were statistically significant ($P < 0.05$) (Table 1).

3.3. Multivariate logistic regression analysis

Markers with $P < 0.05$ in the univariate analysis results were included in the multivariate logistic regression analysis, and forward and backward stepwise regression found that PLT (odds ratio [OR] = 1.055), NLR (OR = 4.998), and AST (OR = 1.074) are independent risk factors for severe tetanus; incubation period (OR = 0.597) is an independent protective factor; and the differences were statistically significant ($P < 0.05$) (Table 2).

3.4. Construction of a nomogram prediction model and performance evaluation

Final progression to severe disease was used as the dependent variable, independent risk factors (including incubation period, PLT, NLR, AST) were used as independent variables, and the rms package in R version 4.2.2 were used to construct the Nomogram for Predicting Severe Tetanus (N-ST) model (Fig. 2A). The N-ST model was used for early prediction of the risk probability of severe adult tetanus. To facilitate precise calculation, the formula was extracted from the nomogramEX package, i.e., total score = −2.842 * incubation period +2.5 * NLR +0.093 * PLT +0.553 * AST +75.102. The ROC curve (Fig. 3) of this model was plotted. When the total score was 108.044 points, the Youden index was highest at 0.758. At this point, the sensitivity was 86.5 %, the specificity was 89.3 %, and the area under the ROC curve was 0.936. In order to decrease bias caused by overfitting, 1000 bootstrap repeated samplings were used for internal calibration to construct the calibration curve for the N-ST model (Fig. 2B); it can be seen that the calibration curve overlaps with the ideal curve. The DCA clinical decision curve, plotted using the rmda package, showed that using this model for intervention demonstrated the greatest clinical net benefits (Fig. 2C).

4. Discussion

The tetanus exotoxin produced by *Clostridium tetani* is the main pathogenic substance that causes lockjaw, a wry countenance, and muscle spasms. This exotoxin is a neurotoxin that can block inhibitory synapses in the central nervous system, causing skeletal muscle

Table 1
Univariate logistic regression analysis of general data and laboratory markers of the severe and mild groups.

Marker	Severe group (n = 28)	Mild group (n = 37)	Statistic	*P* value
Age (years, $\bar{x} \pm s$)	59.04 ± 14.85	52.70 ± 13.68	t = −1.78	0.086
Sex [n (%)]			$X^2 = 0.04$	0.835
Male	19(67.8 %)	26(70.2 %)		
Female	9(32.1 %)	11(29.7 %)		
Incubation period (days, $\bar{x} \pm s$)	6.89 ± 3.27	14.00 ± 8.81	t = 4.05	0.003
Time from disease onset to treatment (days, $\bar{x} \pm s$)	2.46 ± 1.64	3.70 ± 2.69	t = 2.15	0.044
WBC (10^9/L, $\bar{x} \pm s$)	10.31 ± 4.12	7.15 ± 1.95	t = −4.10	0.001
NEU (10^9/L, $\bar{x} \pm s$)	8.69 ± 4.05	5.22 ± 1.88	t = −4.60	<0.001
LYM (10^9/L, $\bar{x} \pm s$)	1.05 ± 0.46	1.46 ± 0.55	t = 3.2	0.005
PLT (10^9/L, $\bar{x} \pm s$)	287.20 ± 81.02	236.20 ± 80.37	t = −2.52	0.027
NLR ($\bar{x} \pm s$)	11.76 ± 10.39	4.17 ± 2.59	t = −4.28	0.002
PLR ($\bar{x} \pm s$)	342.00 ± 201.68	183.36 ± 97.78	t = −4.19	0.003
CK (U/L, $\bar{x} \pm s$)	1183.00 ± 1301.87	758.00 ± 989.30	t = −1.49	0.157
CK-MB (U/L, $\bar{x} \pm s$)	55.02 ± 39.60	35.50 ± 42.32	t = −1.89	0.084
LDH (U/L, $\bar{x} \pm s$)	264.00 ± 98.26	200.50 ± 79.04	t = −2.89	0.013
Mb (U/L, $\bar{x} \pm s$)	460.80 ± 323.66	195.00 ± 127.81	t = −4.56	0.001
ALT (U/L, $\bar{x} \pm s$)	29.54 ± 12.85	25.81 ± 15.29	t = −1.04	0.306
AST (U/L, $\bar{x} \pm s$)	47.36 ± 27.45	32.00 ± 13.49	t = −2.97	0.011

Note: ALT: alanine aminotransferase, AST: aspartate aminotransferase, CK: creatine kinase, CK-MB: creatine kinase isoenzyme, LDH: lactate dehydrogenase, LYM: lymphocyte count, PLT: platelet count, Mb: myoglobin, NEU: neutrophil count, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, WBC: white blood cell count.

Table 2
Multivariate logistic regression analysis of severe tetanus in adult patients.

Marker	Regression coefficient	Wald statistic	SE	OR (95 % CI)	*P* value
Incubation period (days)	−0.515	−2.93	0.176	0.597 (0.423–0.843)	0.003
PLT (10^9/L)	0.055	2.21	0.024	1.055 (1.006–1.106)	0.027
NLR	1.609	2.15	0.748	4.998 (1.154–21.649)	0.031
AST (U/L)	0.071	2.16	0.033	1.074 (1.007–1.146)	0.031

Note: AST: aspartate aminotransferase, NLR: neutrophil-to-lymphocyte ratio, OR: odds ratio, PLT: platelet count, SE: standard error, OR: odds ratio, CI: confidence interval.

spasms and severe autonomic system disruption [8]. Globally, 48,000–80,000 patients die due to tetanus every year, with most of these deaths occurring in low- and middle-income countries [9]. Additionally, the length of hospitalization is longer in severe cases, and subsequent treatments due to delays cause high medical fees, increasing the financial burden of patients [10]. Therefore, early identification of severe tetanus patients and administration of high-dose sedatives to alleviate muscle spasms as well as prompt tracheotomy to prevent asphyxiation are vital [11,12]. The Ablett classification is a commonly used scale in clinical work and it has been used in a number of studies [3,13–15] to assess the severity of tetanus. We also approved the value of this scale in the retrospective evaluation of the severity of tetanus. However, given that it is based on the clinical manifestations that have already occurred, the Ablett classification has only a limited ability to predict the future course of the disease. Our study showed that all patients had lockjaw as the first symptom and muscle spasms on admission, and some patients gradually developed severe disease during hospitalization. Therefore, Ablett classification has limitations with respect to evaluating the patient's condition at admission and predicting whether the patient will develop severe disease. Therefore, it is important to predict which patients will develop severe cases while they are still in the early stages of the disease. If we can predict the course of the disease early and apply prompt treatment, we could reduce both the mortality rate and the economic burden. This was the main purpose of this study. Therefore, an N-ST model was constructed in this study to search for quantitative markers that can be used for simple and prompt evaluation of disease severity, and the capacity of this model in predicting the risk probability of severe tetanus was examined to guide prompt clinical intervention, improve the prognosis of patients with tetanus, and increase the survival rate.

This study shows that incubation period, NLR, PLT, and AST are independent risk factors for severe tetanus. The results of many studies [3,13,16] showed that, the shorter the incubation period, the greater the severity and the poorer the prognosis, which is consistent with the results of this study. Currently, the relationship between the incubation period and disease severity is not clear, although it may be influenced by the site of the wound, bacteria virulence, and immunity. The incubation period is shorter in patients whose wound is closer to the central nervous system, who are infected with more virulent bacteria, and who have weaker immune systems [17]. As the incubation period can be obtained by medical history-taking, it is convenient and fast to record and usually used as a marker to determine disease severity in clinical practice. However, there is a risk of delayed treatment if only the incubation period is used as a predictor [4]. Serum NLR, PLT, and AST in patients with severe cases were higher than in patients with mild cases. This may be related to the severity of inflammatory response in the patients. NLR is a marker that can reflect the degree of inflammation and has predictive effects in various inflammatory diseases, tumors, and immune diseases at present [18–20]. Tetanospasmin can bind irreversibly to neurons and prevent vesicles from releasing inhibitory neurotransmitters [8]. If it inhibits the inhibitory effects of the spinal cord on the sympathetic nervous system, it will cause catecholamine levels to rise. Some studies posit [3] that the increase in catecholamines in tetanus patients and the overactivation of sympathetic nerves promote the production of a large number of cytokines, including TNF-α. TNF-α has a direct toxic effect on body cells, and can coordinate with many inflammatory mediators, resulting in systemic inflammatory response syndrome (SIRS), which leads to tissue damage. Staedtke [21] identified catecholamines as an important component of cytokine release. Catecholamines can contribute to the release of cytokines through the self-amplification production loop in macrophages. In patients with severe tetanus, due to the overactivation of sympathetic nerves, the secretion of catecholamines increases, leading to the release of a large number of cytokines, which can further cause the surge of catecholamines, forming a vicious cycle, and eventually lead to SIRS. Systemic inflammatory response is initially characterized by an imbalance of proinflammatory and anti-inflammatory in the body, resulting in persistent and uncontrolled inflammatory response and low immune defense function, in which neutrophils participate in nonspecific inflammatory response, and lymphocytes participate in the regulation of the immune system. The review by Kim [22] discussed the interaction between platelets and inflammatory responses. Platelets have traditionally been considered key effector cells in hemostasis but are now increasingly recognized as players in innate and adaptive immune inflammatory responses. Platelets can recognize and kill invading pathogens and, when stimulated, they can also release a variety of mediators that regulate immune and endothelial cell responses. Increased platelet activity can protect the host from infectious damage, and these key roles highlight the need for platelet response in inflammatory responses. Therefore, we believe that the increased platelet count in patients in severe cases is reasonable, and a more severe inflammatory response is associated with a stronger platelet response. The changes in these cells reflect the degree of inflammation and immune function of the body. Therefore, NLR can reflect the dynamic changes in the state of acute inflammatory response.

We found significant differences in AST, but not CK, between the two groups. Previous studies [23] have shown that inflammatory responses mediated by proinflammatory cytokines (such as TNF-α) can lead to excessive contraction of muscle cells, increased ATP consumption, increased mitochondrial volume density, and ultimately reduced mitochondrial respiratory capacity. Mediators of systemic inflammatory responses have been shown to directly impair mitochondrial structure and function [24]. In addition, various systemic inflammatory reactions are closely related to oxidative stress. As reported by Wen [25], mitochondria are not only the main

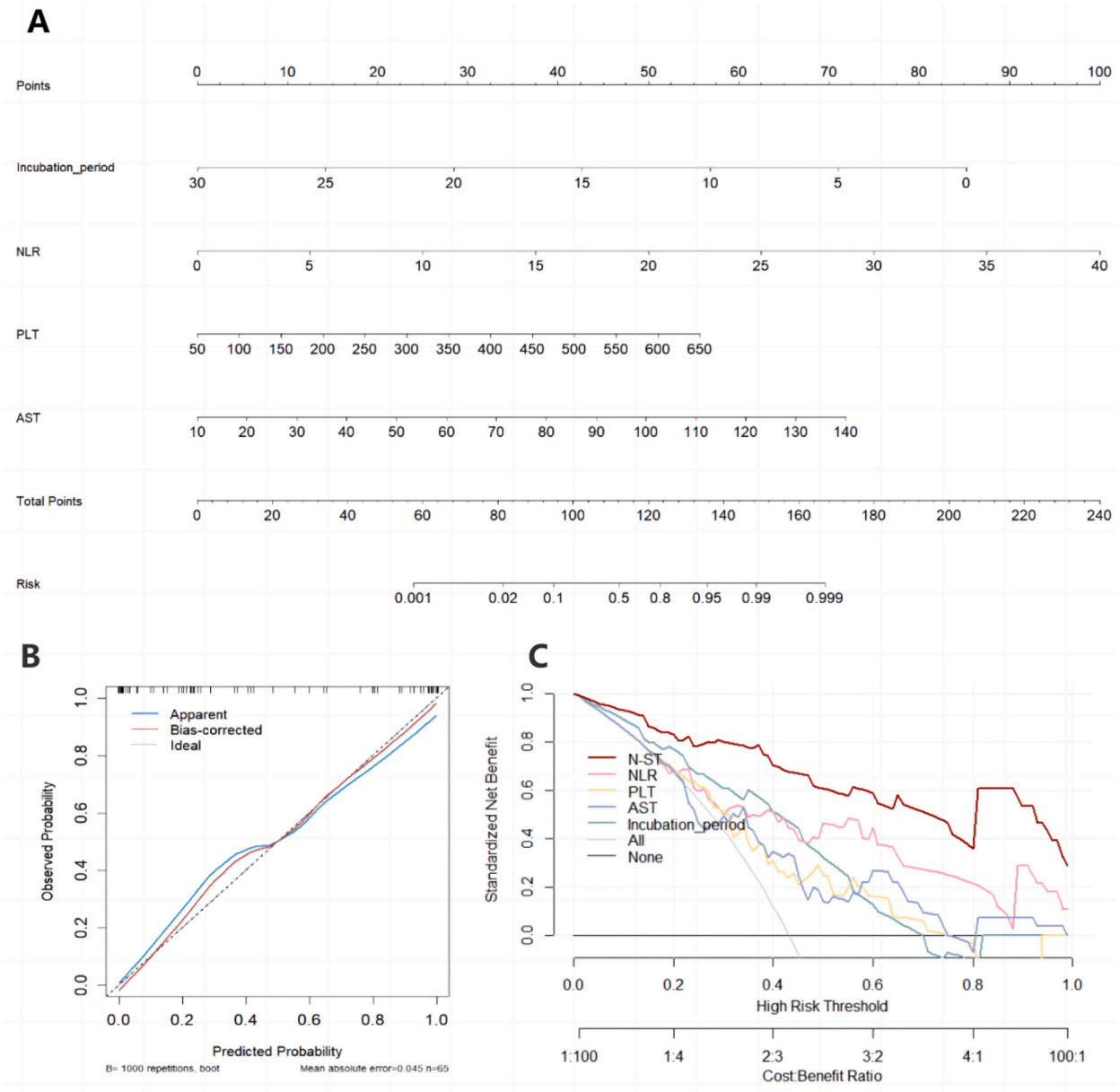

Fig. 2. A. The N-ST nomogram designed for predicting the probability of severe adult tetanus.
Note: In this figure, the regression coefficient of every variable was converted to 0–100 points based on its ratio. The value of the marker is located above its corresponding axis. Specific points can be obtained at the corresponding "points" axis. The total of these points is located on the "total points" axis, and the risk probability of severe tetanus can be obtained from the corresponding "risk" axis below it. In this figure, time is the incubation period (days), NLR is the neutrophil-to-lymphocyte ratio, PLT is platelet count (*10^9/L), and AST is aspartate aminotransferase.
B. The calibration curve of the N-ST model.
C. The DCA clinical decision curve of the N-ST model.

production site of reactive oxygen species (ROS), but also the main target of ROS. The intense inflammatory response in patients with severe cases causes oxidative stress, leading to mitochondrial damage, and the mitochondrial damage induced by the initial ROS increases the production of ROS, which further leads to mitochondrial damage, thereby forming a vicious cycle. AST mainly exists in the mitochondria of muscle cells and hepatocytes [26]. A more intense inflammatory response is associated with more severe mitochondrial damage and greater AST release. There was no significant difference in CK in this study. The reasons for this phenomenon may be as follows. First, all patients were admitted to hospital with lockjaw as the first symptom. Regardless of whether they developed a severe disease in the later stage, all patients showed muscle spasm on the day of admission. CK is a sensitive indicator of muscle spasm, and its expression is the highest in energy-consuming organs such as muscles, heart, and brain. CK rises 1–12 h before muscle

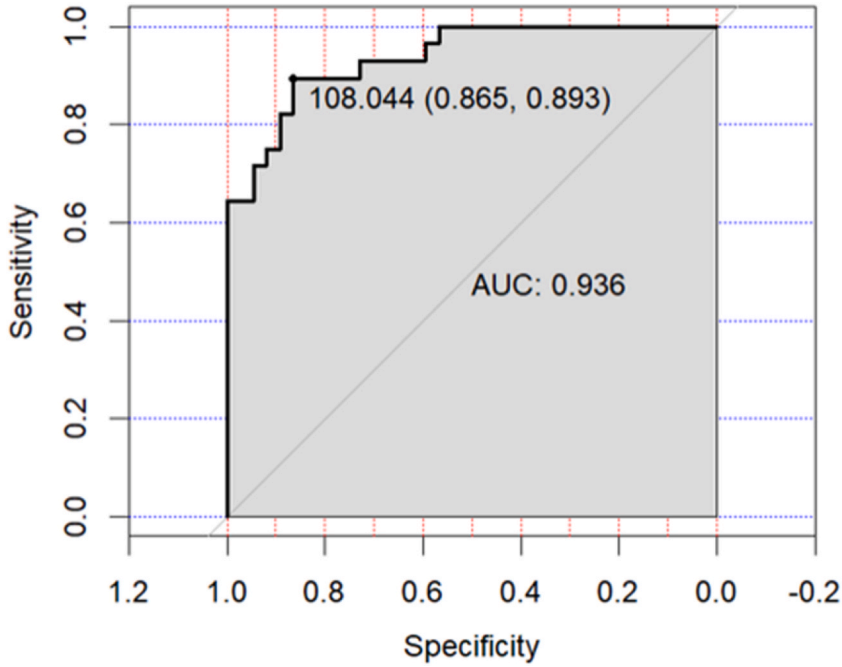

Fig. 3. The ROC curve of the N-ST model.

spasm and peaks 24–72 h later [27]. Hence, CK could have increased in the early stage of muscle spasm, and both the patients in the mild group and those in the severe group had muscle spasm on admission, both groups can show high levels of CK. However, there was no statistically significant difference between the two groups. One multicenter study [2] showed the same results, that AST is a significant predictor of mortality but CK is not. Therefore, CK may not be an optimal indicator for distinguishing between mild and severe cases. Nevertheless, this speculation has to be verified in a larger study.

In summary, the severity of tetanus is affected by many factors, and predictions should not be made using just a single factor. Therefore, an N-ST composite model was constructed in this study based on independent risk factors, and its prediction performance was evaluated. It is worth noting that we used continuous variables and not categorical variables to facilitate personalized prediction of severe disease probability. The ROC curve showed that the optimal cutoff point for the total score was 108.044 points. At this point, the sensitivity was 86.5 %, the specificity was 89.3 %, and the area under the ROC curve was 0.936. It can be seen that the model has good discrimination and can help differentiate between severe and mild cases. The calibration curve obtained after 1000 repeated samplings overlapped with the ideal curve, showing that the model has good calibration and the prediction probability and observation probability have good concordance. The DCA curve showed that the N-ST composite model can provide a certain threshold to bring the highest net benefit and its predictive power is superior to that of a single marker.

Therefore, the N-ST model constructed in this study can be used for early prediction of severe tetanus. For example, when a total score of >108.044 points is obtained from the formula, this means that the patient has an extremely high probability of progressing to severe disease. In this case, it is recommended that high-dose sedatives and analgesics be administered, medical equipment for tracheal intubation and tracheotomy should be prepared timely to ensure that it can be used when necessary, and the patient's condition should be closely monitored for changes to improve the prognosis and increase the survival rate.

This study also had some limitations. First, this was a retrospective study, so it may have selection bias or recall bias. Second, this was a single-center study and the sample size was small. Predictive effectiveness of the N-ST model should be further examined in prospective cohort studies of patients with tetanus with a larger sample size.

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Ethical approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Hainan Medical University (LW2021188).

Data availability statement

All data associated with the study has been deposited into the Mendeley Data.

CRediT authorship contribution statement

Yuyan Wang: Writing - original draft, Resources, Formal analysis, Data curation. **Liyuan Zhang:** Writing - review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23487.

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