Research Article

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Development and Validation of Nomogram for Prognosis of Patients with Severe Fever with Thrombocytopenia Syndrome

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1. Abstract

1.1. Objective:
Severe fever with thrombocytopenia syndrome (SFTS) is an infectious disease with high mortality among patients without timely treatment. The purpose of this study was to develop and validate a nomogram for predicting the prognosis of SFTS patients, which could detect patients with a poor prognosis in time and reduce the mortality rate of the disease.

1.2. Method:
The study included basic information and laboratory indicators collected within 24 hours after admission for 171 patients diagnosed with SFTS in Yantai, China. The patients were randomly divided into training and test sets using a 7:3 ratio. We constructed a multivariate logistic regression model using the training set data to identify the risk factors associated with patient death and used these factors to construct a nomogram. We evaluated the model's performance using the receiver operating curve (ROC) and its area under the curve (AUC). Additionally, we evaluated the calibration curve and performed decision curve analysis (DCA) to determine the net clinical benefit.

1.3. Result:
The nomogram included age, respiratory rate, consciousness changes, white blood cell count (WBC), fibrinogen (FIB), and prothrombin time (PT). The calibration curve indicated that the nomogram had good calibration. In the training cohort, the area under the model curve was 0.903 (95% CI = 0.845-0.9612). In the test set, the AUC value was 0.8785 (95% CI = 0.7561-1). The decision curve analysis (DCA) for both the training and validation sets demonstrated good clinical benefits

1.4. Conclusion:
Our study aimed to identify the risk factors associated with mortality in patients with SFTS and develop a predictive model to aid clinical decision-making.

2. Keywords:
Fever with thrombocytopenia syndrome; New Bunyavirus; Prognosis

3. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a zoonotic disease characterized by high fever, thrombocytopenia, and gastrointestinal symptoms such as diarrhea and vomiting. SFTS is caused by new bunyavirus infection. The virus is a single-stranded RNA virus that is mainly transmitted through arthropods, with ticks being the main source of transmission [1]. The incidence of SFTS is seasonal, occurring mostly from May to July. The disease has an acute onset and an incubation period of 1-2 weeks. Agricultural workers in hilly forest areas are particularly at risk for contracting the disease due to their proximity to tick habitats. The pathogenic mechanism of newbunyavirus is still not fully understood. However, infected patients often exhibit multiple organ dysfunction. Coagulation dysfunction caused by a severe reduction of platelets is the primary cause of death in many cases [2]. Currently, there are no approved drugs or vaccines specifically designed to prevent or treat SFTS.Some patients experience rapid disease progression and may not respond to available treatments. Failure to identify critically ill patients early leads to severe organ failure and death. The prognosis of SFTS patients can vary depending on a range of clinical and experimental indicators. Previous studies have identified several factors that may be associated with a poor prognosis, including advanced age, central nervous system manifestations, diarrhea, vomiting, low platelet count, high creatinine levels, and high viral load. Therefore, predicting the prognosis of SFTS patients is critical for guiding clinical decision-making and optimizing treatment strategies.In 2017, Van et al. reported that age, APTT, and BUN were independent risk factors for death in SFTS patients[3]. In addition, the study identified other potential prognostic variables by combining previous research, including blood glucose, cystatin C, qSOFA, N/L ratio, and ALT/AST levels. These findings emphasize the importance of

closely monitoring these clinical indicators to improve the prognosis and treatment of SFTS patients [4-8].

A systematic review has reported that the mortality rate of SFTS is between 15.1 % and 50.0 %, and is affected by various factors such as hospitalization delay, high viral load, advanced age and complications [9].Through the use of decision trees, we found that certain laboratory indicators were more effective at indicating the critical condition of patients[10].A nomogram is a reliable tool that integrates potential risk factors to predict clinical events, and is increasingly used in clinical research. Decision curve analysis (DCA) is a model evaluation tool that is also gaining popularity in clinical research, as it can help assess the clinical usefulness of a predictive model and aid in clinical decision-making[11]. Compared with the receiver operating characteristic curve (ROC), it can integrate the preferences of patients or policy makers into the analysis to improve clinical utility[12]. By collecting the basic information of patients and laboratory indicators within 24 hours of admission, we constructed a multiple linear regression model and developed Nomograms. Through ROC, DCA and Calibration, we constructed a model to evaluate the prognosis of patients and facilitated identify critically ill SFTS patients early.

4. Method

4.1. Source

We collected the basic information and in-hospital monitoring data of 171 patients with severefever with thrombocytopenia syndrome caused by newbunyavirus in Yantai from January 1,2021 to June 30,2022 through the electronic case system.

4.2. Inclusion criteria.

1 ≥ 18 years ; 2.According to Wang diagnosed with SFTS patients [10], in line with the following 4 (1) epidemiological characteristics (for example, a history of tick bites, in the mountains or within two weeks before the onset of symptoms directly contact with the patient ‘s blood) ; (2) clinical manifestations (such as fever (> 38℃), headache, muscle soreness, skin bruising, bleeding, multiple organ damage, etc.) ; (3) results of laboratory tests (such as leukopenia and thrombocytopenia) ; detection of new bunyavirus nucleic acid positive or IgM antibody positive ; (4) Patients with hemorrhagic fever with renal syndrome (HFRS), dengue fever and other diseases with fever and hemorrhage similar to SFTS were excluded. 3. Sign informed consent.

4.3. Exclusion criteria.

1. age < 18 years. 2. refuse to sign informed consent.

4.4. Methods.

A total of 171 cases were included. Based on the patients’ prognosis, they were divided into a cured group and a deceased group. The electronic case system collected the basic vital signs and laboratory examination results within 24 hours of admission.The basic vital signs, including body temperature, respiratory rate, level of consciousness, and systolic pressure (SBP), were recorded on the first day of admission. Laboratory tests were conducted, including leukocyte counts(LY), neutrophil counts(Neu), platelet counts(PLT), hemoglobin(HB), total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), troponin I (TnI), troponin T (TnT), troponin C (TnC), creatine kinase isoenzyme (CK-MB), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer,fibrous protein(FIB) creatinine(CRE), sodium (Na), and potassium (K).The blood sample analysis results were obtained through hospital instruments, and the qSOFA score was assessed based on the data. The qSOFA score is based on the criteria of SBP < 100mmHg, changes in consciousness, and respiratory rate > 22 breaths/min, and ranges from 0 to 3 points. We made efforts to optimize the patients’ laboratory test results. For missing data, we performed multiple imputation to fill in a small amount of missing data, and we excluded cases and items with excessive missing data [6]. The data were divided into a training cohort and a test cohort with a ratio of 7:3. The training cohort was used to train the model, and the test cohort was used for subsequent verification.

4.5. Outcome.

The outcome measured the effectiveness of treatment for SFTS patients. Patients who died in the hospital or within 7 days after discharge due to SFTS were recorded in the death group, while the remaining patients were recorded in the rehabilitation group.

5. Ethics

Our study was approved by the Ethics Committee of Yantai Yuhuangding Hospital. Patients provided consent for their information to be used for research, and the research process maintained anonymity throughout.

6. Statistical Analysis

All analyses were conducted using R software (version 4.2.1), and P-values less than 0.05 were considered statistically significant in each statistical analysis. Continuous variables were tested for normality and homogeneity of variance. Data conforming to a normal distribution were expressed as mean and standard deviation (SD), and compared using the t-test. Non-normally distributed data were expressed as median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were analyzed using the chi-square test. We constructed the model using the logistic regression method, improved the model by gradually deleting variables, and evaluated its performance using the AIC. The effectiveness of the nomogram was confirmed using calibration, ROC, and DCA curves. Area under the curve (AUC) and calibration curve were used to evaluate the efficiency of the nomogram. Decision Curve Analysis (DCA) receiver operating curve (ROC)

7. Result

7.1. Baseline demographic and clinical characteristics

Our study included 171 patients diagnosed with SFTS, who were divided

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into a cured group (122 cases) and a dead group (49 cases) based on the final outcome. We collected their basic vital signs on the first day of admission and related laboratory indicators, replacing any results that exceeded the detection machine's range with the maximum value. The results are presented in Table 1. We found significant differences between the two groups in age, respiratory rate, consciousness, qSOFA score, white blood cell count, lymphocyte count, and PT.

Table1: Demographic And Clinical Characteristics Of SFTS Patients

	[ALL]	Death	Alive	p. value
	N=171	N=49	N=122	
Age (year)	66.4 (10.6)	70.4 (8.40)	64.8 (11.0)	<0.001
Sex:				0.612
female	108 (63.2%)	29 (59.2%)	79 (64.8%)	
male	63 (36.8%)	20 (40.8%)	43 (35.2%)	
Respiratory Rate (times/min)	19.0 [18.0;23.0]	20.0 [19.0;25.0]	19.0 [18.0;21.0]	0.001
SBP (mmHg)	117 [106;128]	116 [106;126]	118 [106;129]	0.342
Altered States of Consciousness:				<0.001
No	119 (69.6%)	18 (36.7%)	101 (82.8%)	
Yes	52 (30.4%)	31 (63.3%)	21 (17.2%)	
qSOFA:				<0.001
0	78 (45.6%)	12 (24.5%)	66 (54.1%)	
1	59 (34.5%)	14 (28.6%)	45 (36.9%)	
2	31 (18.1%)	20 (40.8%)	11 (9.02%)	
3	3 (1.75%)	3 (6.12%)	0 (0.00%)	
WBC (10^9/L)	2.63 [1.72;3.75]	3.04 [2.20;6.20]	2.34 [1.48;3.40]	0.001
HB (g/L)	138 [125;153]	138 [123;154]	138 [126;152]	0.86
PLT (10^9/L)	56.0 [41.0;75.5]	65.0 [44.0;82.0]	52.5 [41.0;72.0]	0.122
MPV (fl)	10.5 [9.90;11.4]	10.9 [9.90;11.9]	10.5 [9.90;11.3]	0.306
PLCR (%)	29.3 [25.9;36.2]	33.8 [25.4;40.1]	28.6 [26.2;33.8]	0.044
PDW (%)	16.8 [16.3;17.5]	16.9 [16.1;17.5]	16.8 [16.3;17.5]	0.467
LY (10^9/L)	0.60 [0.37;1.18]	0.50 [0.30;0.84]	0.66 [0.40;1.30]	0.01
NL ratio (%)	2.60 [1.19;7.94]	4.88 [1.38;14.6]	2.19 [0.99;5.76]	0.026
DBIL (umol/L)	3.90 [2.79;5.40]	4.29 [2.68;6.70]	3.85 [2.80;5.16]	0.478
IBIL (umol/L)	6.10 [4.55;7.90]	6.30 [4.40;7.95]	6.08 [4.71;7.89]	0.747
AST (U/L)	119 [76.2;309]	144 [72.7;404]	111 [79.2;274]	0.757
ALT (U/L)	61.6 [35.0;110]	73.7 [33.0;118]	60.3 [39.1;104]	0.944
AST/ALT	2.27 [1.69;3.10]	2.27 [1.68;3.75]	2.27 [1.71;3.01]	0.691
APTT (s)	45.1 [39.3;55.1]	45.1 [39.6;51.7]	45.3 [39.3;55.3]	0.959
FIB (g/L)	2.53 [2.10;3.00]	2.49 [2.10;3.10]	2.54 [2.10;2.99]	0.948
PT (s)	12.5 [11.8;13.3]	12.8 [12.1;13.8]	12.3 [11.8;13.1]	0.008
TT (s)	22.1 [19.5;26.5]	22.6 [20.1;27.9]	21.7 [19.2;25.9]	0.378
PCT (ng/L)	0.21 [0.11;0.64]	0.27 [0.11;0.41]	0.20 [0.11;0.64]	0.99
CRE (umol/L)	73.0 [56.8;95.6]	78.0 [63.0;96.0]	71.6 [55.5;94.5]	0.325
K (umol/L)	3.70 [3.40;4.10]	3.70 [3.50;4.00]	3.70 [3.40;4.13]	0.69
Na (umol/L)	135 (4.79)	136 (4.21)	135 (4.97)	0.091
LDH (U/L)	574 [374;900]	592 [420;900]	572 [368;900]	0.827
TnI (ng/mL)	90.0 [39.5;195]	90.0 [45.0;186]	90.0 [35.8;198]	0.687
CKMB (ng/mL)	10.0 [3.35;21.6]	10.0 [5.00;21.3]	9.50 [2.73;21.8]	0.165

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7.2. Construction and calibration of predictive nomogram in training cohort

The patient information was divided into training cohort and test cohort according to the ratio of 7:3, and the proportion of dead patients and cured patients between the two groups was roughly equal.We constructed a logistic regression model based on the outcome of patients in the training cohort, using variables obtained through backward stepwise screening. During the model construction, we monitored the collinearity among the variables using the variance inflation factor (VIF) and found that all influencing factors had a VIF of less than 5, indicating low collinearity. After multiple screening processes, we included the following variables in the model: age, respiratory rate, systolic blood pressure, consciousness change (defined as blurred consciousness, lethargy, or coma based on admission records), PLT, FIB, and PT. We constructed a nomogram based on the model to predict the likelihood of patient recovery. We verified the performance of the nomogram using calibration curve analysis and found that it accurately predicted patient outcomes in the training cohort (Figure 1-4).

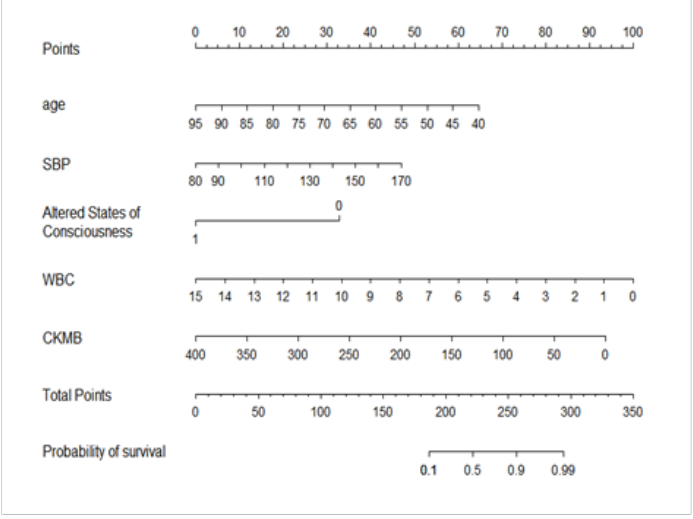

Figure 1: The Nomogram for Nomogram for Prognosis of Patients with Severe Fever with Thrombocytopenia Syndrome. SBP (systolic pressure), PLT (platelet counts), FIB (fibrous protein), PT (prothrombintime).

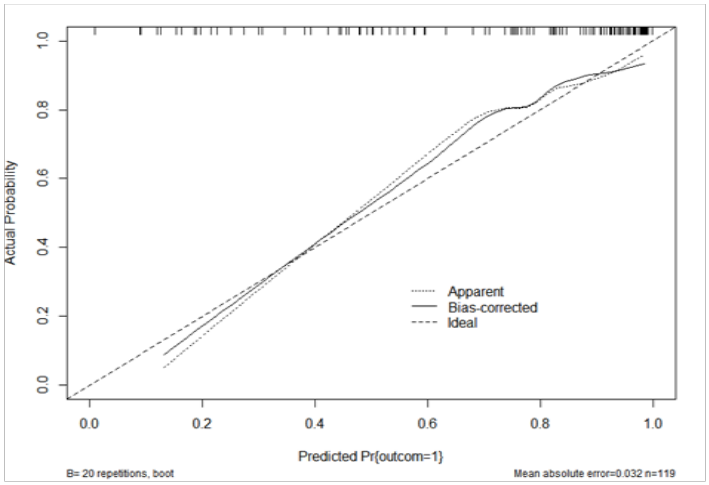

Figure 2: The Calibration curves of the nomogram

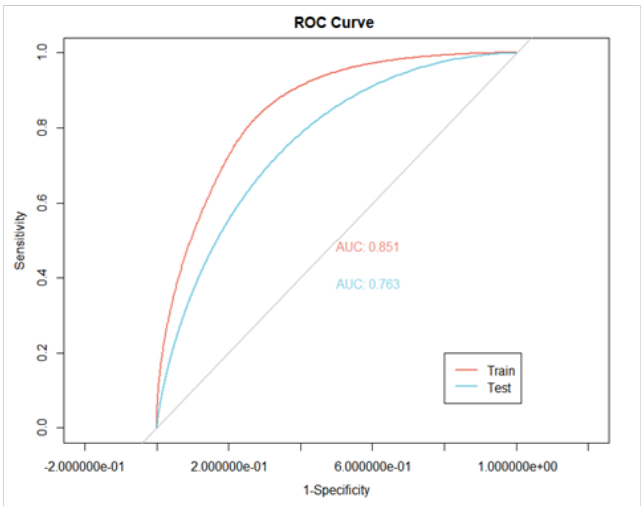

Figure 3: The receiver operating characteristiccurves of the nomogram in training and test group.

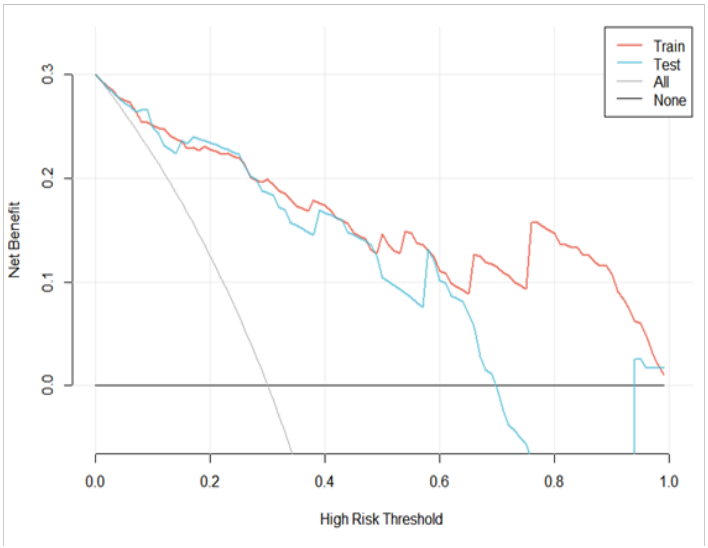

Figure 4: The decision curve analysis of training and test group. (A) training group,(B)validation group.

To evaluate the performance of the nomogram, we constructed receiver operating characteristic (ROC) curves and decision curve analysis (DCA) curves for both the training and test cohorts. In the training cohort, the area under the ROC curve (AUC) of the model was 0.903 (95% confidence interval [CI] = 0.845-0.9612), and in the test cohort, it was 0.8785 (95% CI = 0.7561-1), indicating high sensitivity and specificity. These results demonstrate the clinical value of the model. Furthermore, the DCA curves showed that the model provided high net benefits for clinical decision-making in both the training and test cohorts.

8. Discussion

To better understand the progression of SFTS and identify potential risk

factors for mortality, we conducted a retrospective study of 171 SFTS cases and collected relevant data. Using logistic regression analysis, we identified risk factors associated with patient outcomes and developed a nomogram to predict these outcomes. We constructed additional models using age, respiratory rate, consciousness change, white blood cell count, fibrinogen, and prothrombin time, which can be easily obtained and used to assess patient prognosis. Through calibration, ROC, and DCA analyses, we confirmed the superior predictive ability of the nomogram and its utility in predicting patient outcomes. Many predictors of SFTS prognosis have been identified in current research, and several risk factors have been found to be consistently associated with poor outcomes. Advanced age is a commonly reported risk factor in many studies, as it can weaken the immune system and increase the risk of complications [3,13].Our study also found that advanced age was a risk factor for poor prognosis, with the death group being older than the survival group. Previous research has identified several laboratory markers, including neutrophil and lymphocyte counts, as important predictors of SFTS outcomes [14]. Our study similarly found significant differences in lymphocyte counts between the death and survival groups. As important indicators of immune function in response to viral infections, alterations in lymphocyte counts may reflect the severity of the patient's immune response to SFTS.A decrease in lymphocyte counts is indicative of impaired immune function, which can lead to a poorer prognosis for SFTS patients. Thrombocytopenia and coagulation dysfunction have also been identified in previous research as important factors in SFTS prognosis. While thrombocytopenia is often associated with coagulation dysfunction, we found no significant difference in coagulation function between the death and survival groups, except for PT.While other studies have found that organ dysfunction, such as liver function measured by ALT/AST ratio, is related to the prognosis of patients, our study did not find a significant statistical difference in liver or renal function (measured by creatinine) between the two groups.It is possible that the organ function at the time of admission may not fully reflect the long-term prognosis of patients, as it is only a snapshot of their health at that particular moment. Additionally, factors such as medical interventions and treatments during hospitalization can also influence the overall prognosis of patients.

Table2: Logistic of SFTS Patients

	B	Wald	OR_with_CI	P
	1.302	0.255	3.678(0.022~629.143)	0.613
age	-0.058	4.817	0.943(0.893~0.992)	0.028
SBP	0.047	6.812	1.049(1.015~1.091)	0.009
AlteredStates				
OfConsciousness	-2.335	19.171	0.097(0.032~0.263)	<0.001
WBC	-0.324	9.09	0.723(0.576~0.882)	0.003
CKMB	0.008	0.257	1.008(0.977~1.04)	0.613

Therefore, it is important to consider multiple factors when evaluating the prognosis of patients, rather than relying solely on a single measure of organ function.We innovatively incorporated new predictors, including the qSOFA score and platelet-related parameters such as mean platelet volume (MPV) and platelet distribution width (PDW), in order to improve the model. The SOFA score and APACHE II score are commonly used to evaluate critically ill patients. However, many parameters in the APACHE II score cannot be obtained in the general ward. The qSOFA score, on the other hand, is a simple and rapid tool that can help predict the prognosis of patients [15]. Current studies have shown that platelets have immune functions. Platelet-related parameters, such as platelet distribution width (PDW) and platelet large cell ratio (PLCR), can indicate the prognosis of sepsis patients, and were included in our study. Univariate analysis revealed differences in PLCR between the two groups, with the death group having higher PLCR. This finding may suggest impaired platelet formation, a manifestation of decreased platelet maturity, and indicate attenuation of hematopoietic function in the bone marrow of patients in the death group, which is also related to the prognosis of patients. Our study has several limitations. Firstly, it was a retrospective study that only included cases from a single region, which may have led to a small sample size and biased data. Additionally, due to various limitations, many key indicators were not collected. For instance, viral load was found to be an important risk factor for patients, but it was not quantified in some primary hospitals, leading to deficiencies in our study and the exclusion of these indicators. In summary, this study established a nomogram to predict the prognosis of SFTS patients with relatively high accuracy. The model can help doctors identify critically ill patients early, prevent the rapid development of the disease and reduce the mortality of SFTS patients. However, the accuracy and sensitivity of the model need to be validated with a large number of SFTS patients in multiple medical centers.

9. Author Contributions

Liping Ye and Xiangtian Liu are responsible for data analysis and initial drafting, while Xinghan Tian and Puhui Liu are responsible for preliminary data collection.All authors reviewed the manuscript.

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