BMC Infectious Diseases

RESEARCH

Open Access

Construction and validation of a dynamic nomogram using Lasso-logistic regression for predicting the severity of severe fever with thrombocytopenia syndrome patients at admission

Peng Xia[1,2†], Yu Zhai[3†], Xiaodi Yan[4†], Haopeng Li[5], Hanwen Tong[3], Jun Wang[3], Yun Liu[3*], Weihong Ge[1,6*] and Chenxiao Jiang[1,6*]

Abstract

Background Severe fever with thrombocytopenia syndrome (SFTS) is a highly fatal infectious disease caused by the SFTS virus (SFTSV), posing a significant public health threat. This study aimed to construct a dynamic model for the early identification of SFTS patients at high risk of disease progression.

Methods All eligible patients enrolled between April 2014 and July 2023 were divided into training and validation sets. Thirty-four clinical variables in the training set underwent analysis using least absolute shrinkage and selection operator (LASSO) logistic regression. Selected variables were then input into the multivariate logistic regression model to construct a dynamic nomogram. The model's performance was assessed using the area under the receiver operating characteristic curve (AUC-ROC), concordance index (C-index), calibration curve, and decision curve analysis (DCA) in both training and validation sets. Kaplan-Meier survival analysis was utilized to evaluate prognostic performance.

Results 299 SFTS patients entered the final investigation, with 208 patients in the training set and 90 patients in the validation set. LASSO and the multivariate logistic regression identified six significant prediction factors: age (OR, 1.060; 95% CI, 1.017–1.109; $P=0.007$), CREA (OR, 1.017; 95% CI, 1.003–1.031; $P=0.019$), PT (OR, 1.765; 95% CI, 1.175–2.752; $P=0.008$), D-dimer (OR, 1.039; 95% CI, 1.005–1.078; $P=0.032$), nervous system symptoms (OR, 8.244; 95% CI, 3.035–26.858; $P<0.001$) and hemorrhage symptoms (OR, 3.414; 95% CI, 1.096–10.974; $P=0.035$). The AUC-ROC,

†Peng Xia, Yu Zhai and Xiaodi Yan contributed equally to this work.

*Correspondence:
Yun Liu
ly_nn423@163.com
Weihong Ge
glg6221230@163.com
Chenxiao Jiang
sharejcx@163.com

Full list of author information is available at the end of the article

C-index, calibration plots, and DCA demonstrated the robust performance of the nomogram in predicting severity at admission, and Kaplan-Meier survival analysis indicated its utility in predicting 28-day mortality among SFTS patients. The dynamic nomogram is accessible at https://sfts.shinyapps.io/SFTS_severity_nomogram/.

Conclusion This study provided a practical and readily applicable tool for the early identification of high-risk SFTS patients, enabling the timely initiation of intensified treatments and protocol adjustments to mitigate disease progression.

Keywords Severe fever with thrombocytopenia syndrome, Prediction model, Nomogram, Severe status

Background

Severe fever with thrombocytopenia syndrome (SFTS) is a concerning infectious disease caused by the novel Bunyavirus known as SFTS virus (SFTSV) [1]. It has garnered increasing attention in the realm of public health in Asian countries due to its significant morbidity and mortality rates [2–8]. Clinically, SFTS is characterized by fever and thrombocytopenia, with a subset of patients progressing rapidly to a critically ill state, collectively termed severe SFTS. These severe cases often manifest with multi-organ failure and are susceptible to secondary complications. Notably, the morbidity rate of SFTS patients complicated by multiple organ failure and central nervous system involvement can reach as high as 44.7% [9]. Consequently, the timely identification of patients with a high likelihood of disease progression is crucial for effective treatment and management.

Although various scoring methods exist to predict the prognosis of SFTS [10–12], a standardized scoring system tailored to differentiate critically ill patients within the SFTS population is lacking. Typically, previous studies have employed non-specific scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score [13], Charlson comorbidity index (CCI) score [14], or self-developed score systems [15], to classify patients into mild and severe groups,. However, these existing scoring methods may lack the sensitivity and specificity required to predict severe outcomes in SFTS patients, potentially leading to misclassification and suboptimal treatment strategies. Moreover, their applicability may vary across different patient populations and healthcare settings, highlighting the necessity for a validated scoring system tailored specifically for severe SFTS.

This study aims to develop a prediction model for identifying severe SFTS patients in the early stage of the disease, addressing the limitations of current scoring methods. By elucidating the factors associated with disease severity and employing a dynamic nomogram, this model seeks to furnish clinicians with a more precise and reliable tool for risk stratification and treatment decision-making. The anticipated findings hold significant promise for expediting the early identification of critically ill patients and the timely initiation of enhanced therapeutic interventions.

Method

Study design and participants

This retrospective study aimed to identify predictors for severe status in patients with SFTS. We collected and analyzed demographic features, clinical manifestations, laboratory parameters and clinical outcomes of confirmed SFTS patients admitted to Nanjing Drum Tower Hospital between April 2014 and July 2023. All SFTS patients met the following diagnostic criteria: (1) clinical manifestations with acute fever and thrombocytopenia; (2) positive serum nucleic acid test for SFTSV RNA using real-time polymerase chain reaction (RT-PCR) or PCR. Inclusion criteria comprised hospitalized subjects meeting the diagnostic criteria for SFTS. The excluded criteria included: (1) Patients with admission time ≤ 3 days; (2) Patients lost to follow-up.

This study was approved by the Medical Ethical Committee in Nanjing Drum Tower Hospital (NO.2023-488-02). Given the retrospective nature of the study, written informed consent was waived. All procedures adhered to the Helsinki Declaration and relevant guidelines and regulations.

Data collection and definitions

Data on demographic features, clinical manifestations, laboratory parameters, and clinical outcomes of enrolled SFTS patients were extracted from electronic medical records by physicians using a standardized format. Two well-trained staff members reviewed the data for accuracy and consistency. Laboratory parameters included blood routine tests and biochemical tests for liver, kidney, heart, and coagulation functions conducted at admission. Parameters with missing values exceeding 20%, such as SFTS viral loads, immune index, and other inflammatory biomarkers, were excluded from the analysis. Clinical manifestations encompassed respiratory symptoms, gastrointestinal symptoms, nervous system symptoms, and hemorrhagic symptoms. Respiratory symptoms were defined as cough, expectoration, and dyspnea. Gastrointestinal symptoms were defined as nausea, vomiting, stomachache, and diarrhea. Nervous system symptoms

were defined as headache or dizziness, disturbance of consciousness, and convulsions or tics. Hemorrhagic symptoms were defined as purpura or petechiae, hemoptysis, gingival bleeding, melena, and hematemesis. The primary clinical outcome was defined as death or survival within 28 days from admission. Two specialized doctors from our team conducted the follow-up process through phone calls or outpatient visits to ensure data accuracy and consistency. All follow-up data was precisely recorded in standardized forms and promptly entered into an electronic database for analysis.

Given the absence of clear criteria for defining severe SFTS patients, severe status was determined based on classic clinical manifestations and severe complications according to the consensus [16, 17]. The definition of severe SFTS patients encompasses the presence of any of the following features within 3 days of admission: (1) multiple organ failure, respiratory failure, heart failure, renal failure, disseminated intravascular coagulation (DIC), or viral encephalitis; (2) pronounced neurological symptoms such as coma, delirium, or recurrent convulsions; (3) significant hemorrhage in the brain, digestive tract, lung, or uterus; (4) severe infection including bacteremia or septic shock.

Statistical analysis

Statistical description and methods

All statistical analysis in this study was conducted using R software (version 4.3.2). Categorical variables were presented as frequency and percentages, and differences between groups were compared using the Chi-square test or Fisher's exact test. The independent Student's t-test was utilized for continuous variables with normal distributions, which were presented as mean ± standard deviation, while the Mann-Whitney test was employed for continuous variables with non-normal distributions which were expressed as median and interquartile range (IQR). All statistical tests were two-sided, with significance set at P-values < 0.05.

Variables selection and identification of candidate prediction factors

Initially, missing values for laboratory indicators were imputed using the "mice" package in R. Subsequently, all eligible patients were randomly assigned to the training set and validation set at a 70%/30% ratio. In the training set, the "glmnet" package was used to conduct LASSO regression analysis for screening potential predictors. LASSO regression, a novel method for variable selection, applies penalized regression to exclude the coefficients of less important variables from the model [18–20]. This approach effectively addresses multicollinearity and is particularly useful for handling high-dimensional data and reducing overfitting [21]. Ten-fold cross-validation was utilized for internal validation. Following this, the variables selected by the LASSO regression analysis were input into the multivariate logistic regression model. Significant variables ($P<0.05$) were considered independent predictive factors for establishing the nomogram, incorporating combined scores for predicting the incidence of severe disease in patients with severe fever with thrombocytopenia syndrome.

Construction and validation of Nomogram

The performance of the nomogram was evaluated in both training and validation sets for discrimination and calibration. Firstly, the area under the receiver operating characteristic (ROC) curve was utilized to quantify and evaluate the discrimination of the nomogram, with the curve plotted using the "pROC" package. Secondly, calibration curves were employed to assess the concordance between the nomogram-predicted probability with the actual outcome, with the calibration plotting performed using the "rms" package. The predictive accuracy of the nomogram was quantified by the concordance index (C-index) via the "Hmisc" package. Finally, to estimate the clinical utility of the nomogram by quantifying net benefits at different threshold probabilities. Decision curve analyses (DCA) curves were constructed using the "rmda" package.

Kaplan-Meier survival analysis

The duration from patient admission to death for SFTS cases was analyzed using Kaplan-Meier estimates in the "survival" package. Comparison was made between severe and mild groups to identify the effects of disease severity on 28-day survival time.

Result

Patient characteristics

A total of 332 laboratory-confirmed SFTS cases were enrolled in our study from April 2014 to July 2023. Following the application of the exclusion criteria, 24 patients were excluded, comprising 12 with admission time ≤ 3d, and 12 lost to follow-up. Finally, 298 patients including 74 severe SFTS patients and 224 mild SFTS patients were eligible for the further investigation. Then, 298 SFTS patients were randomly assigned into the training set and the validation set at a ratio of 7:3, with 208 patients in the training set and 90 patients in the validation set (Fig. 1).

Table 1 summarized the baseline characteristics and outcomes of individuals in both the training and validation sets. The overall mortality rate among all patients was 14.8% (44/298). No significant differences were observed between the sets, indicating consistent demographic and clinical characteristics across the datasets. The severe group was compared with the mild group in

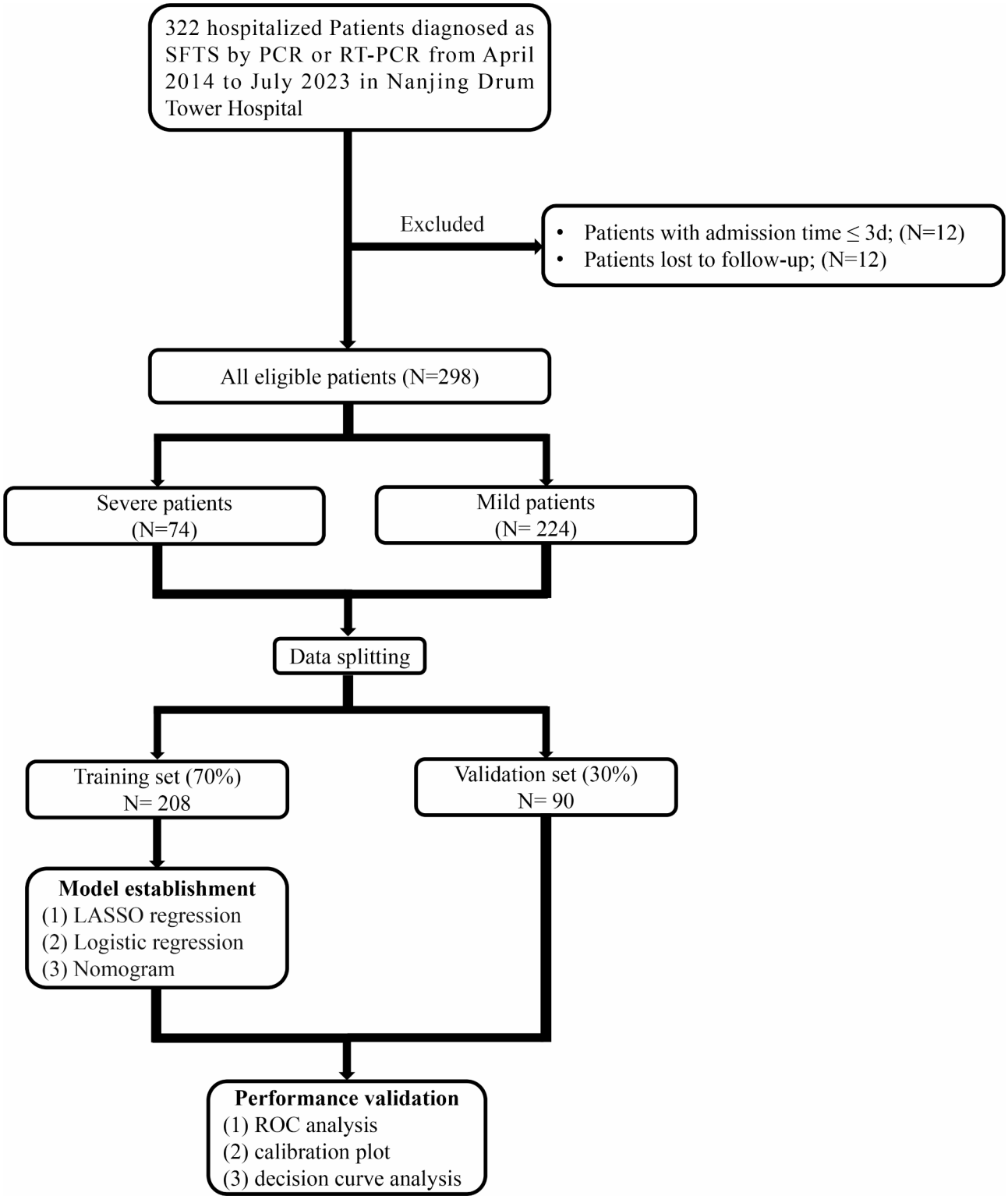

Fig. 1 Flow chart of the study. SFTS, severe fever with thrombocytopenia syndrome; PCR/RT-PCR, real-time polymerase chain reaction; LASSO, least absolute shrinkage and selection operator; ROC, receiver operating characteristic

Table 1 Baseline characteristics and outcomes of the individuals in the training and validation sets

	Total (*N* = 299)	Training set (*N* = 208)	Validation set (*N* = 90)	*P* value
Demographic characteristics				
Sex (Male), n %	143 (48.0)	105 (50.0)	39 (43.3)	0.352
Age, years (median, IQR)	62.00 (52.00, 70.75)	62.00 (52.75, 70.00)	62.00 (52.00, 71.00)	0.865
Interval period, days, median (IQR)				
Onset to admission	6.00 (4.00, 7.00)	6.00 (4.00, 7.00)	6.00 (4.00, 7.00)	0.788
Comorbidities, n (%)				
Cancer	12 (4.0)	6 (2.9)	6 (6.7)	0.195
Hypertension	71 (23.8)	50 (24.0)	21 (23.3)	1.000
Diabetes mellitus	23 (7.7)	14 (6.7)	9 (10.0)	0.463
Hepatitis	23 (7.7)	19 (9.1)	4 (4.4)	0.247
COPD or asthma	7 (2.3)	5 (2.4)	2 (2.2)	1.000
Specific clinical symptoms, n (%)				
Respiratory symptoms	116 (38.9)	86 (41.3)	30 (33.3)	0.241
Gastrointestinal symptoms	285 (95.6)	199 (95.7)	86 (95.6)	1.000
Hemorrhagic symptoms	43 (14.4)	26 (12.5)	17 (18.9)	0.207
Nervous system symptoms	150 (50.3)	104 (50.0)	46 (51.1)	0.960
Laboratory results on admission, (median, IQR)				
WBC (10^9/L)	2.30 (1.60, 3.60)	2.20 (1.60, 3.30)	2.60 (1.63, 3.70)	0.169
NEUT (10^9/L)	1.30 (0.90, 2.20)	1.30 (0.90, 2.00)	1.50 (1.00, 2.40)	0.140
LYM (10^9/L)	0.60 (0.40, 1.00)	0.60 (0.40, 0.90)	0.60 (0.40, 1.00)	0.895
RDW (%)	13.05 (12.50, 13.60)	13.00 (12.47, 13.60)	13.20 (12.70, 13.90)	0.094
PLT (10^9/L)	62.00 (42.00, 80.75)	62.00 (41.75, 82.00)	61.50 (45.00, 77.75)	0.889
PT (s)	11.90 (11.10, 12.70)	11.90 (11.00, 12.60)	12.05 (11.30, 12.70)	0.084
APTT (s)	37.50 (33.40, 43.60)	37.40 (32.90, 43.35)	38.00 (34.80, 44.12)	0.317
TT (s)	22.25 (20.00, 25.90)	22.10 (19.98, 25.63)	22.40 (20.02, 27.15)	0.503
D-dimer (mg/L)	2.60 (1.24, 5.76)	2.52 (1.22, 5.94)	2.67 (1.27, 5.53)	0.727
CRP (mg/L)	4.85 (3.00, 10.95)	4.80 (3.00, 10.40)	5.17 (2.75, 12.50)	0.636
ALT (mmol/L)	64.90 (42.00, 105.30)	64.45 (43.72, 105.10)	65.80 (39.25, 105.53)	0.715
AST (mmol/L)	134.50 (73.00, 260.45)	133.35 (73.12, 275.58)	136.00 (73.00, 235.00)	0.845
LDH (U/L)	784.50 (466.00, 1493.75)	775.00 (463.00, 1417.75)	819.00 (495.25, 2150.00)	0.371
ALB (g/L)	35.70 (32.00, 38.88)	35.50 (32.08, 38.80)	36.55 (31.85, 39.42)	0.675
TBIL (μmol/L)	9.40 (6.70, 13.28)	9.25 (6.40, 13.12)	10.15 (7.40, 13.75)	0.177
CREA (μmol/L)	68.75 (56.02, 85.15)	71.10 (58.38, 85.45)	63.40 (54.95, 82.95)	0.142
BUN (mmol/L)	5.16 (3.88, 7.09)	5.15 (3.87, 7.06)	5.20 (3.92, 7.14)	0.938
UA (mmol/L)	269.50 (205.00, 339.00)	276.00 (215.75, 342.25)	238.50 (188.25, 333.75)	0.059
FBG (mmol/L)	6.40 (5.50, 7.94)	6.30 (5.45, 7.80)	6.55 (5.70, 8.75)	0.144
CK (U/L)	349.50 (127.00, 853.00)	364.00 (140.75, 853.00)	339.00 (110.00, 886.00)	0.373
CKMB (U/L)	17.00 (12.00, 27.00)	18.00 (12.00, 29.25)	17.00 (11.00, 23.75)	0.120
Amylase (U/L)	115.00 (77.25, 191.00)	112.50 (76.00, 185.50)	132.00 (81.25, 208.25)	0.108
Outcome, n (%)				
Lenth of hospitalization	10.00 (7.00, 14.00)	10.00 (7.00, 14.00)	9.00 (6.00, 13.00)	0.218
28-day mortality	44 (14.8)	27 (13.0)	17 (18.9)	0.253

IQR, interquartile range; COPD, chronic obstructive pulmonary diseases; WBC, white blood cell; NEUT, neutrophil count; LYM, lymphocyte count; RDW, red blood cell distribution width; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALB, albumin; TBIL, total bilirubin; CREA, creatinine; BUN, blood urea nitrogen; UA, uric acid; FBG, fasting blood glucose; CK, creatine kinase; CKMB, creatine kinase isoenzymes

terms of clinical characteristics and outcomes (Table 2). The severe groups, comprising 24.04% (50/208) in the training set and 26.67% (24/90) in the validation set, were notably older, with median ages of 70 (62, 74) and 72 (59, 78) respectively (all $P<0.05$). They also exhibited higher frequencies of hemorrhage and nervous system symptoms (all $P<0.001$). Additionally, compared with the mild group, the severe groups showed prolonged prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT), along with elevated levels of D-dimer, lactate dehydrogenase (LDH), albumin (ALB), creatinine (CREA), uric acid (UA), blood urea nitrogen (BUN), creatine kinase (CK), C-reactive protein (CRP) and fasting blood glucose (FBG) (all $P<0.05$). In the training set, the severe group presented with a higher prevalence of hypertension ($P<0.05$), elevated levels of white blood cell (WBC), and red blood cell distribution width (RDW) compared to the mild group (all $P<0.05$). In the validation set, the severe group exhibited higher levels of alanine transaminase (ALT), aspartate aminotransferase (AST), creatine kinase isoenzymes (CKMB), and amylase (all $P<0.05$). Prognostically, the severe group experienced a higher 28-day mortality rate than the mild group (all $P<0.001$).

Nomogram establishment and validation

Utilizing the baseline demographic features, clinical manifestations, and laboratory parameters from the training set, we employed LASSO regression to analyze 34 variables. Subsequently, we selected lambda.1se which was 0.052 as the optimal lambda, leading to the identification of seven potential candidate factors: age, hemorrhage symptoms, nervous system symptoms, PT, D-dimer, CRP, and CREA, after filtering out nonzero coefficient features (Fig. 2). Multivariable logistic regression analysis was then conducted, incorporating these seven nonzero coefficient features (Table 3). The results revealed that older age (OR, 1.060; 95% CI, 1.017–1.109; $P=0.007$), prolonged PT (OR, 1.765; 95% CI, 1.175–2.752; $P=0.008$), elevated levels of CREA (OR, 1.017; 95% CI, 1.003–1.031; $P=0.019$) and D-dimer (OR, 1.039; 95% CI, 1.005–1.078; $P=0.032$), along with the presence of hemorrhage symptoms (OR, 3.414; 95% CI, 1.096–10.974; $P=0.035$) and nervous system symptoms (OR, 8.244; 95% CI, 3.035–26.858; $P<0.001$), were identified as independent risk factors for severe SFTS patients. Subsequently, a predictive model was constructed incorporating these six independent risk factors and visualized through a dynamic nomogram. To illustrate the model's utility, we selected a specific participant to demonstrate the prediction process. For instance, a patient aged 72, with PT of 14.4s, CREA of 66.4μmol/L, D-dimer of 41.52 mg/L, and presenting with nervous system symptoms at admission, would yield a total point score of 343 and an estimated probability of progressing to severe disease of 90.3% (Fig. 3).

The ROC curve analysis was employed to assess the discriminative capacity of the prediction model. The area under the curve (AUC) values of the ROC were 0.9009 (95% CI, 0.8563–0.9455) and 0.9312 (95% CI, 0.8796–0.9827) in the training set and the validation set, respectively (Fig. 4), indicating favorable specificity and sensitivity. The calibration curves demonstrated that the predicted probabilities aligned well with the actual incidence of severe disease, and mean absolute errors were 0.019 and 0.032 in the training and validation set, respectively (Fig. 5). The C-index for severe SFTS prediction for the training set and validation set was 0.901 (95% CI, 0.857–0.945) and 0.931 (95% CI, 0.880–0.982) respectively. The DCA curves illustrated that the threshold probabilities of the prediction model in the training and validation sets were 24.2–88.2% and 27.9–82.6%, indicating that the model had clinical decision-making value evaluated by balancing discrimination and calibration (Fig. 6).

The dynamic nomogram-derived scores were calculated for the training and validation sets, with patients categorized into low-risk and high-risk groups based on the median scores. Kaplan-Meier curves revealed a significantly higher risk of death in patients classified as high risk of severity (Fig. 7). These findings suggested that the nomogram could also exhibit good performance in predicting SFTS prognosis.

Discussion

SFTS, a newly emerged hemorrhagic fever identified in rural China in the 21st century, carries a mortality rate of 5-30% among hospitalized patients [22]. Initially, SFTS patients commonly exhibited symptoms including fever, vomiting, diarrhea, thrombocytopenia, and leukopenia, which can rapidly progress to multi-organ failure or death in severe cases [23, 24]. Furthermore, severe cases of SFTS frequently entail complications such as pulmonary infections, respiratory failure, or shock, substantially contributing to mortality [10, 25]. Patients present with diverse clinical manifestations at admission, posing a challenge for physicians to differentiate mild and severe cases based on clinical symptoms. Consequently, early identification of severe cases according to systematic criteria is of paramount importance. In this study, LASSO and multivariate logistic regression analysis were both employed to identify predictive factors in the training set, followed by the development of a dynamic prediction nomogram. Moreover, this model demonstrated favorable predictive performance, validated by the AUC curve, calibration curve, and DCA curve in both the training and validation sets. The findings revealed that older age, nervous system symptoms, hemorrhage symptoms,

Table 2 Baseline characteristics of SFTS patients in the training and validation sets

	Training set (*N* = 208)			Validation set (*N* = 90)		
	Mild (*N* = 158)	Severe (*N* = 50)	*P* value	Mild (*N* = 66)	Severe (*N* = 24)	*P* value
Demographic characteristics						
Sex (Male), n (%)	76 (48.1)	28 (56.0)	0.417	29 (43.9)	10 (41.7)	1.000
Age, years (median, IQR)	61 (52, 67)	70 (62, 74)	**< 0.001**	59 (50., 70)	72 (59, 78)	**0.003**
Interval period, days, (median IQR)						
Onset to admission	6.00 (4.00, 8.00)	5.00 (4.00, 6.00)	0.252	6.00 (4.25, 7.00)	5.00 (4.00, 8.00)	0.810
Comorbidities, n (%)						
Cancer	5 (3.2)	1 (2.0)	1.000	5 (7.6)	1 (4.2)	1.000
Hypertension	31 (19.6)	19 (38.0)	**0.014**	12 (18.2)	9 (37.5)	0.102
Diabetes mellitus	9 (5.7)	5 (10.0)	0.332	5 (7.6)	4 (16.7)	0.240
Hepatitis	16 (10.1)	3 (6.0)	0.574	2 (3.0)	2 (8.3)	0.288
COPD or asthma	4 (2.5)	1 (2.0)	1.000	1 (1.5)	1 (4.2)	0.464
Specific clinical symptoms, n (%)						
Respiratory symptoms	62 (39.2)	24 (48.0)	0.352	20 (30.3)	10 (41.7)	0.448
Gastrointestinal symptoms	150 (94.9)	49 (98.0)	0.597	63 (95.5)	23 (95.8)	1.000
Hemorrhage symptoms	11 (7.0)	15 (30.0)	**< 0.001**	6 (9.1)	11 (45.8)	**< 0.001**
Nervous system symptoms	59 (37.3)	45 (90.0)	**< 0.001**	23 (34.8)	23 (95.8)	**< 0.001**
Laboratory results on admission, (median, IQR)						
WBC (10^9/L)	11 (7.0)	15 (30.0)	**< 0.001**	2.70 (1.52, 3.80)	2.40 (1.80, 3.52)	0.544
NEUT (10^9/L)	2.25 (1.60, 3.40)	2.00 (1.52, 2.80)	0.340	1.45 (1.00, 2.48)	1.70 (1.37, 2.20)	0.468
LYM (10^9/L)	1.30 (0.83, 2.18)	1.30 (1.00, 1.80)	0.732	0.70 (0.40, 1.00)	0.40 (0.40, 0.65)	0.064
RDW (%)	13.00 (12.40, 13.60)	13.20 (12.80, 13.67)	**0.049**	13.10 (12.62, 13.50)	13.90 (12.70, 14.22)	0.804
PLT (10^9/L)	64.50 (43.25, 82.00)	53.00 (36.00, 75.00)	0.052	66.00 (46.25, 80.50)	53.00 (34.25, 66.50)	0.910
PT (s)	11.50 (10.90, 12.50)	12.40 (11.83, 13.10)	**< 0.001**	11.70 (11.20, 12.50)	12.75 (12.07, 13.93)	**< 0.001**
APTT (s)	36.60 (32.50, 40.95)	43.20 (36.35, 47.50)	**< 0.001**	36.70 (33.92, 41.17)	44.50 (38.88, 55.90)	**0.001**
TT (s)	21.40 (19.80, 24.37)	24.00 (21.22, 31.85)	**0.001**	21.75 (19.65, 24.58)	26.40 (22.15, 53.17)	**0.001**
D-dimer (mg/L)	2.16 (1.00, 4.15)	6.02 (2.06, 19.10)	**< 0.001**	2.48 (1.05, 4.00)	4.42 (2.33, 12.74)	**0.002**
CRP (mg/L)	4.10 (2.92, 8.28)	7.30 (3.50, 31.88)	**0.001**	4.54 (2.60, 8.08)	14.62 (4.47, 47.58)	**< 0.001**
ALT (mmol/L)	64.45 (42.45, 105.30)	68.00 (46.67, 99.38)	0.982	60.80 (37.95, 91.38)	96.00 (55.30, 167.50)	**0.030**
AST (mmol/L)	121.00 (70.30, 232.75)	186.55 (89.50, 310.80)	0.057	98.50 (64.25, 174.50)	362.00 (137.50, 565.00)	**< 0.001**
LDH (U/L)	733.50 (429.25,1261.25)	1018.50 (540.75, 1960.50)	**0.020**	751.5 (405.3, 1325.3)	1644.0 (726.75, 3586.0)	**0.002**
ALB (g/L)	35.95 (32.45, 39.10)	33.15 (30.90, 36.77)	**0.008**	36.95 (33.83, 39.80)	31.55 (28.78, 36.62)	**0.001**
TBIL (μmol/L)	9.10 (6.15, 13.28)	10.10 (6.82, 11.93)	0.821	10.75 (7.60, 13.75)	9.35 (7.05, 13.42)	0.632
CREA (μmol/L)	67.95 (56.25, 80.62)	85.60 (66.47, 110.75)	**< 0.001**	60.25 (54.40, 70.80)	100.55 (66.80, 130.18)	**< 0.001**
BUN (mmol/L)	4.95 (3.81, 6.52)	5.93 (4.03, 8.89)	**0.038**	4.65 (3.73, 6.16)	7.80 (5.55, 11.47)	**< 0.001**
UA (mmol/L)	269.00 (209.25, 329.75)	304.50 (231.75, 436.75)	**0.009**	216.00 (181.25, 299.75)	329.50 (245.25, 459.50)	**< 0.001**
FBG (mmol/L)	6.19 (5.40, 7.40)	7.10 (5.81, 9.13)	**0.003**	6.20 (5.56, 8.29)	7.54 (6.85, 9.90)	**0.004**

Table 2 (continued)

	Training set (*N* = 208)			Validation set (*N* = 90)		
	Mild (*N* = 158)	**Severe (*N* = 50)**	***P* value**	**Mild (*N* = 66)**	**Severe (*N* = 24)**	***P* value**
CK (U/L)	341.00 (108.75, 752.75)	593.00 (259.75, 989.25)	**0.007**	186.50 (81.50, 567.50)	655.50 (370.25, 1128.0)	**< 0.001**
CKMB (U/L)	17.00 (12.25, 27.00)	22.50 (11.00, 31.50)	0.396	15.00 (11.00, 20.75)	23.00 (12.50, 33.75)	**0.010**
Amylase (U/L)	110.00 (76.00, 177.00)	127.00 (79.50, 209.75)	0.165	111.50 (75.75, 173.00)	192.50 (135.00, 317.00)	**0.013**
Outcomes, n (%)						
Length of hospitalization	10.00 (7.00, 13.00)	11.00 (6.00, 15.00)	0.957	11.00 (7.00, 12.75)	6.50 (3.00, 14.75)	0.180
28-day mortality	6 (3.8)	21 (42.0)	**< 0.001**	1 (1.5)	16 (66.7)	**< 0.001**

IQR, interquartile range; COPD, chronic obstructive pulmonary diseases; WBC, white blood cell; NEUT, neutrophil count; LYM, lymphocyte count;; RDW, red blood cell distribution width; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALB, albumin; TBIL, total bilirubin; CREA, creatinine; BUN, blood urea nitrogen; UA, uric acid; FBG, fasting blood glucose; CK, creatine kinase; CKMB, creatine kinase isoenzymes;

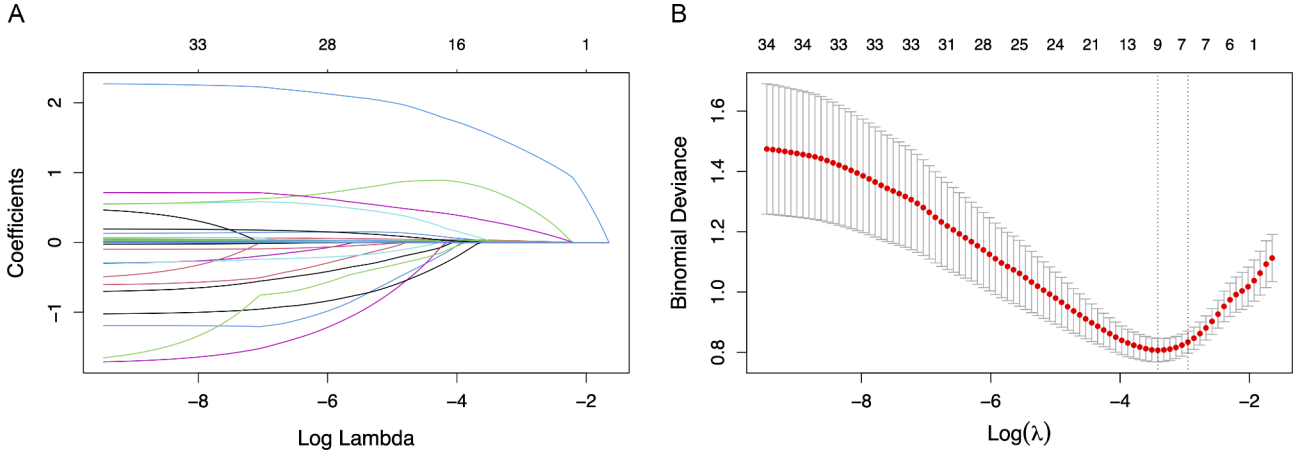

Fig. 2 Potential predictive variables selection by LASSO regression. (**A**) Seven predictors with non-zero coefficients were screened among 34 variables by deriving the optimal lambda. (**B**) Range of lambda and optimal lambda selection in the LASSO model

Table 3 Multivariate logistic regression analysis of factors associated with the severity of SFTS patients in the training set

Variables	Estimate	Z value	*P* value	Odds Ratio (95% CI)
Age	0.059	2.683	0.007	1.060 (1.017–1.109)
Hemorrhage symptoms	1.228	2.104	0.035	3.414 (1.096–10.974)
Nervous system symptoms	2.110	3.859	< 0.001	8.244 (3.035–26.858)
PT	0.568	2.637	0.008	1.765 (1.175–2.752)
D-dimer	0.038	2.143	0.032	1.039 (1.005–1.078)
CRP	0.007	0.779	0.436	-
CREA	0.016	2.349	0.019	1.017 (1.003–1.031)

PT, prothrombin time; CRP, C-reactive protein; CREA, creatinine; CI, confidence interval

prolonged PT, elevated serum CREA, and D-dimer levels could serve as significant predictive factors for stratifying SFTS patients into low- and high-risk categories. The model holds promise in identifying patients with severe illness, and diagnosing those at higher risk of mortality, thus facilitating prompt and efficient treatment interventions.

Prior research has identified advanced age as an independent risk factor for the severity and mortality of SFTS. A retrospective study highlighted individuals over 65 years old as a high-risk group for disease progressing [26]. In our study, the median age of patients with severe SFTS was 70 years, further confirming age as a predictive factor for the severity of SFTS (OR, 1.060; 95% CI, 1.017–1.109; $P=0.007$). Moreover, research by Li et al. [27]and Chen et al. [28] underscored advanced age as one of the independent mortality risk factors among SFTS patients in China from 2011 to 2021. The aging process correlates

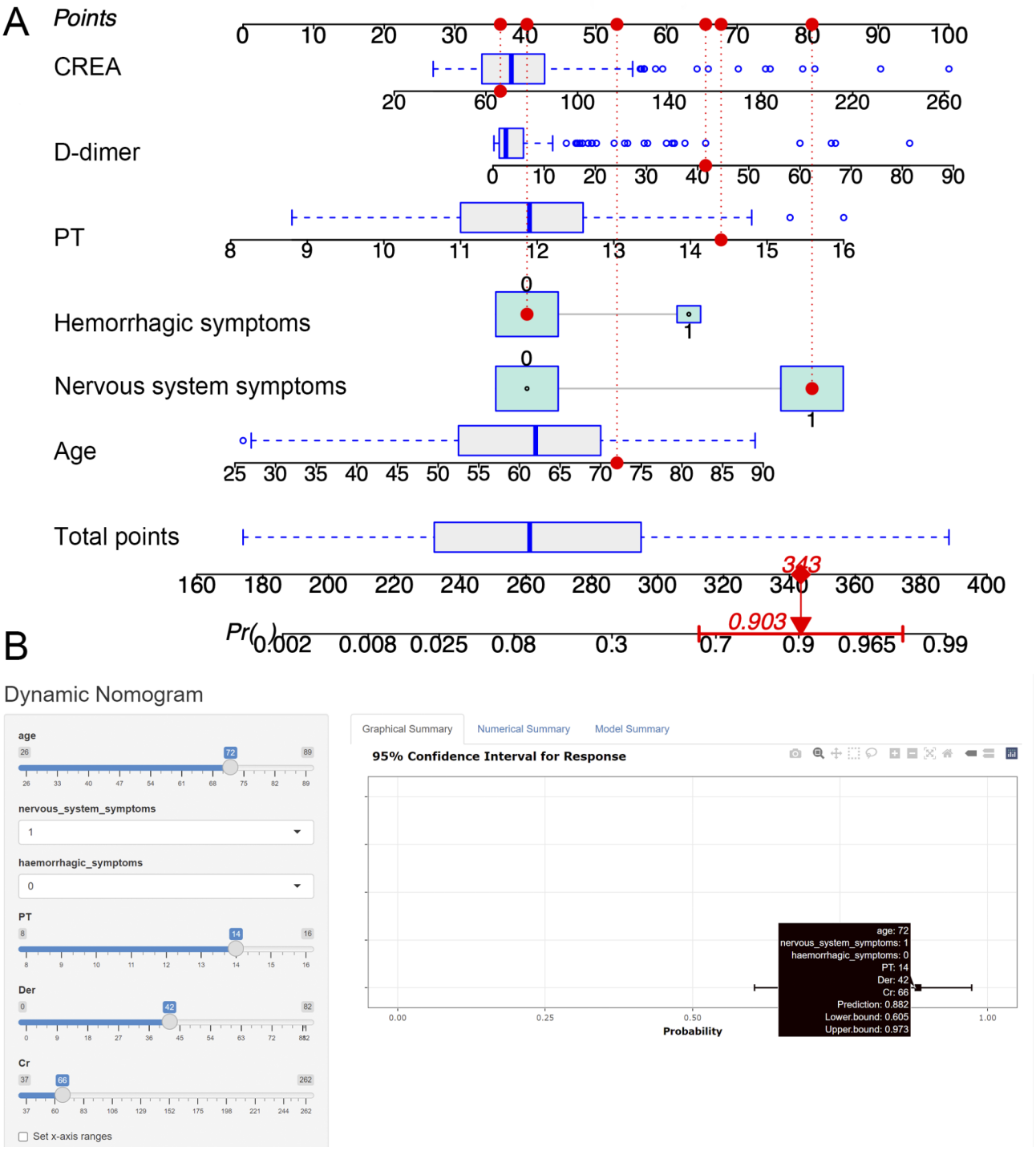

Fig. 3 Dynamic nomogram for predicting of the severity of SFTS patients. (**A**) The dynamic nomogram. Assign points to each predictor by drawing vertical lines to the "Points" axis followed by calculating the total points as their sum. The probability of disease progression can be easily acquired according to the total points. The example in the figure above showed that a patient aged 72, with PT of 14.4s, CREA of 66.4μmol/L, D-dimer of 41.52 mg/L, and presenting with nervous system symptoms at admission, would yield a total point score of 343 and an estimated probability of progressing to severe disease of 90.3%. (**B**) The interactive interface of the online dynamic nomogram (https://sfts.shinyapps.io/SFTS_severity_nomogram/). PT, prothrombin time; CREA, creatinine, SFTS, severe fever with thrombocytopenia syndrome

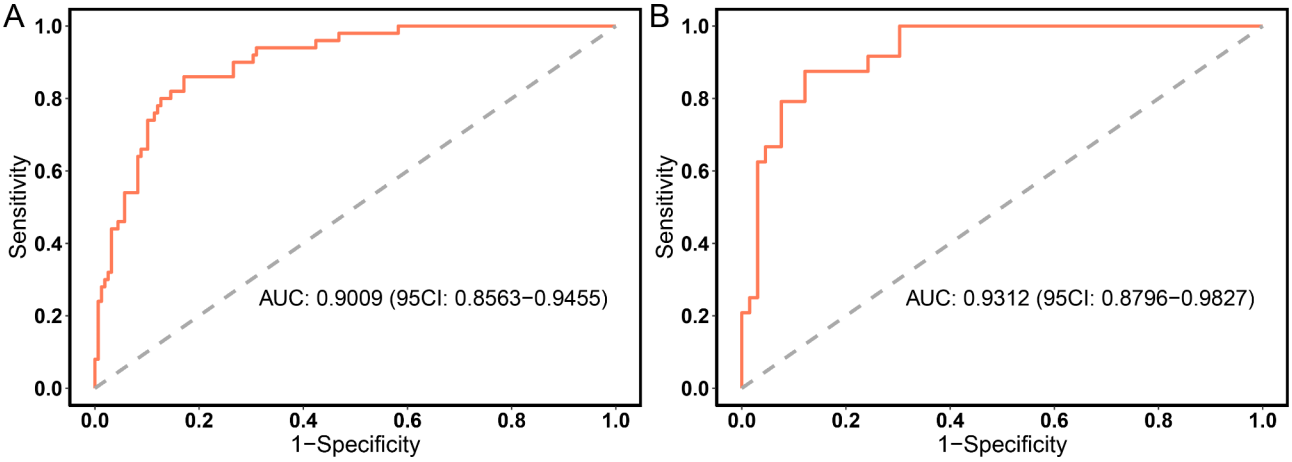

Fig. 4 ROC curve and AUC of the nomogram for predicting the severity of SFTS patients. (**A**) ROC curve of the training set. (**B**) ROC curve of the validation set. ROC, receiver operating characteristic; AUC, area under the ROC curve; SFTS, severe fever with thrombocytopenia syndrome

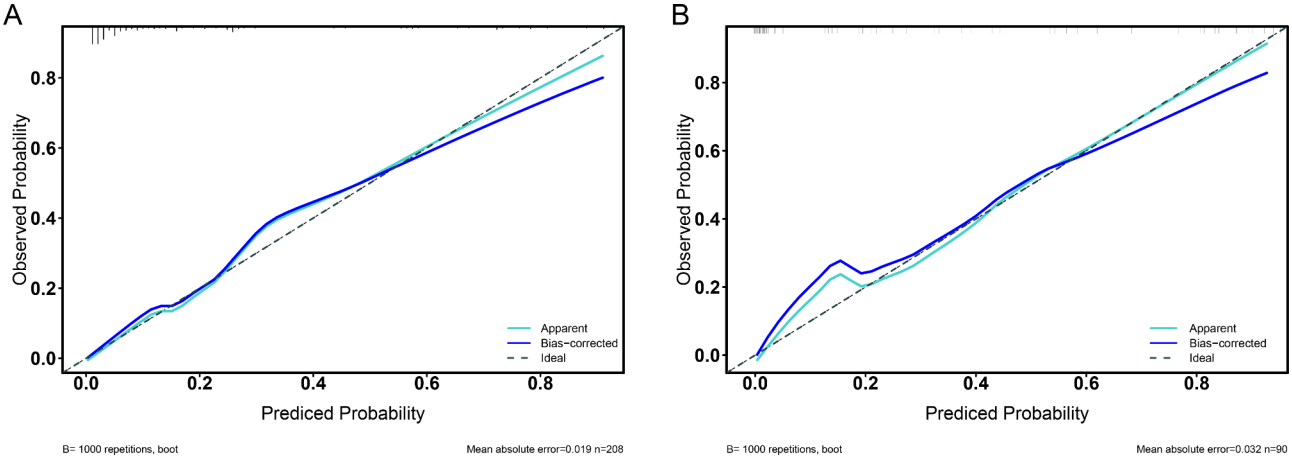

Fig. 5 Calibration plots of the severe SFTS risk nomogram in the training set (**A**) and validation (**B**) set

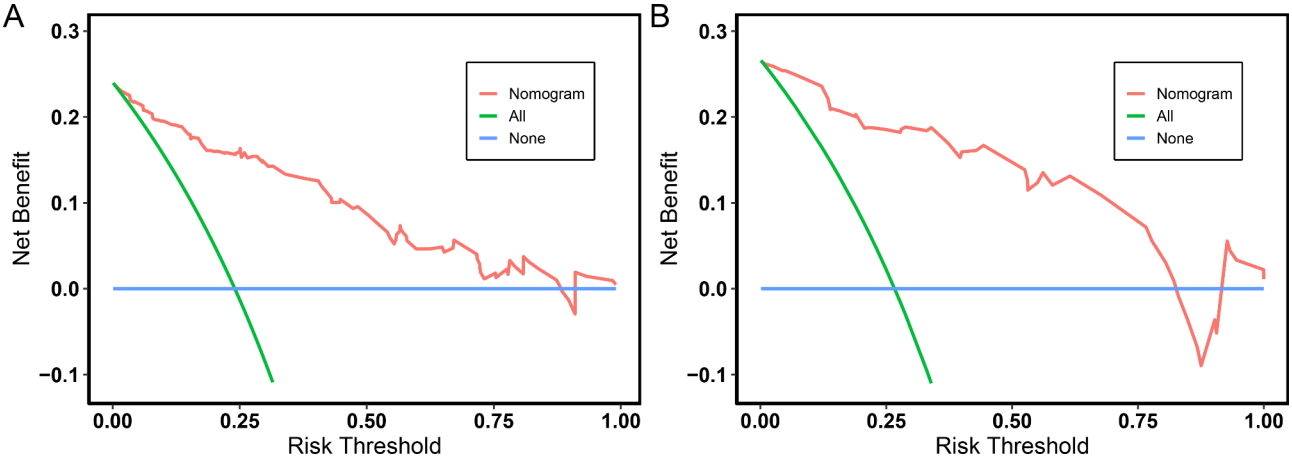

Fig. 6 Decision curve analysis for the severe SFTS risk nomogram from the training set (**A**) and the validation set (**B**)

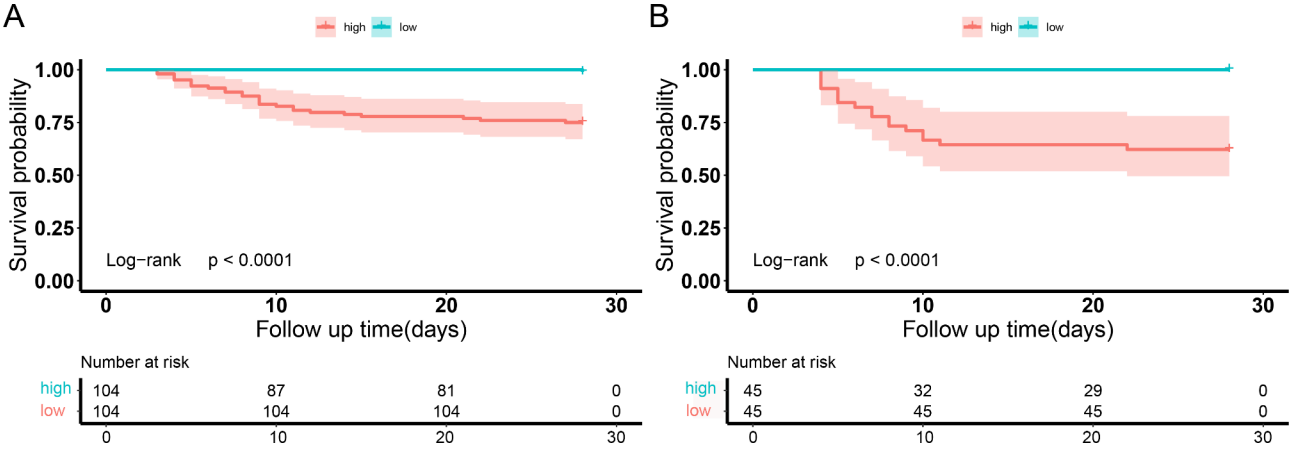

Fig. 7 Kaplan-Meier survival analysis of SFTS patients in the low-risk and high-risk groups from the training set (**A**) and the validation set (**B**)

strongly with heightened susceptibility to SFTSV and compromised immune function [29]. Notably, an animal experiment reported that elderly ferrets, when compared to young ones, exhibited higher virus loads and more severe clinical symptoms post-SFTSV infection. This phenomenon was attributed to heightened inflammatory immune responses. In aged ferrets, upregulation of inflammatory pathways, including dendritic cell maturation, leucocyte extravasation, and IL-6 signaling, led to the recruitment of inflammatory cells to sites of inflammation, exacerbating tissue damage and mortality. The compromised immune function in the elderly may serve as the pathological basis for the robust replication of SFTSV in the body [30]. Given these findings, clinicians should exercise heightened vigilance for disease progression in elderly patients.

Independent studies have indicated a significant association between nervous system symptoms and fatal outcomes [31, 32]. Earlier studies revealed that 19.1% (103/538) of cases were complicated by encephalitis, with a mortality of 44.7% among patients suffering from viral encephalitis [9]. In the study of Liu et al., nervous system symptoms were observed in 27.8% (62/223) of patients, with a mortality rate of 41.9% (26/62) [33]. Animal models have demonstrated that SFTSV can breach the blood-brain barrier (BBB) in newborn mice within 3 h post-infection, showing exponential growth after 24 h [34]. Furthermore, the successful isolation of SFTSV gene fragments from the brain tissue of patients suggested the virus's ability to infect the human nervous system [42], potentially enabling SFTSV to penetrate the BBB in adults and induce encephalitis. Encephalitis, stemming from virus invasion and replication in brain tissue, may underly the association between nervous system symptoms and mortality risk, with elevated cytokine levels in cerebrospinal fluid (CSF) potentially contributing to its encephalitis [35]. Li et al. reported multiple nervous system symptoms were associated with an elevated risk of mortality (OR, 30.26; 95% CI, 21.39–42.81; $p<0.0001$), with the significantly increasing number of symptoms [27]. Within the predictors we screened, nervous system symptoms ranked as the most important indicators of severity among patients (OR, 8.244; 95% CI, 3.035–26.858; $P<0.001$) in our study. Hence, even mild nervous system symptoms such as headache, dizziness, or confusion in the early stage of the disease warrant adequate attention. This underscores the critical importance of evaluating various nervous system symptoms when assessing the severity and prognosis of SFTS.

In our study, hemorrhage symptoms were identified as an independent risk factor for the severity of SFTS at admission. This finding aligns with a large-scale population study, where 35% of SFTS patients presented with bleeding signs, strongly correlated with mortality (OR, 2.79; 95% CI, 2.18–3.57; $P<0.0001$) [27]. Hemorrhage symptoms may signify disease deterioration and multi-organ damage, suggesting a more severe condition in afflicted patients. Furthermore, they can lead to fluid loss and destabilized blood circulation [36], further exacerbating the patient's condition. These findings underscore the significance of hemorrhage symptoms as crucial indicators of disease severity and prognosis in SFTS patients. Consequently, physicians should diligently monitor SFTS patients for hemorrhage symptoms at admission, intervening promptly to enhance patient outcomes.

Studies have highlighted endothelial dysfunction and thrombocytopenia as primary factors contributing to hemorrhage in SFTS patients [37–39]. SFTSV directly damages vascular endothelial cells and induces cytokine storms, leading to vascular endothelial dysfunction, activation of the coagulation system, and increased vascular permeability, potentially resulting in hemorrhagic manifestations [37]. Several studies have identified APTT or PT as independent risk factors for predicting the prognosis of SFTS patients [11, 40, 41]. Elevated D-dimer levels, indicative of fibrin degradation, are commonly

observed during viral infections [42], with significantly higher levels observed in deceased SFTS patients compared to survivors [40]. Our study corroborates these findings, showing elevated TT, APTT, PT, and D-dimer levels in severe cases, with PT and D-dimer identified as independent risk factors for severe disease at admission. Platelets play a critical role in maintaining endothelial integrity, but SFTSV-induced platelet activation promotes their involvement in immune modulation, which increases the depletion of platelets [43, 44]. However, our study found no statistically significant difference in PLT levels between severe and mild groups, possibly due to the inherent variability in platelet counts among SFTS patients and the lack of standardized criteria for assessing disease severity based on platelet counts [39, 45]. Additionally, the direct and indirect depletion of platelets by SFTSV may lead to fluctuations in platelet counts throughout the disease course, further complicating their role as a prognostic marker [46]. Future studies with larger sample sizes and comprehensive clinical data collection are warranted to better understand the dynamics of platelet count changes in SFTS patients and their potential implications.

Patients afflicted with severe SFTS often exhibit multiorgan dysfunction, prominently featuring renal impairment alongside aberrant laboratory parameters. Renal function decline commonly heralds severe disease progression and consistently emerges as a pivotal predictor for anticipating early adverse outcomes in SFTS [10, 47]. However, the precise mechanisms underpinning SFTSV-induced renal function impairment remain incompletely elucidated. Evidence from both clinical observations in patients [48] and animal models [30, 49] suggests potential links between SFTSV replication and renal tissue damage, possibly mediated by direct viral invasion and subsequent immune responses. Notably, a separate clinical investigation showcased markedly elevated CREA levels in acute kidney injury (AKI) patients compared to non-AKI counterparts [112.6 (85.9-177.1) vs. 63.1 (53.4–74.3); $P<0.001$], with AKI patients exhibiting heightened mortality rates [14 (50.0%) vs. 1 (1.4%), $P<0.001$] [50]. Hence, SFTSV infection may induce direct renal injury by targeting and compromising kidney tissue cells, consequently impacting kidney function. Moreover, systemic inflammatory responses and immune-mediated damage triggered by SFTSV infection could contribute to multiorgan dysfunction, including renal function deterioration. Our study's findings corroborate these observations, revealing elevated blood levels of BUN, UA, and CREA in severe patients compared to mild patients in both the training and validation sets, with CREA emerging as a promising predictor for assessing the severity of SFTS patients at admission.

Currently, several prediction models are available for forecasting fatal outcomes of SFTS [51–54], but few specifically address its severity. For instance, a clinical risk score was established to assess critical illness in hospitalized SFTS patients based on a severity nomogram, incorporating age>65 and elevated serum levels of PT, TT, and bicarbonate [26]. However, this model lacked validation, potentially undermining its reliability due to the absence of specific value predictions. Additionally, another model proposed by Wei et al. focused on predicting disease progression among hospitalized SFTS patients using neurological symptoms and AST/ALT levels [55]. Nevertheless, this model, validated solely by AUC with a relatively small sample size of 121, warrants optimization to accurately distinguish severe SFTS from mild cases. In our study, we classified mild and severe SFTS cases based on the occurrence of severe complications within three days of admission. We developed a dynamic scoring system incorporating categorical and continuous variables. Leveraging continuous variables offers several advantages, including richer information, greater flexibility, and enhanced predictive performance [56, 57]. They facilitate more precise capture of relationships between variables and adaptability to diverse numerical ranges, ultimately bolstering prediction accuracy and reliability. SFTS presents a challenge in distinguishing between severe and mild cases based solely on early symptoms. Accurate classification of disease severity is crucial, as severe patients may benefit significantly from interventions such as corticosteroids or intravenous immunoglobulins [33, 58]. Early identification of severe cases allows for timely initiation of appropriate treatments, which can improve patient outcomes and potentially reduce the progression of the disease. Our dynamic scoring system addresses the need by enabling clinicians to rapidly input patients' signs and laboratory results. This facilitates the assessment of disease progression risk and the necessity for early intensive treatment, thereby supporting better clinical decision-making and improving patient treatment management.

Undoubtedly, the study encountered several limitations. Firstly, it was a single-center retrospective study with limited sample size, possibly introducing bias and compromising validity. Secondly, due to the absence of prior treatment data from other medical facilities, this study exclusively focused on the clinical features and laboratory indicators of hospitalized patients. Thirdly, certain potentially crucial parameters, such as SFTS viral loads, immune index, and other inflammatory biomarkers, were omitted due to missing values surpassing 20% of the total.

Conclusion

Our study constructed a nomogram model to assess the severity of SFTS patients based on CREA, PT, and D-dimer levels, along with the presence of nervous system symptoms and hemorrhage symptoms at admission. Notably, the nomogram model exhibited outstanding performance in predicting severe SFTS and 28-day mortality, providing physicians with an intuitive and convenient visualization tool to guide preventive interventions and therapeutic adjustments prior to the progression of patients to severe cases.

Abbreviations

SFTS	Severe fever with thrombocytopenia syndrome
SFTSV	Severe fever with thrombocytopenia syndrome virus
LASSO	Least absolute shrinkage and selection operator
AUC-ROC	Area under the receiver operating characteristic curve
C-index	Concordance index
DCA	Decision curve analysis
APACHE	Acute Physiology and Chronic Health Evaluation
CCI	Charlson comorbidity index
IQR	Interquartile range
RT-PCR	Real-time polymerase chain reaction
DIC	Disseminated intravascular coagulation
PT	Prolonged prothrombin time
APTT	Activated partial thromboplastin time
TT	Thrombin time
LDH	Lactate dehydrogenase
ALB	Albumin
CREA	Creatinine
UA	Uric acid
BUN	Blood urea nitrogen
CK	Creatine kinase
CRP	C-reactive protein
FBG	Fasting blood glucose
WBC	White blood cell
RDW	Red blood cell distribution width
ALT	Alanine transaminase
AST	Aspartate aminotransferase
CKMB	Creatine kinase isoenzymes
OR	Odds Ratio
CI	Confidence interval
CSF	Cerebrospinal fluid
AKI	Acute kidney injury

Acknowledgements
The authors thank all the patients and the participants.

Author contributions
All authors contributed to the intellectual content of this manuscript and approved the final manuscript as submitted. Peng Xia and Chenxiao Jiang conceptualised and designed the study. Peng Xia, Xiaodi Yan and Yu Zhai wrote the main manuscript text. Peng Xia, Yu Zhai and Haopeng Li collected and analysed data. Hanwen Tong and Yun Liu interpreted the data. Weihong Gei and Jun Wang provided administraive support.

Funding
This study was supported by the Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University (2023-LCYJ-PY-24); Project of China Hospital Reform and Development Research and Development Research Institute, Nanjing University [grant number NDYGN2023007]; Aid project of Nanjing Drum Tower Hospital Health, Education & Research Foundation; The funders had no involvement in the preparation or writing up of this research.

Data availability
The original contributions presented in the study are included in the article. Further inquiries for datasets utilized and analysed in the study can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval to report this work was obtained from the Ethics Committee of Nanjing Drum Tower Hospital (Ethics Number: 2023-488-02), and the requirement for written informed consent for this retrospective analysis was waived by our Institutional Review Board.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pharmacy, Nanjing Drum Tower Hospital, School of Pharmacy, Nanjing Medical University, Nanjing, Jiangsu, China
[2]School of Pharmacy, Nanjing Medical University, Nanjing, Jiangsu, China
[3]Department of Emergency Medicine, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China
[4]Department of Pharmacy, the Affiliated Lianyungang Hospital of Xuzhou Medical University, Lianyungang, Jiangsu, China
[5]Department of Emergency Medicine, Nanjing Drum Tower Hospital, School of Clinical Medicine, Xuzhou Medical University, Nanjing, Jiangsu, China
[6]Department of Pharmacy, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Received: 20 April 2024 / Accepted: 3 September 2024
Published online: 18 September 2024

References

1. Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med. 2011;364(16):1523–32.
2. Chen QL, Zhu MT, Chen N, Yang D, Yin WW, Mu D, et al. [Epidemiological characteristics of severe fever with Thtrombocytopenia syndrome in China, 2011–2021]. Zhonghua Liu Xing Bing Xue Za Zhi. 2022;43(6):852–9.
3. Choi SJ, Park SW, Bae IG, Kim SH, Ryu SY, Kim HA, et al. Severe fever with Thrombocytopenia Syndrome in South Korea, 2013–2015. PLoS Negl Trop Dis. 2016;10(12):e0005264.
4. Kato H, Yamagishi T, Shimada T, Matsui T, Shimojima M, Saijo M, et al. Epidemiological and clinical features of severe fever with Thrombocytopenia Syndrome in Japan, 2013–2014. PLoS ONE. 2016;11(10):e0165207.
5. Tran XC, Yun Y, Van An L, Kim SH, Thao NTP, Man PKC, et al. Endemic severe fever with Thrombocytopenia Syndrome, Vietnam. Emerg Infect Dis. 2019;25(5):1029–31.
6. Win AM, Nguyen YTH, Kim Y, Ha NY, Kang JG, Kim H, et al. Genotypic heterogeneity of Orientia tsutsugamushi in Scrub Typhus patients and Thrombocytopenia Syndrome co-infection, Myanmar. Emerg Infect Dis. 2020;26(8):1878–81.
7. Rattanakomol P, Khongwichit S, Linsuwanon P, Lee KH, Vongpunsawad S, Poovorawan Y. Severe fever with Thrombocytopenia Syndrome Virus infection, Thailand, 2019–2020. Emerg Infect Dis. 2022;28(12):2572–4.
8. Zohaib A, Zhang J, Saqib M, Athar MA, Hussain MH, Chen J, et al. Serologic evidence of severe fever with Thrombocytopenia Syndrome Virus and related viruses in Pakistan. Emerg Infect Dis. 2020;26(7):1513–6.
9. Cui N, Liu R, Lu QB, Wang LY, Qin SL, Yang ZD, et al. Severe fever with thrombocytopenia syndrome bunyavirus-related human encephalitis. J Infect. 2015;70(1):52–9.

10. He F, Zheng X, Zhang Z. Clinical features of severe fever with thrombocytopenia syndrome and analysis of risk factors for mortality. BMC Infect Dis. 2021;21(1):1253.
11. Qian F, Zhou W, Liu Y, Ge Z, Lai J, Zhao Z, et al. High C-reactive protein to lymphocyte ratio predicts mortality outcomes of patients with severe fever with thrombocytopenia syndrome: a multicenter study in China. J Med Virol. 2023;95(2):e28546.
12. Wang X, Lin L, Zhao Z, Zhou W, Ge Z, Shen Y, et al. The predictive effect of the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) on the risk of death in patients with severe fever with thrombocytopenia syndrome (SFTS): a multi-center study in China. Ann Transl Med. 2021;9(3):208.
13. Jung SI, Kim YE, Yun NR, Kim CM, Kim DM, Han MA, et al. Effects of steroid therapy in patients with severe fever with Thrombocytopenia syndrome: a multicenter clinical cohort study. PLoS Negl Trop Dis. 2021;15(2):e0009128.
14. Shuto H, Komiya K, Usagawa Y, Yamasue M, Fushimi K, Hiramatsu K, et al. Corticosteroid therapy for patients with severe fever with Thrombocytopenia Syndrome: a Nationwide Propensity score-matched study in Japan. Open Forum Infect Dis. 2023;10(8):ofad418.
15. Wang G, Xu YL, Zhu Y, Yue M, Zhao J, Ge HH, et al. Clinical efficacy of low-dose glucocorticoid therapy for critically ill patients with severe fever with thrombocytopenia syndrome: a retrospective cohort study. Int J Infect Dis. 2023;130:153–60.
16. Cheng G, Shu SN, Ma K, Wang XJ, Wu D, et al. Expert consensus on dignosis and treatment of severe fever with thrombocytopenia syndrom. Infect Dis Info. 2022;35(05):385–93.
17. Chinese Society of Infectious Disease. Consensus of the diagnosis of severev fever with Thromboccytopenia syndrome. Chin J Infect Dis. 2022;40(12):711–21.
18. Tibshirani R. Regression shrinkage and Selection Via the Lasso. J Roy Stat Soc: Ser B (Methodol). 2018;58(1):267–88.
19. Gu Z, Du Y, Wang P, Zheng X, He J, Wang C, et al. Development and validation of a novel nomogram to predict postoperative pancreatic fistula after pancreatoduodenectomy using lasso-logistic regression: an international multi-institutional observational study. Int J Surg. 2023;109(12):4027–40.
20. Tang G, Qi L, Sun Z, Liu J, Lv Z, Chen L, et al. Evaluation and analysis of incidence and risk factors of lower extremity venous thrombosis after urologic surgeries: a prospective two-center cohort study using LASSO-logistic regression. Int J Surg. 2021;89:105948.
21. Bunea F, She Y, Ombao H, Gongvatana A, Devlin K, Cohen R. Penalized least squares regression methods and applications to neuroimaging. NeuroImage. 2011;55(4):1519–27.
22. Miao D, Liu MJ, Wang YX, Ren X, Lu QB, Zhao GP, et al. Epidemiology and Ecology of severe fever with Thrombocytopenia Syndrome in China, 2010–2018. Clin Infect Dis. 2021;73(11):e3851–8.
23. Gai ZT, Zhang Y, Liang MF, Jin C, Zhang S, Zhu CB, et al. Clinical progress and risk factors for death in severe fever with thrombocytopenia syndrome patients. J Infect Dis. 2012;206(7):1095–102.
24. Zhao J, Ge HH, Wang G, Lin L, Yuan Y, Xu YL, et al. Fatal patients with severe fever with thrombocytopenia syndrome in China. Int J Infect Dis. 2022;125:10–6.
25. Zuo Y, Wang H, Huang J, Zhang F, Lv D, Meng T, et al. Pulmonary infection in patients with severe fever with thrombocytopenia syndrome: a multicentre observational study. J Med Virol. 2023;95(4):e28712.
26. Zhang Y, Zhong P, Wang L, Zhang Y, Li N, Li Y, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with SFTS. J Infect Public Health. 2023;16(3):393–8.
27. Li H, Lu QB, Xing B, Zhang SF, Liu K, Du J, et al. Epidemiological and clinical features of laboratory-diagnosed severe fever with thrombocytopenia syndrome in China, 2011-17: a prospective observational study. Lancet Infect Dis. 2018;18(10):1127–37.
28. Chen Q, Yang D, Zhang Y, Zhu M, Chen N, Yushan Z. Transmission and mortality risk assessment of severe fever with thrombocytopenia syndrome in China: results from 11-years' study. Infect Dis Poverty. 2022;11(1):93.
29. Ding S, Niu G, Xu X, Li J, Zhang X, Yin H, et al. Age is a critical risk factor for severe fever with thrombocytopenia syndrome. PLoS ONE. 2014;9(11):e111736.
30. Park SJ, Kim YI, Park A, Kwon HI, Kim EH, Si YJ, et al. Ferret animal model of severe fever with thrombocytopenia syndrome phlebovirus for human lethal infection and pathogenesis. Nat Microbiol. 2019;4(3):438–46.
31. Wang Y, Song Z, Xu X, Wei X, Yuan H, Liang H, et al. Clinical symptoms associated with fatality of severe fever with thrombocytopenia syndrome: a systematic review and meta-analysis. Acta Trop. 2022;232:106481.
32. Shin J, Kwon D, Youn SK, Park JH. Characteristics and Factors Associated with death among patients hospitalized for severe fever with Thrombocytopenia Syndrome, South Korea, 2013. Emerg Infect Dis. 2015;21(10):1704–10.
33. Liu Y, Tong H, He F, Zhai Y, Wu C, Wang J, et al. Effect of intravenous immunoglobulin therapy on the prognosis of patients with severe fever with thrombocytopenia syndrome and neurological complications. Front Immunol. 2023;14:1118039.
34. Chen R, Li Q, Chen H, Yang H, Wei X, Chen M, et al. Severe fever with thrombocytopenia syndrome virus replicates in brain tissues and damages neurons in newborn mice. BMC Microbiol. 2022;22(1):204.
35. Park SY, Kwon JS, Kim JY, Kim SM, Jang YR, Kim MC, et al. Severe fever with thrombocytopenia syndrome-associated encephalopathy/encephalitis. Clin Microbiol Infect. 2018;24(4):432. e1- e4.
36. Fecher A, Stimpson A, Ferrigno L, Pohlman TH. The pathophysiology and management of hemorrhagic shock in the Polytrauma patient. J Clin Med. 2021;10(20).
37. Li XK, Zhang SF, Xu W, Xing B, Lu QB, Zhang PH, et al. Vascular endothelial injury in severe fever with thrombocytopenia syndrome caused by the novel bunyavirus. Virology. 2018;520:11–20.
38. Li XK, Yang ZD, Du J, Xing B, Cui N, Zhang PH, et al. Endothelial activation and dysfunction in severe fever with thrombocytopenia syndrome. PLoS Negl Trop Dis. 2017;11(8):e0005746.
39. Li XK, Dai K, Yang ZD, Yuan C, Cui N, Zhang SF, et al. Correlation between thrombocytopenia and host response in severe fever with thrombocytopenia syndrome. PLoS Negl Trop Dis. 2020;14(10):e0008801.
40. Zhang Y, Miao W, Xu Y, Huang Y. Severe fever with thrombocytopenia syndrome in Hefei: clinical features, risk factors, and Ribavirin therapeutic efficacy. J Med Virol. 2021;93(6):3516–23.
41. Wang F, Wu Y, Jiao J, Wang J, Ge Z. Risk factors and clinical characteristics of severe fever with Thrombocytopenia Syndrome. Int J Gen Med. 2020;13:1661–7.
42. Thachil J, Lippi G, Favaloro EJ. D-Dimer Testing: Laboratory aspects and current issues. Methods Mol Biol. 2017;1646:91–104.
43. Fang L, Yu S, Tian X, Fu W, Su L, Chen Z, et al. Severe fever with thrombocytopenia syndrome virus replicates in platelets and enhances platelet activation. J Thromb Haemost. 2023;21(5):1336–51.
44. Li YH, Wang XH, Huang WW, Tian RR, Pang W, Zheng YT. Severe fever with thrombocytopenia syndrome virus induces platelet activation and apoptosis via a reactive oxygen species-dependent pathway. Redox Biol. 2023;65:102837.
45. Cui N, Bao XL, Yang ZD, Lu QB, Hu CY, Wang LY, et al. Clinical progression and predictors of death in patients with severe fever with thrombocytopenia syndrome in China. J Clin Virol. 2014;59(1):12–7.
46. Xu L, Wang H, Liang BY, Wang T, Zheng X, Peng C. [Clinical features and significance of coagulation dysfunction in severe fever with thrombocytopenia syndrome]. Zhonghua Nei Ke Za Zhi. 2022;61(7):793–6.
47. Yu XJ. Risk factors for death in severe fever with thrombocytopenia syndrome. Lancet Infect Dis. 2018;18(10):1056–7.
48. Hiraki T, Yoshimitsu M, Suzuki T, Goto Y, Higashi M, Yokoyama S, et al. Two autopsy cases of severe fever with thrombocytopenia syndrome (SFTS) in Japan: a pathognomonic histological feature and unique complication of SFTS. Pathol Int. 2014;64(11):569–75.
49. Liu Y, Wu B, Paessler S, Walker DH, Tesh RB, Yu XJ. The pathogenesis of severe fever with thrombocytopenia syndrome virus infection in alpha/beta interferon knockout mice: insights into the pathologic mechanisms of a new viral hemorrhagic fever. J Virol. 2014;88(3):1781–6.
50. Zhang Q, Zhao J, Dai Y, Jiang Z, Chen T, Hu N, et al. A high viral load in urine correlates with acute kidney Injury and poor outcomes in hospitalized patients with severe fever with Thrombocytopenia Syndrome: a noninvasive and convenient prognostic marker. Open Forum Infect Dis. 2023;10(4):ofad085.
51. Xia G, Sun S, Zhou S, Li L, Li X, Zou G, et al. A new model for predicting the outcome and effectiveness of drug therapy in patients with severe fever with thrombocytopenia syndrome: a multicenter Chinese study. PLoS Negl Trop Dis. 2023;17(3):e0011158.
52. Wang L, Zou Z, Hou C, Liu X, Jiang F, Yu H. Score risk model for predicting severe fever with thrombocytopenia syndrome mortality. BMC Infect Dis. 2017;17(1):42.

53. Guo C, Wang H, Wang X, Tian S. High CRP/PNI levels predict an unfavorable prognosis in severe fever with thrombocytopenia syndrome: a propensity score matching study. Immun Inflamm Dis. 2024;12(2):e1184.
54. Li Z, Zhang Z, Chen C. Novel nomograms to predict risk and prognosis in hospitalized patients with severe fever with thrombocytopenia syndrome. Front Med (Lausanne). 2023;10:1321490.
55. Wei X, Tu L, Qiu L, Chen M, Wang Y, Du M, et al. Scoring Model for Predicting the occurrence of severe illness in hospitalized patients with severe fever with Thrombocytopenia Syndrome. Jpn J Infect Dis. 2022;75(4):382–7.
56. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332(7549):1080.
57. Zheng S, Lubin B, Au R, Murabito JM, Benjamin EJ, Shwartz M. Advantages of continuous-valued risk scores for predicting long-term costs: the Framingham coronary heart disease 10-year risk score. Adv Geriatric Med Res. 2019;1(1).
58. Nakamura S, Azuma M, Maruhashi T, Sogabe K, Sumitani R, Uemura M, et al. Steroid pulse therapy in patients with encephalopathy associated with severe fever with thrombocytopenia syndrome. J Infect Chemother. 2018;24(5):389–92.

Publisher's note