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Development and validation of a clinical and laboratory-based nomogram to predict mortality in patients with severe fever with thrombocytopenia syndrome

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Abstract

Background Severe fever with thrombocytopenia syndrome (SFTS) is an emerging global infectious disease with a high mortality rate. Clinicians lack a convenient tool for early identification of critically ill SFTS patients. The aim of this study was to construct a simple and accurate nomogarm to predict the prognosis of SFTS patients.

Methods We retrospectively analyzed the clinical data of 372 SFTS patients collected between May 2015 and June 2023, which were divided 7:3 into a training set and an internal validation set. We used LASSO regression to select predictor variables and multivariable logistic regression to identify independent predictor variables. Prognostic nomograms for SFTS were constructed based on these factors and analysed for concordance index, calibration curves and area under the curve (AUC) to determine the predictive accuracy and consistency of the model.

Results In the training set, LASSO and multivariate logistic regression analyses showed that age, SFTSV RNA, maximum body temperature, pancreatitis, gastrointestinal bleeding, pulmonary fungal infection (PFI), BUN, and PT were independent risk factors for death in SFTS patients. There was a strong correlation between neurological symptoms and mortality ($P < 0.001$, OR = 108.92). Excluding neurological symptoms, nomograms constructed based on the other eight variables had AUCs of 0.937 and 0.943 for the training and validation sets, respectively. Furthermore, we found that age, gastrointestinal bleeding, PFI, bacteraemia, SFTSV RNA, platelets, and PT were the independent risk factors for neurological symptoms, with SFTSV RNA having the highest diagnostic value (AUC = 0.785).

Conclusions The nomogram constructed on the basis of eight common clinical variables can easily and accurately predict the prognosis of SFTS patients. Moreover, the diagnostic value of neurological symptoms far exceeded that

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of other predictors, and SFTSV RNA was the strongest independent risk factor for neurological symptoms, but these need to be further verified by external data.

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

Background

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging global infectious disease caused by the SFTS virus (SFTSV), which was first reported in rural China in 2011. It is characterized by fever, thrombocytopenia, leukopenia, gastrointestinal symptoms and multiple organ dysfunction syndrome (MODS), and the mortality rate has been reported in the literature to range from 5 to 30% [1–3]. The disease is transmitted to humans, mainly rodents and small mammals such as domestic animals, through tick bites or contact with infected animals, and human-to-human transmission has been reported in some clusters and patients [4–7].The clinical course of SFTS varies widely, with some patients recovering from mild symptoms with supportive care, while others rapidly progress to severe disease leading to death [8].Given that SFTS has become endemic in countries such as Japan, Korea, and Southeast Asia, it has become a serious threat to public health. The World Health Organization listed it, along with Ebola, as one of the top 10 serious infectious diseases requiring priority attention in 2017 [9].

Early identification of patients at risk for poor prognosis is essential to improve prognosis and guide treatment strategies. Therefore, there is an urgent need for a mortality risk prediction scoring system that assesses the severity of the disease and predicts the risk of death in order to identify patients who require early intervention. Numerous studies have demonstrated that additional prognostic indicators in patients with SFTS, such as viral load, central nervous system disorders, and coagulation function, can significantly affect the prognosis of patients [10–13]. However, the currently existing prediction models constructed based on the basis of risk factors all have certain limitations, such as only including laboratory indicators, few clinical indicators, low predictive sensitivity, etc., and their clinical utility is not yet significant [14–18].

The aim of this study was to establish a simple, accurate and practical prognostic model based on early clinical manifestations and laboratory examination of SFTS patients.

Materials and methods

Study population

In this study, we retrospectively collected clinical data from patients diagnosed with STFS at the Second Affiliated Hospital of Anhui Medical University from May 2015 to June 2023. We collected clinical data within 24 h of admission, including epidemiologic and demographic details, clinical symptoms, physical examination findings, and laboratory tests.

Inclusion criteria were as follows: STFS was diagnosed based on the criteria of the Guideline for Prevention and Treatment of Severe Fever with Thrombocytopenia Syndrome version 2010 [19], including epidemiologic history, clinical symptom profile and monitoring results of laboratory indices. Suspected cases were those with epidemiologic history (history of working, living or travelling in mountainous areas during the epidemic season, etc. or history of tick bite within two weeks before the onset of illness), body temperature (T) ≥ 38 °C on admission, symptoms such as fatigue and nausea, myalgias, and blood cell counts indicating decreased leukocytes and platelets on admission. Confirmed cases have one of the following conditions on the basis of suspected cases: (1) positive nucleic acid test for SFTSV; (2) positive transfer of IgG antibody to SFTVS or a 4-fold or more increase in titer in the recovery phase compared to the acute phase; (3) detection of IgM antibody specific for fever with thrombocytopenia syndrome in the acute phase. Exclusion criteria: (1) severe clinical data deficiencies; (2) comorbid immunodeficiencies, malignancies, and hematologic disorders; (3) patients with laboratory-confirmed infections with other pathogens, such as hantaviruses, dengue viruses, and rickettsiae.

Data collection

We collected demographic and clinical data from 377 patients diagnosed with SFTS. Demographic data included sex, age, and occupation; clinical data included clinical manifestations and laboratory indices: (1) clinical manifestations: maximum body temperature (T_{max}), fever course, diarrhea, pancreatitis, neurological symptoms, gastrointestinal bleeding, pulmonary fungal infection (PFI), and bacteremia; and (2) Laboratory tests: SFTSV RNA, white blood cell (WBC), neutrophil, lymphocyte, erythrocyte, hemoglobin, platelet, ALT, AST, TBIL, Crea, BUN, LDH, CK, CK-MB, PT, TT, D-Dimer, TT, FIB, K^+, and TCO_2. SFTSV RNA was detected by real-time quantitative reverse transcription-polymerase chain reaction (Applied Biosystems 7500, USA). The limit of detection was 1000 copies/mL, and 1000 copies/mL were recorded when negative. viral loads were recorded as copies/mL, and statistics were converted using log10 transformation. The above indicators were based on the results of blood samples taken within 24 h of admission. For indicators of multiple laboratory tests within 24 h of admission, only the first test results were collected. T_{max} is the highest

body temperature detected during the period from the onset of fever to the time of admission. Fever duration is defined as the number of days in which fever occurs during the period from the onset of fever to admission to hospital. Pancreatitis can be diagnosed when two of the three conditions are met: abdominal pain, amylase/lipase greater than 3 times the upper limit, and abdominal CT indicating pancreatic exudation. Patients with black stool, hematochezia, hematemesis or vomit drinking blood test or stool occult blood test 3+or more, meet one of them is defined as gastrointestinal bleeding; Bacteremia is defined as a definite pathogen in blood culture and clinically excluded as a contaminating strain. Neurological symptoms were defined as the presence of neurological involvement manifestations such as impaired consciousness, epilepsy, and convulsions; PFI was diagnosed according to clinical criteria defined in the guideline [20]. The primary outcome was in-hospital mortality.

Statistical analysis

The final dataset was randomized 7:3 into a training cohort and a validation cohort with clinical outcome as the dependent variable, and variables were compared. Measures for normal and non-normal distributions were expressed as mean±standard deviation or median (interquartile range) using the independent samples t-test and Mann-Whitney U test. The Pearson chi-squared test and the Fish exact test were used to determine the differences between the groups, respectively. Missing values were imputed using the random forest method. Least Absolute Shrinkage and Selection Operator (LASSO) regression was used for analyses in the training cohort, and screened variables were subjected to multivariable logistic analysis to obtain independent risk factors and construct a nomogram to predict outcomes. Concordance index (C-index), calibration curves, receiver operating characteristic (ROC) curves and receiver area under the ROC curve (AUC) were analyzed to determine the predictive accuracy and conformity of the model. Decision curve analysis (DCA) showed the overall utility of the model. All statistical analyses and graphs were performed using R software (version 4.2.2) and Graphpad Pism 9.5. Statistical significance was considered at $P<0.05$.

Results

Patient characteristics

A total of 377 SFTS patients were diagnosed in this study, of which 2 were rickettsiae combined with SFTS infection, another 2 patients had acute leukaemia and 1 patient had lymphoma. Finally, 372 patients were included, of which 344 were positive for viral nucleic acid test and 28 were positive for IgM test but negative for viral nucleic acid test. Males accounted for 44.6% of the patients and 83% were farmers by occupation. 362 patients (97.3%) were treated with ribavirin and only 10 patients (2.7%) did not receive ribavirin. 79 patients died, with an in-hospital mortality rate of 21.2% (Table 1).

Baseline demographic and clinical characteristics of the study population were assessed in the training cohort ($n=260$) and the internal test cohort ($n=112$) (Table S1) to evaluate potential predictors. The two groups differed in gender distribution ($P=0.040$), whereas there were no differences in age, clinical symptoms and comorbidities. Wtih regard to laboratory parameters, except for CK, which was significantly different ($P=0.004$), other laboratory parameters did not differ significantly between the two groups. Overall, these baseline characteristics revealed major differences and similarities between the training cohort and the internal test cohort.

Screening of predictor variables

In the training cohort, candidate predictors were reduced to nine potential predictors by LASSO regression analysis (Fig. 1 and S1), which were age, SFTSV RNA, T_{max}, pancreatitis, neurologic symptoms, gastrointestinal bleeding, PFI, BUN and PT. Multivariate logistic regression for these nine variables showed a strong correlation between neurological symptoms and fatal outcomes ($P<0.001$, OR=108.92) (Table S2). Considering that neurological symptoms affected other variables when included in the multivariate analysis, we performed a multivariate analysis of eight variables except neurological symptoms, and the results showed that these eight variables were independent risk factors for fatal outcomes (Table 2).

The establishment of a nomogram

The predictive outcome nomogram was constructed based on the 8 variables finally selected (Fig. 2). The C-index for the nomogram to predict the risk of death was 0.937(95%CI: 0.908–0.966) in the training set and 0.943(95%CI: 0.903–0.984) in the internal test set, respectively. For each case, a high total score indicates an increased risk of death.

The ROC curve (Fig S2) and calibration curve (Fig S3-S4) showed that the nomogram has excellent prediction accuracy in both the training set and the validation set DCA shows good prediction model net benefit (Fig S5-S6), indicating good consistency and reliability.

Neurologic symptoms

Neurological symptoms were not included in the nomogram because the diagnostic value of neurologic symptoms far exceeded that of the remaining predictors, and the inclusion of multifactorial analysis affected the values of the remaining variables. Of the 372 cases, 41 and 75 patients in the survival and death groups, respectively, had neurological symptoms, ($P<0.001$), and univariate and multivariate analyses of the variables showed that

Table 1 Comparison of clinical features of patients with SFTS in the survival and death subgroups

Characteristics	Total (*n* = 372)	Survival Group (*n* = 293)	Death Group (*n* = 79)	*P* Value
Demographic feature				
Male, n (%)	166 (44.6%)	125 (42.7%)	41 (51.9%)	0.143
Famer, n (%)	309 (83.1%)	247 (84.3%)	62 (78.5%)	0.221
Age, years	67 (58, 73)	65 (56, 71)	73 (67, 78)	< 0.001
Clinical manifestation				
T_{max}, ℃	39.0 (38.4, 39.4)	38.9 (38.3, 39.4)	39.2 (39.0, 39.5)	< 0.001
Fever duration, days	7.0 (5.0, 9.3)	7.0 (5.0, 9.0)	9.0 (7.0, 11.0)	< 0.001
Diarrhea, n (%)	189 (50.8%)	138 (47.1%)	51 (64.6%)	0.006
Pancreatitis, n (%)	219 (58.9%)	147 (50.2%)	72 (91.1%)	< 0.001
Neurologic symptoms, n (%)	116 (31.2%)	41 (14.0%)	75 (94.9%)	< 0.001
Gastrointestinal bleeding, n (%)	94 (25.3%)	44 (15.0%)	50 (63.3%)	< 0.001
PFI, n (%)	106 (28.5%)	53 (18.1%)	53 (67.1%)	< 0.001
Bacteremia, n (%)	29 (7.8%)	17 (5.8%)	12 (15.2%)	0.006
Laboratory tests				
SFTSV RNA (lg, copies/ml)	5 (3, 6)	4 (3, 5)	6. (5, 6)	< 0.001
WBC ($\times 10^9$/L)	2.01 (1.44, 3.31)	2.07 (1.48, 3.56)	1.81 (1.25, 2.95)	0.076
Neut$^{\#}$ ($\times 10^9$/L)	1.21 (0.77, 2.02)	1.21 (0.77, 2.04)	1.25 (0.78, 1.88)	0.939
Lymp$^{\#}$ ($\times 10^9$/L)	0.51 (0.34, 0.85)	0.55 (0.38, 0.89)	0.42 (0.28, 0.59)	< 0.001
RBC ($\times 10^{12}$/L)	4.33 (4.00, 4.71)	4.35 (4.01, 4.72)	4.27 (3.94, 4.55)	0.129
Hb (g/L)	131 (121, 142)	131 (121, 142)	128 (119, 140)	0.373
PLT ($\times 10^9$/L)	50 (33, 70)	53 (36, 72)	40 (29, 55)	< 0.001
ALT (U/L)	73 (121, 142)	66 (38, 113)	99 (56, 173)	< 0.001
AST (U/L)	50 (33, 70)	139 (80, 290)	376 (148, 548)	< 0.001
TBIL (μmol/L)	9.2 (7.2, 11.6)	9.1 (7.1, 11.3)	9.8 (8.0, 12.9)	0.099
Crea (μmol/L)	80 (61, 103)	74 (59, 92)	109 (80, 137)	< 0.001
BUN (mmol/L)	6.4 (4.9, 9.3)	6.1 (4.7, 8.2)	8.9 (6.3, 12.9)	< 0.001
LDH (U/L)	555 (356, 923)	507 (336, 817)	836 (535, 1,349)	< 0.001
CK (U/L)	387 (167, 860)	361 (150, 757)	568 (267, 1,603)	< 0.001
CKMB (U/L)	30 (20, 48)	28 (19, 43)	39 (27, 65)	< 0.001
PT (s)	11.5 (10.8, 12.7)	11.4 (10.6, 12.5)	12.3 (11.3, 13.3)	< 0.001
D-D dimer (μg/ml)	3.1 (1.6, 6.7)	2.5 (1.3, 5.6)	7.0 (3.8, 10.8)	< 0.001
TT (s)	23.0 (20.0, 31.0)	23.0 (20.0, 28.0)	29.0 (23.0, 45.0)	< 0.001
FIB (g/L)	2.30 (1.97, 2.61)	2.36 (2.01, 2.67)	2.12 (1.81, 2.47)	< 0.002
K^+ (mmol/L)	3.79 (3.48, 4.18)	3.72 (3.46, 4.12)	3.95 (3.63, 4.35)	0.017
T-CO_2 (mmol/L)	23.2 (20.9, 25.6)	23.6 (21.3, 26.2)	22.1 (19.5, 24.2)	< 0.001

PFI: Pulmonary fungal infection; T_{max}: Maximum body temperature; Neut$^{\#}$: Neutrophil count; Lymp$^{\#}$: Lymphocyte count; T-CO_2: Total carbon dioxide concentration

the OR for neurological symptoms was 131.35 (Table S3-S4), and the AUC for predicting the outcome of death in patients with SFTS was 0.905 (Fig S7), with a sensitivity of 0.949, specificity of 0.860, and diagnostic index of 0.809, which far exceeded the remaining variables (Table S5).

The differences between the groups were analyzed with neurological symptoms as the dependent variable and the other variables as independent variables, and the results of univariate and multivariate logistic regression showed that age, gastrointestinal bleeding, fungal lung infection, sepsis, SFTSV RNA, platelet, and PT were the independent risk factors for it (Table S6 and Table 3). According to the ROC curve analysis, SFTSV RNA had the highest diagnostic value for patients with neurological symptoms, with AUC = 0.785(Fig S8), sensitivity of 828, and specificity of 0.609 (Table S7).

Disscusion

In this study, we constructed a simple and accurate model to predict the prognosis of SFTS patients based on their clinical characteristics and laboratory tests, and confirmed its efficacy through internal validation. In addition, neurological symptoms were found to have a diagnostic value far exceeding other predictors, and further analysis revealed that SFTSV RNA was the strongest independent risk factor for neurological symptoms in SFTS patients.

SFTSV has become a global epidemic, with a high mortality rate in critically ill SFTS patients and no specific treatment or vaccine available. Clinical prediction models

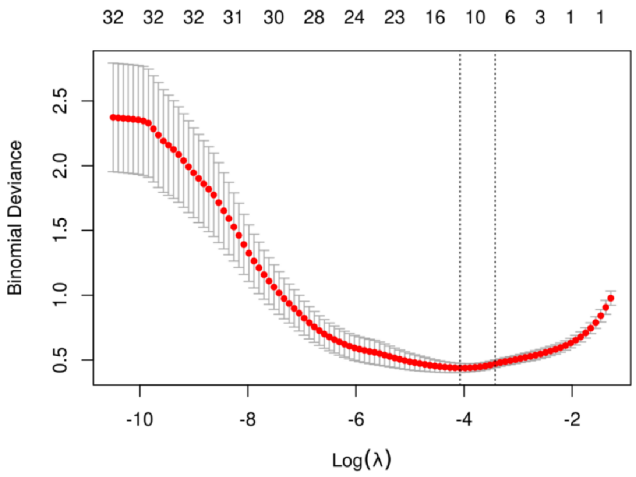

Fig. 1 Demographic and clinical feature selection using the LASSO binary logistic regression model

Table 2 Results of multivariate logistic regression of training cohort excluding neurologic symptoms

Characteristic	β	OR (95%CI)	*P*-Value
Age, years	0.122	1.13 (1.06, 1.20)	< 0.001
T_{max}, °	1.115	3.05 (1.29, 7.21)	0.011
Pancreatitis	1.206	3.34 (1.04, 10.72)	0.043
Gastrointestinal bleeding	1.447	4.25 (1.65, 10.93)	0.003
PFI	1.428	4.17 (1.66, 10.44)	0.002
SFTSV RNA (lg, copies/ml)	0.476	1.61 (1.09, 2.38)	0.016
BUN (mmol/L)	0.095	1.10 (1.01, 1.20)	0.022
PT (s)	0.495	1.64 (1.14, 2.35)	0.008

PFI: pulmonary fungal infection; T_{max}: maximum body temperature

reported in previous studies have few clinical variables and low predictive accuracy, therefore, clinicians urgently need a simple and accurate prediction model. By LASSO regression analysis, we identified nine potential predictors strongly correlated with the prognosis of SFTS, among which neurological symptoms showed a particularly strong association with fatal outcomes. After excluding neurological symptoms, our nomogram based on eight other predictors accurately predicted the prognosis of patients with SFTS. As in previous studies, we found that mortality in SFTS patients was independently associated with advanced age, and the older the age, the higher the mortality rate, which might be related to the poor organ reserve function and higher complication rate in advanced age patients [15]. During the inflammatory phase of infection, body temperature (especially hyperthermia) is important in regulating the immune function of the body [21], and it has been reported that all patients with COVID-19 died shortly after the onset of hyperthermia (T_{max} > 41.5 °C) [22], but the pathophysiological mechanisms of hyperthermia are still unclear. And in this study we also found that the presence of hyperthermia in SFTS patients often indicates a poor prognosis. Therefore, further studies are needed to investigate the pathogenic mechanism of hyperthermia in SFTS.

Li et al. reported that decreased percentages and numbers of CD4 T cells (including Th1, Th2) and regulatory T cells (Treg) were associated with increased disease severity in SFTS. In addition, increased percentages of Th2, Th17, and Treg, as well as skewed Th17/Treg and Th2/Th1 ratios among the remaining CD4 T cells, may contribute to poor junction in SFTS patients [23]. In addition, lymphocyte damage or depletion was more severe in deceased patients, suggesting that acquired immune injury is more severe in deceased patients [15]. This may also explain that SFTS patients are prone to co-infection with pulmonary fungal infections and the pathogen is mainly Aspergillus fumigatus, and once co-infected with pulmonary fungal infections the mortality rate of SFTS patients is significantly higher than that of non-co-infected SFTS patients [24].

Pancreatic injury is another important factor leading to exacerbation and mortality in SFTS patients. Acute pancreatitis is more common in patients with severe SFTS. In most SFTS patients, pancreatic injury is mild and can be reversed by conservative treatment [25]; however, severe pancreatic injury may be secondary to gastrointestinal haemorrhage, which in turn causes a series of pathophysiological alterations, such as increased catabolism, insufficient circulating volume, and impaired renal function, which can directly and indirectly lead to elevated BUN [11, 26]. These may explain the fact that GI bleeding with elevated BUN is an independent risk factor for mortality [25, 26]. It is worth mentioning that thrombocytopenia may be caused by SFTSV adherence to platelets, which subsequently triggers macrophage phagocytosis in the spleen.PT and APTT have also both been shown to be high risk factors in patients with SFTS [16]. These are all associated with secondary bleeding in SFTS patients, further exacerbating their condition and leading to death.

In addition, we found significant differences between the death group and the survival group in patients with neurological involvement manifestations, such as disturbance of consciousness, epilepsy, and convulsions.The central nervous system damage in SFTS patients mainly manifests as encephalopathy in the early stage, such as lethargy, anxiety, or convulsions, convulsions and seizures may occur in the later stage [13]. Numerous studies have confirmed that high serum SFTSV RNA levels are an independent risk factor for the development of central nervous system (CNS) complications, and serum SFTSV RNA has a good predictive value for CNS complications in patients with SFTS [10, 25, 26], which is also consistent with our findings. The pathogenesis and risk factors of SFTSV-induced CNS complications are not known. One study found that SFTSV was frequently detected in the cerebrospinal fluid of SFTS patients and was

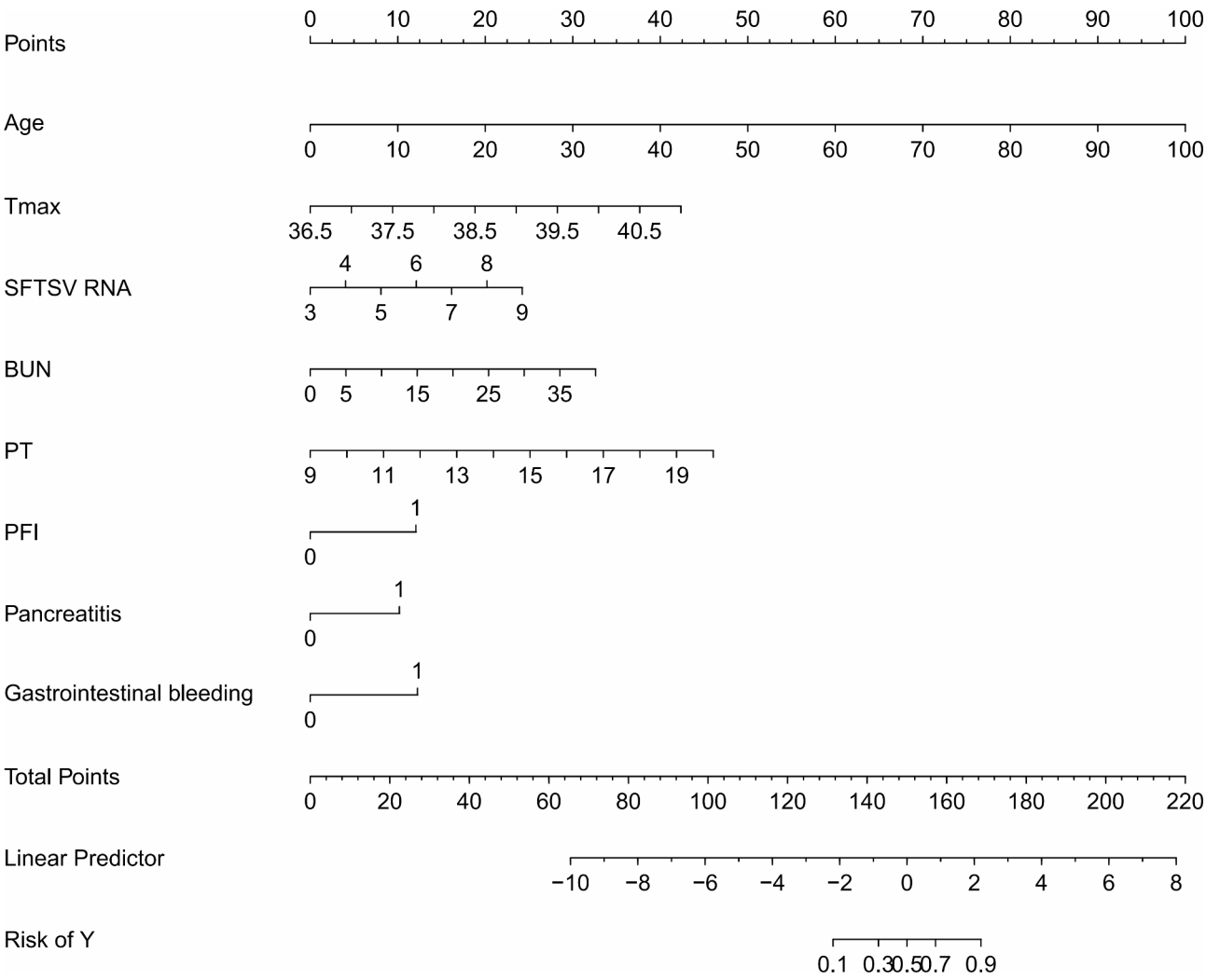

Fig. 2 Nomogram for predicting risk of death infection with SFTS. PFI: Pulmonary fungal infection; T_{max}: Maximum body temperature

Table 3 Results of multivariate logistic regression of neurologic symptoms groups

Variable	B value	SE	Wald	OR Value (95% CI)	*P* Value
Age, years	0.087	0.020	19.084	1.09 (1.05, 1.14)	< 0.001
Gastrointestinal bleeding	0.933	0.371	6.324	2.54 (1.23, 5.26)	0.012
PFI	1.155	0.367	9.901	3.17 (1.55, 6.51)	0.002
Bacteremia	1.501	0.657	5.219	4.49 (1.24, 16.27)	0.022
SFTSV RNA (lg, copies/ml)	0.399	0.151	6.976	1.49 (1.11, 2.00)	0.008
PLT ($\times 10^9$/L)	-0.021	0.009	6.255	0.98 (0.96, 1.00)	0.012
PT (s)	0.283	0.133	4.521	1.33 (1.02, 1.72)	0.033

PFI: Pulmonary fungal infection

accompanied by elevated monocyte chemotactic protein 1 (MCP-1) and IL-8. These results suggest that SFTSV directly invades the central nervous system through elevated cytokine levels, which may play an important role in the pathogenesis of SFTS-associated encephalopathy/encephalitis (SFTS-AE) [27]. And in this study, we found that age, gastrointestinal bleeding, pulmonary fungal infection, bacteremia, SFTSV RNA, platelet, and PT were independent risk factors for the development of CNS symptoms in patients with SFTS, with SFTSV RNA having the highest diagnostic value.

Our study has several limitations. First, this study is a single-center retrospective study, and although we validated the nomogram internally, further validation using external data is required. In addition, there may be potential unmeasured confounders not included in our model due to the local data structure. External validation in different populations is essential to confirm the generalizability of our study. Future studies should aim to externally validate our column line plots in different populations and settings. In addition, the integration of new predictors or biomarkers may improve the predictive accuracy of column line plots and warrants further investigation.

In conclusion, SFTS has a rapid progression and high mortality rate, with the main clinical manifestations of acute fever, thrombocytopenia, and often accompanied by multi-organ damage to the central nervous system, myocardium, liver, and coagulation function. Our model based on eight common clinical variables, including patient age, Tmax, BUN, PLT and SFTSV RNA, can easily and accurately predict the prognosis of SFTS patients. In addition, neurological symptoms have a diagnostic value that far exceeds that of other predictors.These facilitate clinicians' early identification of critically ill SFTS patients and timely initiation of personalised treatment, which still requires further external data validation.

Abbreviations

SFTS	Severe fever with thrombocytopenia syndrome
MODS	Multiple organ dysfunction syndrome
WBC	White blood cell
AUC	Area under the curve
ROC	Receiver Operating Characteristic
C-index	Concordance index
DCA	Decision curve analysis
LASSO	Least Absolute Shrinkage and Selection Operator
CNS	Central nervous system
SFTS-AE	SFTS-associated encephalopathy/encephalitis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10106-8.

Supplementary Material 1

Supplementary Material 2

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Author contributions

X-WY, Z-LL, and YM designed the study; Z-LL, H-JJ, D-WG, and J-MK collected data and statistical analysis; X-WY and H-TF conducted data quality management and drafted the manuscript; CC and ZY participated in the literature search; ZJ, YM, and H-TF critically revised the manuscript; All authors reviewed the manuscript.

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Data availability

The dataset used in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Second Affiliated Hospital of Anhui Medical University approved the study and agreed to waive informed consent statement given the retrospective nature of the study (No. YX2022-041).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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