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A Scoring Model for Predicting the Occurrence of Severe Illness in Hospitalized Patients with SFTS

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Keywords: Severe fever with thrombocytopenia syndrome; Risk model; Prediction; severe illness

Abstract

Severe fever with thrombocytopenia syndrome is an emerging hemorrhagic fever disease with high mortality. Severe cases progressed rapidly, with deaths occurring within two weeks. Therefore, the construction of a model to predict the disease progression among hospitalized SFTS infected patients plays an important role in clinical practice. The development cohort including 121 SFTS patients, 25 were severe and 96 were mild. 2 of the 64 variables were independent risk factors, including neurological symptoms (OR, 12.915; 95% *CI*, 3.342-49.916; $P<0.001$) and AST/ALT levels (OR, 1.891; 95% *CI*, 1.272-2.813; $P=0.002$). The AUC of the model was 0.882 (95%*CI*: 0.808-0.956). The mean AUC value obtained from internal validation was 0.883 (95%*CI*: 0.809-0.957). The AUC in the external validation cohort was 0.873 (95%*CI*: 0.775-0.972). This model can be used for helping identifying severe patients as early as possible with high predictive value, stability, and repeatability. This model can help clinicians in their treatment plan making.

INTRODUCTION

Severe fever with thrombocytopenia syndrome is an emerging hemorrhagic fever disease caused by SFTS virus (SFTSV), a tick-borne bunyavirus that was first discovered in 2009(1). As of 2018, SFTS cases

have appeared in 25 provinces in China, as well as countries such as South Korea and Japan(2-5). SFTS has become an endemic in East Asia. There are thousands of cases in China each year(6). SFTSV is mainly transmitted through tick bites(7). Some cases showed that SFTSV could be transmitted through contact with infected body fluids, such as blood and bloody droplet(8). In addition, pets suffering from SFTS can also directly transmit SFTSV to humans(9). These findings indicate that SFTS has become a serious public health problem.

Most SFTS patients initially present with nonspecific clinical symptoms like fever, fatigue, decreased platelet and white blood cell counts, and gastrointestinal symptoms, etc.(1) In the severe cases, the disease progresses rapidly, with bleeding, respiratory failure, etc.(10, 11). The death cases occurred less than two weeks of onset(12). The case fatality rate of SFTS in China is about 16%(13). The case fatality rate is higher in South Korea and Japan, respectively 22%, 27%(12, 14). Additionally, there are no effective antiviral drugs and vaccines. Intensive surveillance and conservative treatment are still the main prevention and treatment measures for SFTS. Early identification of severe patients is conducive to reducing the economic burden and mortality of patients. However, less progress has been made in predicting the risk of serious diseases in patients with SFTS. Therefore, we aimed to construct an easy-to-use risk prediction score by analyzing patients' clinical data to help

identifying severe patients as early as possible.

MATERIALS AND METHODS

Patients: For the development cohort, we recruited cases of suspected SFTS in Shandong Provincial Public Health Clinical Center from June to December 2020. Suspected SFTS patients were defined as having acute fever with reduced white blood cell and/or platelet counts. Laboratory confirmed case met one or two of the following criteria: (1) a positive result for SFTSV RNA by Nest PCR assay. (2) a positive result for anti-SFTSV total antibodies by ELISA kit. Patients were divided into severe and mild groups according to whether they had been in the intensive care unit (ICU) and met one of the following criteria: (1) Acute lung injury or acute respiratory distress syndrome. (2) Heart failure. (3) Acute renal failure. (4) Encephalitis. (5) Shock. (6) Sepsis. (7) Diffuse intravascular coagulation(15). For external validation cohort, we used clinical data on SFTS patients in Shandong Provincial Public Health Clinical Center from June to December 2019.

Data collection: A total of 64 indicators including the demographic characteristics, date of illness onset, duration of hospitalization, clinical manifestations, and laboratory test results were retrospectively collected. Most of the data on Demographics and clinical characteristics were obtained from a standardised questionnaire inquired by a health-care

clinician on the first day of admission. The deadline time for data collection of the patient's neurological symptoms was within 3 days of the patient's admission. The data collected in this study on laboratory characteristics were obtained from the first test after the patient was admitted to the hospital.

Statistical analysis: All 121 patients hospitalized with SFTS were included for variable selection and identify variables related to severe illness of SFTS cases. A total of 64 variables were participated in the selection process. Least Absolute Shrinkage and Selection Operator (LASSO) regression was applied to screen variables to prevent overfitting of variables. We carried out a five-fold cross-validation to compute the weight of LASSO penalty (expressed as λ). LASSO regression compresses the variable coefficients by generating a penalty function, and the penalty intensity is controlled by the λ value. The greater the punishment, the closer the variable coefficients of the factors with weak predictive power are to zero, and finally only the factors with strong remain. λ is set to 0.1870 for subsequent variable screening. Variables screened by LASSO regression were included in binary logistic regression analysis. Statistically significant variables were used to construct the model. Internal validation was completed using 200 bootstrap resamples to correct the overestimation. To verify the generality of the model, we used data from Shandong Provincial Public Health

Clinical Center in 2019, including 51 SFTS patients. The predictive value of the model was assessed through the receiver operating characteristic (ROC) curve. All statistical analyses were performed with R software (version 4.0.5, R Foundation), and a two-sided P value < 0.05 was considered statistically significant.

Ethical review: The study was approved by the Ethics Committee of Shandong Provincial Public Health Clinical Center. Patient consent was waived due to the design of the retrospective study.

RESULTS

Patient description: The development cohort included a total of 121 laboratory-confirmed SFTS cases, including 25 severe cases and 96 mild cases. The median age of patients was 65 years (interquartile range [IQR], 55–71 years). 68 (56.2%) patients were men. 77 (63.6%) patients were farmers. 38 (31.4%) patients had a history of tick bites, and 49 (40.5%) had a history of field or forest work. The median time from the onset of the disease to the patient's admission was 7 days (IQR, 6–9 days). Gastrointestinal symptoms, fever during hospitalization, fatigue and neurological symptoms were the most common clinical manifestations (Table 1). During the entire hospitalization period, the proportion of severe patients (40%) with a body temperature over 39°C exceeded that of mild patients (12.5%), and the median highest body

temperature (39C°) was also higher than that of mild patients (38.1C°).

The results of the laboratory indicators were presented in Table 2.

Variable selection and construction of the risk model: The 64 variables collected were included in the LASSO regression. After the selection of LASSO regression, 2 indicators were still considered to be significant predictors for severe illness, including neurological symptoms and glutamic oxaloacetic transaminase/glutamic pyruvic transaminase (AST/ALT) levels (Figure 1). Incorporating two variables into logistic regression model, it turned out that neurological symptoms (OR, 12.915; 95% CI, 3.342-49.916; $P<0.001$) and AST/ALT levels (OR, 1.891; 95% CI, 1.272-2.813; $P=0.002$) were the independent risk factors of severe illness (Table 3).

Based on the two independent predictors mentioned above, a risk model predicting the risk of severe diseases was constructed. Below is the built model (M):

$$M = \frac{1}{1 + e^{-4.531 + 2.558 \times \text{neurological symptoms} + 0.637 \times (\text{AST/ALT})}}$$

ROC analysis was used to evaluate the predictive value of the model.

Area under ROC curve (AUC) of the model was 0.882 (95%CI: 0.808-0.956) (Figure 2A).

Internal and external validation: The model was validated internally by bootstrapping. The mean AUC obtained from internal validation was 0.883 (95%CI: 0.809-0.957), which was similar to the primary model

(Figure 2B).

The external validation cohort included 51 SFTS patients, 10 of whom were severe case. The median age of patients was 67 years (IQR, 62–72 years). 25 (49%) patients were men. The variables used in the risk model for the validation cohort were those used in the previous model construction, including neurological symptoms and AST/ALT levels. The AUC obtained by external validation was 0.873(95%CI: 0.775-0.972), which was slightly lower to the AUC in the development cohort (Figure 2C).

DISCUSSION

In this study, a model predicting the risk of serious diseases in hospitalized patients with SFTS was established. The AUC validated internally and externally was similar to AUC of the development cohort, indicating that high predictive value, stability and repeatability of the model. The independent risk factors included in this model were neurological symptoms and AST/ALT levels.

Several researches have shown that older age was associated with fatal outcome(16, 17). However, we did not find that older age increased substantially the risk of severe illness in SFTS. This may be because the age distribution of the developmental cohort was different from that of previous studies, with an overall older age(16, 17). Related studies

showed serum viral load at admission and some cytokines, such as IL-6, IL-10, were associated with fatal outcome of SFTS(18, 19). Nevertheless, in practice, many hospitals, limited by laboratory facilities, send serum samples to companies or municipal Centers for Disease Control for testing these indicators, which delays clinicians' treatment of patients while waiting for results.

The patient with neurological symptoms accounted for 42.1%, including sleepiness, unresponsiveness, limb trembling, consciousness disorder. Physical examination of meningeal irritation sign mainly showed stiff neck. Based on the published reports, high levels of MCP-1 and IL-8 in cerebrospinal fluid contributed to the direct invasion of SFTSV on the central nervous system(20). The direct damage caused by systemic hemophagocytic lymphohistiocytosis and SFTSV-positive cells infiltrating brain tissue leads to the rapid progression of the patient's neurological symptoms (11). In addition, there is a hypothesis that kidney or liver dysfunction is also related to SFTS central nervous system syndrome(21).

The liver plays a key role in the pathogenesis of SFTSV. The liver damage of SFTS is caused by secondary pathological processes, such as shock and hematopoietic shock, rather than the direct invasion of SFTSV(10). Of the 121 confirmed cases, liver injury markers, such as AST level, ALT level and AST / ALT level, increased in more than 50%

of patients, especially in patients with severe diseases.

As far as we know, the previously established SFTS risk models divided patients into survival and death groups to predict the patient's disease progression, which might underestimate the proportion of severe patients. Therefore, a model to evaluate the severity of patients with mild and severe diseases is necessary. Currently, a few studies have investigated the risk factors of severe SFTS, including abdominal pain, gingival bleeding and heat shock protein 70 (HSP70) levels(22).

However, HSP70 detection is not available in some hospitals, which limits its application as an independent risk factor for predicting severe illness. AST/ALT levels is not only the most important predictor of SFTS infection in patients within 1-7 days, but also one of the most commonly tested laboratory indicators in hospitals(23). Previous studies have not found that AST/ALT levels were independent risk factors for SFTS, which may be caused by the following difference: The selection criteria for index values were different. In their article, the AST/ALT levels used was the highest value detected during the patient's hospitalization, and we used the AST/ALT levels detected for the first time after the patient was admitted to the hospital.(15). However, the value detected for the first time in hospital was not necessarily the highest value, which may lead to inconsistencies in our results. Based on these, a risk model was developed, including neurological symptoms and objective laboratory

indicators, which is fully feasible in clinical practice.

This study has the following limitations: 1. This study is a single-center study. 2. There is one external validation cohort. Therefore, a multicenter study should be conducted to increase the sample size and the number of external validation cohorts in the future.

In conclusion, the present study used neurological symptoms and AST/ALT levels to construct a simple and feasible model for predicting patients' progression. This model helps clinicians implement reasonable treatment schemes to block the course of severe diseases, so as to reduce the proportion of serious diseases, shorten the course of diseases and improve the cure rate.

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Conflict of interest None to declare.

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Figure Legends

Figure 1 Variables selection using the least absolute shrinkage. (A) LASSO coefficient profiles of the 64 variables: Non-zero coefficient variables with different values of tuning parameter (λ). (B) Range of λ in the LASSO model.

Figure 2 The area under the receiver-operator characteristic (ROC) curve (AUC) of predicting critical illness among SFTS patients. (A) The AUC in the development cohort. (B) The AUC in the internal validation cohort. (C) The AUC in the external validation cohort.

Tables

Table 1 Demographics and clinical characteristics among patients in the development cohort

Characteristic	Total	mild illness	severe illness
No.	121	96	25
Age, y	65 (55, 71)	63.5 (54, 70)	69 (59, 72)
Male, No./No. (%)	68 (56.2)	49 (51)	19 (76)
Work, No./No. (%)	77 (63.6)	65 (67.7)	12 (48)
Exposure, No./No. (%)	87 (71.9)	70 (72.9)	17 (68.0)
History of tick bites, No./No. (%)	38 (31.4)	31 (32.3)	7 (28)
Field or forest operation history, No./No. (%)	49 (40.5)	39 (40.6)	10 (40)
Time from onset to hospital admission, d	7 (6, 9)	8 (6, 9)	7 (5, 8)
The number of days in hospital, d	9 (8, 13)	9 (8, 11.2)	13 (6, 17)
Comorbidities, No./No. (%)	38 (31.4)	24 (25)	14 (56)
Hypertension, No./No. (%)	26 (21.5)	18 (18.8)	8 (32)
Diabetes, No./No. (%)	9 (7.4)	5 (5.2)	4 (16)
Brain disease, No./No. (%)	8 (6.6)	5 (5.2)	3 (12)
Cardiovascular disease, No./No. (%)	4 (3.3)	3 (3.1)	1 (4)
Symptoms, No./No. (%)			
Fever during hospitalization, No./No. (%)	89 (73.6)	67 (69.8)	22 (88)
Maximum body temperature during hospitalization, °C	38.5 (37.1, 39)	38.1 (37, 38.8)	39 (38.5, 39.2)
Body temperature 39°C during hospitalization, No./No. (%)	22 (18.2)	12 (12.5)	10 (40)
Gastrointestinal symptom, No./No. (%)	107 (88.4)	86 (89.6)	21 (84)
Fatigue, No./No. (%)	72 (59.5)	58 (60.4)	14 (56)
Headache and dizziness, No./No. (%)	30 (24.8)	19 (19.8)	11 (44)
Muscle ache, No./No. (%)	11 (9.1)	7 (7.3)	4 (16)
Cough, No./No. (%)	46 (38)	31 (32.3)	15 (60)
Expectoration, No./No. (%)	39 (32.2)	26 (27.1)	13 (52)
Neurological symptoms, No./No. (%)	51 (42.1)	29 (30.2)	22 (88)

Data are No. (%) of patients, median (IQR).

Table 2 Laboratory characteristics among patients in the development cohort

Variable	Total	mild illness	severe illness
Creatine kinase, U/L	420 (146, 971)	347.5 (135.2, 873)	954 (437, 2137.2)
Red blood cell count, 10 ¹² /L	4.5 (4, 4.7)	4.5 (4, 4.7)	4.4 (4, 4.8)
White blood cell count, 10 ⁹ /L	4 (2.5, 6.4)	3.9 (2.5, 6.1)	4.6 (2, 8)
Neutrophil cell count, 10 ⁹ /L	2.4 (1.2, 4.6)	2.2 (1.2, 4.4)	3 (1.3, 6)
Lymphocyte count, 10 ⁹ /L	0.8 (0.5, 1.2)	0.8 (0.6, 1.2)	0.8 (0.4, 1.2)
Monocyte count, 10 ⁹ /L	0.4 (0.2, 0.7)	0.4 (0.2, 0.6)	0.3 (0.1, 0.9)
Eosinophilic count, 10 ⁹ /L	0.01 (0.00, 0.01)	0.01 (0.00, 0.02)	0.01 (0.00, 0.01)
Basophil count, 10 ⁹ /L	0.02 (0.01, 0.05)	0.02 (0.01, 0.05)	0.02 (0.01, 0.04)
Hemoglobin content, g/L	133 (121, 142)	132.5 (121.8, 140)	137 (120, 146)
Platelet count, 10 ⁹ /L	55 (38, 73)	58.5 (43.8, 76.2)	45 (32, 60)
Plateletocrit	0 (0, 0.1)	0.1 (0, 0.1)	0 (0, 0)
Mean platelet volume, fL	8.7 (8.2, 9.6)	8.9 (8.3, 9.7)	8.3 (8, 9.1)
Platelet distribution width, %	17.8 (17.2, 18.6)	17.7 (17.1, 18.5)	18.2 (17.8, 19)
Prothrombin time, S	11.8 (11, 12.8)	11.8 (11, 12.6)	12.4 (11.3, 15)
Activated partial thromboplastin time, S	36.5 (32, 43.5)	33.8 (31, 40.8)	46.2 (40.5, 53.2)
Fibrinogen, g/L	2.4 (1.8, 3)	2.5 (2.1, 3.2)	1.8 (1.2, 2.2)
Thrombin time, S	16.3 (15.2, 18.3)	15.8 (14.6, 17.7)	18.3 (17.4, 23.5)
D-Dimer, ug/ml	1.1 (0.6, 2.3)	0.9 (0.5, 1.8)	2.1 (1, 3.9)
Alanine aminotransferase, U/L	101 (57, 191)	96 (54.8, 182.2)	142 (64, 241)
Aspartate aminotransferase, U/L	155 (89, 428)	135.5 (77, 300)	504 (177, 889)
AST/ALT	1.9 (1.3, 2.7)	1.7 (1.2, 2.3)	3 (2.3, 4)
Total protein, g/L	58.4 (52.9, 62.9)	58.3 (53.3, 63.3)	59.1 (52, 61.9)
Albumin, g/L	30.1 ± 5.2	30.5 ± 5.1	28.6 ± 5.2
Globulin, g/L	26.5 (24.2, 31.9)	26.4 (24.3, 31.4)	27.7 (24.1, 33.4)
Albumin / Globulin	1.1 (0.9, 1.3)	1.1 (1, 1.3)	1 (0.8, 1.3)
Prealbumin, g/L	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
Alkaline phosphatase, U/L	61 (48, 84)	59 (47.8, 77)	82 (58, 142)
Glutamyl transpeptidase, U/L	43 (24, 103)	42.5 (23.8, 91.2)	93 (24, 180)
Cholyglycine, ug/ml	48 (38, 67)	43.5 (37, 57)	74 (44, 91)
Glutamate dehydrogenase, U/L	11.7 (5, 23.2)	8.5 (4.5, 19.3)	27.8 (12.7, 81.3)
Sialic acid, mg/L	672 (629, 757)	671.5 (628.5, 756.5)	675 (645, 757)
5'-Nucleotidase, U/L	9 (4, 14)	8.5 (4, 12.2)	10 (5, 35)
K, mmol/L	3.7 (3.4, 4.1)	3.7 (3.3, 4)	3.9 (3.6, 4.5)
Na, mmol/L	134.1 ± 5.1	134 ± 4.8	134.8 ± 6.4
Glucose, mmol/L	7.1 (5.6, 9.6)	7 (5.5, 9.4)	7.9 (6.7, 10.5)
Urea, mmol/L	5.3 (4.3, 7.4)	5 (4, 6.7)	7.2 (5.5, 10.5)
Creatinine, µmol/L	62.4 (54.3, 70.7)	60.7 (53.4, 67.1)	73.1 (64.3, 99)
Cystatin c, mg/L	0.8 (0.7, 1)	0.8 (0.7, 0.9)	1.1 (0.8, 1.3)
Anion gap, mmol/L	15 (12, 16)	14 (12, 16)	16 (15, 18)
α-hydroxybutyrate dehydrogenase, U/L	425 (273, 623)	365.5 (250.2, 552.8)	829 (351, 1108)
Lactate dehydrogenase, U/L	607 (409, 1062)	555.5 (371, 882.2)	1100 (582, 1120)

Data are No. (%) of patients, mean value ± standard deviation, or median (IQR).

Table 3 Results of the multivariable logistic regression analysis in the development cohort.Factors	OR (95% <i>CI</i>)	<i>P</i> value
Neurological symptoms	3.342- 49.916	<0.00 1
AST/ALT levels	1.272- 2.813	0.002

Figures

Figure 1 Variables selection using the least absolute shrinkage. (A) LASSO coefficient profiles of the 64 variables:

Non-zero coefficient variables with different values of tuning parameter (λ). (B) Range of λ in the LASSO model.

Figure 2 The area under the receiver-operator characteristic (ROC) curve (AUC) of predicting critical illness among SFTS patients. (A) The AUC in the development cohort. (B) The AUC in the internal validation cohort. (C) The AUC in the external validation cohort.