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Analysis of early warning indicators of death in patients with severe fever with thrombocytopenia syndrome

Mianyu Yang[1,2†], Ming Yin[3†], Bingmei Hou[4,5], Lijuan Zhou[1,2], Jiling Wang[1,2,7*] and Zonghao Zhao[6,8*]

Abstract

Background Since its discovery, severe fever with thrombocytopenia syndrome (SFTS) has been characterized by rapid progression and poor prognosis, and no specific treatment is available. The aim of this study was to investigate the early warning indicators of mortality in SFTS patients.

Methods This is a retrospective cross-sectional study. The study subjects were patients who were admitted to the hospital with a confirmed diagnosis of SFTS from January 2023 to October 2023, and their clinical symptoms and signs at the time of admission, as well as the laboratory indexes of the first blood collection after admission were collected, grouped according to the prognosis, and statistically analyzed.

Results A total of 141 patients were collected, of which 27 patients died and 114 patients were in the survival group. Through statistical analysis, patients with combined hemorrhagic manifestations, disturbance of consciousness, lymphopenia, elevated lipase, and prolonged thrombin time on admission were independent risk factors for patients' death. By plotting the working characteristic curve of the subjects, as well as calculating the area under the curve, the results showed that the AUC of lymphopenia count was 0.670, 95% CI (0.563–0.776), $P=0.006$; the AUC of elevated serum lipase index was 0.789, 95% CI (0.699–0.878), $p<0.001$; the AUC of prolonged thrombin time was 0.749, 95% CI (0.645–0.854), $p<0.001$.

Conclusion Patients with hemorrhagic manifestations, disturbance of consciousness, lymphocyte reduction, elevated serum lipase, and prolonged thrombin time on admission are more worthy of the clinician's attention, and require early and effective interventions to avoid further disease progression.

Keywords Severe fever with thrombocytopenia syndrome, Death, Prediction, Hemorrhagic manifestations

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a new zoonotic infectious disease caused by the sever fever with thrombocytopenia syndrome virus (SFTSV), characterized by fever, thrombocytopenia, leukopenia, and most of the infected populations are found in Southeast Asia, such as China, Japan, Vietnam, Myanmar [1–5]. The SFTSV virus belongs to the genus Bunyavirus of the family Bunyaviridae, which is capable of causing viral hemorrhagic fevers and is transmitted mainly through the bites of ticks (the long-horned blood tick, the mouse blood tick, the Japanese hard tick, and the microtome tick). Since the first discovery of this virus, SFTS has been included in Chinese list of legally recognized infectious diseases, and sentinel hospitals have been established in endemic areas. Most patients present with fever and gastrointestinal symptoms as their first symptoms. Mild cases present with high fever, thrombocytopenia, and leukopenia with respiratory or gastrointestinal symptoms; severe cases are associated with severe psychiatric symptoms, acute respiratory failure, severe pancreatitis, and multiorgan failure, and even more life-threatening [6]. It has been reported that the overall incidence rate of SFTS has shown an upward trend between 2011 and 2021 The overall incidence of SFTS has been reported to be on the rise between 2011 and 2021, with most of them distributed in central China [7]. In this study, 81 patients came from Hefei, which is now under the jurisdiction of Feidong, Lujiang, Changfeng, Feixi, and Chaohu, and includes four districts, Luyang, Shushan, Baohai, and Yaohai [8]. Hefei City has a hilly terrain with mountain ranges, and most people in the rural areas are engaged in agricultural activities, which increases the exposure risk to some extent. So far there is no vaccine for SFTSV and there is a lack of specific treatment, therefore the prevention of tick bites, early detection of severe disease, and timely and effective intervention are the most effective measures to reduce the mortality rate of SFTS [9, 10].

In this study, we retrospectively analyzed the basic data of 141 SFTS patients admitted to two hospitals in Hefei from January 2023 to October 2023, aiming to explore the early warning indicators that can be used as the mortality of SFTS patients.

Materials and methods

Research objects

Retrospective analysis of 141 patients diagnosed with SFTS from January 2023 to October 2023 in two hospitals in Hefei, divided into 114 patients in the survival group and 27 patients in the death group according to the prognosis.

Diagnostic criteria for SFTS (Guideline for prevention and treatment of severe fever with thrombocytopenia syndrome (2010 version)): diagnosis is made based on epidemiological history (history of working, living, or traveling in hilly, forested, or mountainous areas or history of being bitten by ticks within 2 weeks before the onset of the disease), clinical manifestations and laboratory test results. (a) Suspected cases: those with the above epidemiological history, clinical manifestations such as fever, and decreased peripheral blood platelets and leukocytes. (b) Confirmed cases: those with one of the following in a suspected case: (1) a positive test for nucleic acid of the new type of bunyaviruses in a case specimen; (2) the case specimen is positive for novel Bunyavirus IgG antibody or the titer in the recovery phase is more than 4 times higher than that in the acute phase; (3) the case specimen is isolated with novel Bunyavirus [11].

Inclusion criteria: (1) diagnosis of SFTS according to the diagnostic criteria recommended in the Guideline for prevention and treatment of severe fever with thrombocytopenia syndrome (2010 version) issued by the Ministry of Health of the People's Republic of China (specific diagnostic criteria); [11] (2) no history of overseas travel in the 6 months before the onset of the disease; (3) no history of hospitalization for other illnesses in the last 6 months after the onset of the disease; and (4) complete data from the clinical diagnosis and treatment. As this was a retrospective study in which the investigators collected data mainly by reviewing the electronic medical record system and using blood specimens discarded during clinical visits, and would not use medical records and specimens that patients had previously explicitly refused to use, and would not adversely affect patients' rights and health, the Ethics Committees of the Second People's Hospital of Hefei and the First Affiliated Hospital of the University of Science and Technology of China (USTC) waived the patient informed consent requirement.

Methods

General information, epidemiological characteristics, disease history, complaints and clinical symptoms at admission and relevant serological indicators of the first blood collection after admission were retrospectively analyzed for patients in the survival and death groups.

Data analysis

This study was statistically analyzed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism (ver. 9.5; San Diego, USA) for plotting. Dichotomous variables were expressed using the number of cases and percentage (%), and comparisons between the two groups were made using the Chi-square test; measures conforming to normal distribution were expressed as mean ± standard deviation, and comparisons between the two groups were made using the independent samples *t*-test; non-normally distributed measures were expressed as median (interquartile range), and comparisons between

Table 1 Comparison of general characteristics in the two study groups

General information	Death group (27 cases)	Survivor group (114 cases)	Statistical analysis value	*p*-Value
Age, years	74(68,81)	69(57,74)	z=-3.385	***0.001***
Sex			x^2=0.695	***0.405***
Female	13(48.1)	65(57.0)		
Male	14(51.9)	49(43.0)		
BMI	17(33.3)	34(66.7)	x^2=10.383	***0.001***
Underlying diseases, *n*	13(18.6)	57(81.4)	x^2=0.030	***0.863***
History of tick bite, *n*	4(13.8)	25(86.2)	x^2=0.676	***0.411***
Rural residence	19(21.6)	58(78.4)	x^2=0.615	***0.433***

Table 2 Comparison of clinical symptoms and signs between the two groups

Symptoms and signs	Death group (27 cases)	Survivor group (114 cases)	Statistical analysis value	*p*-Value
Fever	25(92.6)	92(80.7)	1.425	***0.233***
Fatigue	12(44.4)	35 (30.7)	1.855	***0.173***
Myalgia	1(3.7)	25(21.9)	3.686	***0.055***
Cough	5(18.5)	16(14.0)	0.083	***0.774***
Chest tightness	1(3.7)	9(7.9)	0.120	***0.729***
Anorexia	16(59.3)	70(61.4)	0.042	***0.837***
Vomiting	6(22.2)	18(15.8)	0.265	***0.607***
Diarrhea	9(33.3)	28(24.6)	0.868	***0.352***
Dizzy	5(18.5)	11(9.6)	0.939	***0.332***
Headache	4(14.8)	8(7.0)	0.850	***0.356***
Hemorrhagic manifestations	13(86.7)	2(13.3)	49.425	***< 0.001***
Disturbance of consciousness	13(48.1)	9(7.9)	23.891	***< 0.001***
Neurological signs	9(33.3)	3(2.6)	22.631	***< 0.001***

the groups were made using the Mann-Whitney U test. Risk factors for SFTS were analyzed using binary logistic regression and included in multifactor logistic regression analysis to determine independent predictors of SFTS. The receiver operating characteristic (ROC) curve was also constructed, and the area under the curve (AUC) was calculated, which was used to assess the diagnostic accuracy of the related indexes in predicting patients' prognosis. When $P<0.05$, the difference was statistically significant.

Results

General information

A total of 141 patients were included in this study, including 63 males and 78 females, with a sex ratio of 0.81:1 and a mean age of (67.48±11.55) years. More than half of the patients were farmers by occupation (74 cases, 52.5%), 29 patients (20.6%) explicitly stated that they had been bitten by ticks, and the onset of the disease was mostly concentrated from April to October, and all 141 cases were disseminated, with the majority of patients residing in rural areas. (Table 1)

Clinical symptoms and signs

The Chi-square test and Fisher's exact method were used to test the 13 clinical signs and symptoms integrated at the time of admission for all patients (Table 2). The results showed that there were three variables with statistically significant differences between the two groups: (1) hemorrhagic manifestations, i.e., internal or external bleeding; (2) disturbance of consciousness, i.e., lethargy, confusion, and severe disorders of consciousness (no Glasgow Coma Score assessment was done); (3) neurological symptoms, i.e., cerebral neurological abnormalities, abnormalities of the motor system function(e.g., muscular dystrophy, muscle tone and strength, posture and gait, involuntary movements, and ataxia), abnormal sensory function (hypesthesia and sensory abnormalities), abnormal nerve reflexes (e.g., superficial reflexes, deep reflexes, pathological reflexes, and signs of meningeal stimulation), and abnormalities of the autonomic system.

A total of 15 patients presented with hemorrhagic manifestations on admission, with 8 of 13 patients in the death group presenting with bleeding from the oral mucosa, 3 with coughing up blood, and 2 with subcutaneous petechiae and ecchymoses, while 2 patients in the survival group presented with bleeding from the oral mucosa. 22 patients presented with disturbances of consciousness, with 8 of the 13 patients in the death group presenting with somnolence, 4 with blurred consciousness, and 1 with delirium, while 9 patients in the survival group presented with drowsiness. None of the patients were evaluated on the Glasgow Coma Scale. Twelve

Table 3 Univariate analysis of laboratory test indicators

Laboratory test results	Death group (27 cases)	Survivor group (114 cases)	Statistical analysis value	*p*-Value
Hypersensitive C-reative protein, Hs-CRP(×10^9/L)	5.34(2.19–8.91)	4.19(1.40-10.23)	z=-1.10	***0.271***
Leukocyte count, WBC(×10^9/L)	2.46(1.67–4.46)	2.83(1.64–5.25)	z=-0.472	***0.637***
Platelet count, PLT(×10^9/L)	40(19.00–49.00)	49.50(32.50–69.50)	z=-2.668	***0.008***
Neutrophil count, N(×10^9/L)	1.87(1.01–3.09)	1.58(0.93–3.86)	z=-0.068	***0.945***
Lymphocyte count, L(×10^9/L)	0.50(0.32–0.72)	0.63(0.44–1.03)	z=-2.738	***0.006***
Serum sodium, Na	131.85 ± 3.86	133.15 ± 5.17	t = 1.227	***0.222***
Serum potassium, K	3.70(3.49–4.07)	3.76(3.35–4.15)	z=-0.084	***0.933***
Serum calcium, Ca	1.92 ± 0.19	2.01 ± 0.15	t = 2.828	***0.005***
Serum creatinine, SCr	81.10(64.00-102.00)	69.00(57.70–88.50)	z=-2.086	***0.037***
Urea nitrogen, BUN	7.00(5.30-10.14)	6.37(4.60–9.13)	z=-0.839	***0.402***
Uric acid, UA	236.60(188.00-365.40)	238.95(173.35–322.90)	z=-0.422	***0.673***
Total protein, TP	59.85 ± 4.71	61.91 ± 6.69	t = 1.52	***0.132***
Albumin, ALB	32.98 ± 2.55	34.90 ± 4.40	t = 2.988	***0.004***
Alanine aminotransferase, ALT	56.00(41.00-129.00)	64.00(39.00-108.25)	z=-0.058	***0.954***
Aspartate aminotransferase, AST	160.00(105.00-539.00)	123.00(72.75-263.03)	z=-1.842	***0.066***
Lactate dehydrogenase, LDH	773.30(445.00-1974.00)	545.00(326.75–946.50)	z=-2.049	***0.040***
Creatine kinase, CK	719.00(327.00-2776.00)	311.50(123.75–791.50)	z=-2.864	***0.004***
Alkaline phosphatase, AKP	60.00(52.00-86.80)	63.30(52.15–85.58)	z=-0.220	***0.826***
Serum amylase, AMY	160.00(84.00-240.00)	75.00(47.00-123.50)	z=-4.617	***< 0.001***
Serum lipase, LIP	364.00(160.00-693.00)	79.00(47.00-193.25)	z=-4.654	***< 0.001***
Prothrombin time, PT	13.10(12.00-14.30)	12.05(11.30–13.20)	z=-2.623	***0.009***
Thrombin time, TT	24.90(20.80–31.80)	19.10(17.68–21.50)	z=-4.03	***< 0.001***
Activated partial thromboplastin time, APTT	53.60(46.30–71.30)	41.00(35.48–49.50)	z=-4.087	***< 0.001***
D-dimer, DD	3.67(1.38–6.16)	1.51(0.75–3.46)	z=-2.664	***0.008***
Fibrinogen, FIB	2.16(1.67–2.58)	2.32(1.97–2.81)	z=-2.093	***0.036***
Procalcitonin, PCT	0.36(0.10–1.07)	0.12(0.10–0.21)	z=-2.485	***0.013***
Hs-PCR/ALB	0.17(0.07–0.30)	0.13(0.04–0.28)	z=-1.276	***0.202***

Table 4 Multivariate logistic regression analysis of risk factors for death

Clinical manifestation	β-value	Sx value	Wald x^2 value	*p*-Value	OR (95% CI)
Hemorrhagic manifestations	6.257	1.834	10.402	***0.001***	521.847(14.324-19012.271)
Disturbance of consciousness	5.226	3.198	2.670	***0.041***	28.324(1.144-700.977)
L	-6.036	2.768	4.756	***0.029***	0.002(0.00-0.543)
LIP	0.005	0.003	3.985	***0.046***	1.005(1.000-1.010)
TT	0.103	0.050	4.315	***0.038***	1.109(1.006–1.223)

patients presented with neurological symptoms, all of which were characterized by tremors and convulsions of the extremities.

Other signs such as fever and malaise on admission were not statistically significant between the two groups. ($p > 0.05$).

Laboratory test results

Univariate analysis was performed on the relationship between the results of the first blood test and the prognosis of the patients (Table 3). The results showed that there were significant differences in platelet count (PLT), Lymphocyte count (L), Serum calcium (Ca), Serum creatinine (SCr), Albumin (ALB), Lactate dehydrogenase (LDH), Creatine kinase (CK), Serum amylase (AMY), Serum lipase (LIP), Prothrombin time (PT), Thrombin time (TT), Activated partial thromboplastin time (APTT), D-dimer (DD), fibrinogen(FIB) and Procalcitonin (PCT) between survival group and death group ($p < 0.05$). There was no significant difference in serological test indexes between the other two groups ($p > 0.05$).

Multifactorial analysis

Several indicators that were statistically significant in the univariate analysis were included in the binary logistic analysis (Table 4), which showed that admission with hemorrhagic manifestations, disturbance of consciousness, reduction in L count, elevated LIP, and prolongation of TT were independent risk factors for patient's death.

ROC curve analysis

The ROC curve were plotted for L, LIP, and TT, and the AUC was also calculated, and the results showed that the AUC for L was 0.670, 95% CI (0.563–0.776), $p = 0.006$; the

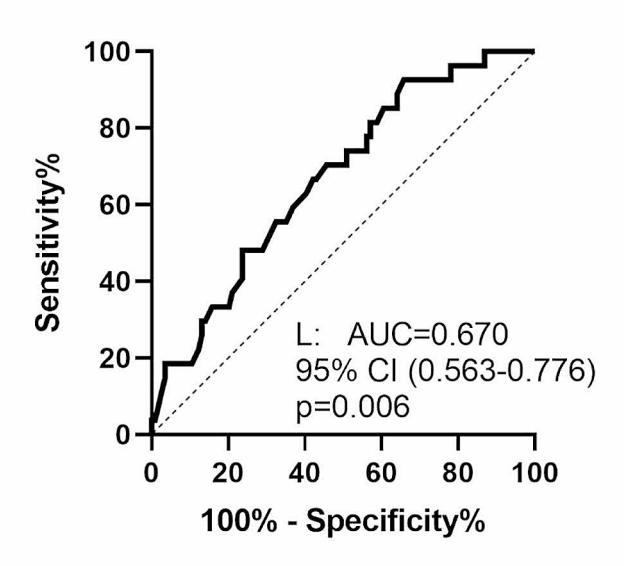

Fig. 1 Predictive value of reduction in L count in death in SFTS patients (ROC curve analysis). AUC, area under the curve; 95% CI, 95% confidence interval

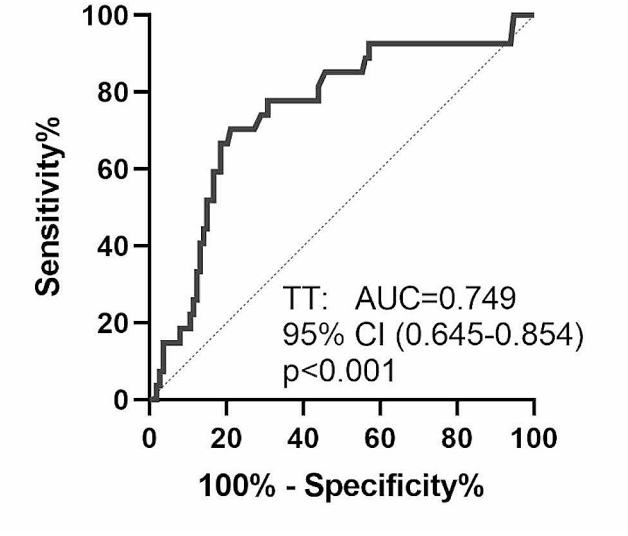

Fig. 2 Predictive value of prolongation of TT in death in SFTS patients (ROC curve analysis). AUC, area under the curve; 95% CI, 95% confidence interval

AUC for LIP was 0.789, 95% CI (0.699–0.878), $p<0.001$; and the AUC for TT was 0.749, 95% CI (0.645–0.854), $p<0.001$.(Figures 1, 2 and 3).

Discussion

SFTS was first identified in 2004 in Weifang, Shandong Province, China, and named after "anaplasmosis", and SFTSV was extracted for the first time from the sera of SFTS patients in 2010 [1, 6]. SFTSV belongs to the Bunyaviridae family of viral hemorrhagic fevers [12], which

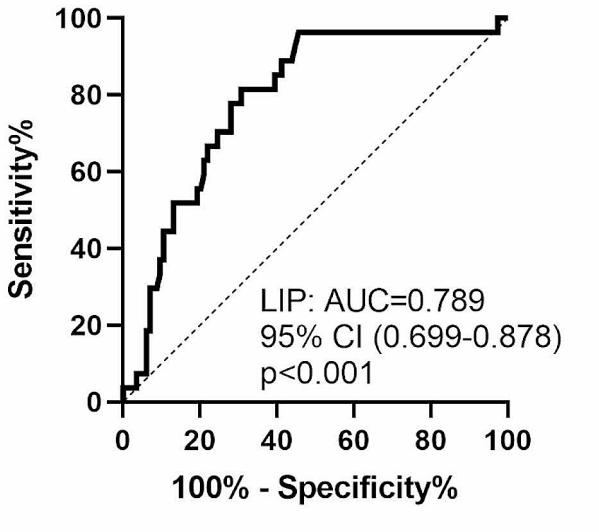

Fig. 3 Predictive value of elevated LIP in death in SFTS patients (ROC curve analysis). AUC, area under the curve; 95% CI, 95% confidence interval

are caused by four families of viruses (Serratoviridae, Bunyaviridae, Filoviridae, and Flaviviridae), and they often cause similar clinical symptoms, and the patients may all initially be admitted to the hospital due to high fever accompanied by generalized malaise, and even the presence of similar serological indicators [12, 13]. Many types of laboratory tests have been developed for better identification, including viral culture, nucleic acid amplification tests, and viral antigen tests [13–16]. For more than 20 years, most cases of SFTS have been sporadic with rapid progression and high morbidity and mortality, and early diagnosis of the disease and early intervention are the best means of improving prognosis [17]. Through discussion, during the process of collecting patient information, we found that due to differences in cognition and deficiencies in education, most patients expressed a lack of knowledge about SFTS, so they often overlooked the physical changes in the early stages of the disease, which led to the lack of timely and effective interventions, and missed the optimal time for interventions; and may be limited to the differences in cultural practices and the economic conditions, the majority of patients with severe illnesses chose to give up the costly life instrumentation support, often with extremely poor prognosis, and these patients may even fail to be counted in the China Center for Disease Control and Prevention.

SFTS can cause damage to different organs. In this study, In the univariate analysis, there was a statistically significant difference between the two groups of patients admitted to the hospital combined with impaired consciousness or with neurological signs, and when included in the multivariate analysis, patients admitted to the hospital combined with impaired consciousness was a risk

factor for death, which is similar to previous reports [18, 19]. The mechanism by which SFTS leads to neurologic injury is not clear, and the patients in the mortality group tended to have a combination of abnormal levels of consciousness, seizures, and abnormal neurologic reflexes on admission. Previous reports have suggested that patients with SFTS combined with encephalitis are often associated with a high mortality rate [20]. Studies have shown that magnetic resonance imaging cerebrospinal fluid polymerase chain reaction (PCR) and reverse transcription PCR tests are useful in the diagnosis of acute viral encephalitis [20].

In this study, prolonged admission TT time and combined bleeding manifestations (both internal and external bleeding) were independent risk factors affecting the prognosis of patients in both groups. Close observation of bleeding manifestations and coagulation-related indexes in the early stage of the disease can help predict the prognosis of the disease, which is consistent with the studies of Ding et al. and Wang et al. [19, 21, 22]. There is uncertainty about the cause of coagulation abnormalities in SFTS patients; the liver is the origin of most coagulation factors, and liver injury reduces the synthesis of coagulation factors. Some studies have reported that SFTS patients have multiple abnormalities in liver serology, indirectly reflecting liver injury, which may be related to abnormalities in coagulation indices [19, 22]. However, in this study, elevated alanine aminotransferase and aspartate aminotransferase indexes were not a risk factor for patient death; most of the diseases present with liver function abnormalities in the early stage, and some of the patients were admitted with underlying liver diseases, which may affect our collection of serologic indexes; and we only collected the indexes of the patients' first blood collection, and we did not perform liver puncture to obtain the histopathologic indexes of the patients.

Elevated serum pancreatic enzymes (including serum amylase and serum lipase) are often indicative of critical illness in patients with no prior pancreatic disease, and in the present study, univariate analysis showed statistically significant differences in elevated pancreatic enzymes between the two groups, and when included in multivariate analysis, elevated LIP indexes were an independent risk factor for patient death. Some studies have shown that elevated pancreatic enzymes are associated with poor prognosis in patients with SFTS [23]. Elevated pancreatic enzymes have been reported to be very common in the inflammatory response, and significant elevation of pancreatic enzymes may indicate severe systemic tissue infection [24]. Severe infections cause a drop in blood cells, and in the present study, lymphocytopenia was a risk factor for death in the patients. Generally, most viral infections result in relative lymphocytosis, whereas only a few viruses that cause severe disease result in lymphopenia, such as Severe Acute Respiratory Syndrome Coronavirus-2 and Ebola virus [25–27]. In this study, the patients' first ultrasensitive c-reative protein (CRP) and PCT on admission were collected and the ratio was calculated based on hypersensitive CRP (hs-CRP) and ALB. In univariate analysis, the difference between the two groups with elevated PCT was statistically significant, while the difference between the two groups with hs-CRP and hs-CRP/ALB was not statistically significant. Viral infections usually cause mild elevation or no significant change in CRP because they mostly occur within cells and do not damage cell membranes, and therefore do not cause phospholipid elevation to stimulate CRP elevation. However, severe viral infections may produce extensive damage to tissues, leading to significant elevations in CRP early in the disease [28, 29]. In this study, inflammatory markers such as hs-CRP/ALB were calculated, which suggests that patients may have a severe systemic inflammatory response; however, statistically, there was no statistically significant difference between the two groups for this indicator, which is not consistent with the study by Kutluhan et al. [30]. This may be because our sample size was insufficient and we did not perform dynamic continuous monitoring.

Combined advanced age and underlying disease in patients have been reported as indicators of poor prognosis [31–33]. However, in the present study, advanced age and the presence of underlying diseases were not independent risk factors for patient mortality, and it was found that the median age of the patients in the death group and the survival group was 74 and 69 years, respectively, which may be because most of our patients' residences were in rural areas, where young people tend to go out to work for many years, which inadvertently increases the risk of exposure of the elderly. Although this study showed that advanced age and the presence of underlying diseases were not independent risk factors for patient mortality, several studies have shown that advanced age is associated with an increased risk of other diseases and decreased immunity [32–34], so there is a need to strengthen the education of elderly people in rural areas, and at the same time need to pay close attention to patients with advanced age and the presence of underlying diseases in the course of treatment.

This study has several limitations. First, this study was a retrospective analysis, and all patients originated from only 2 general hospitals, so there may be a selection bias and a small sample size; in terms of data collection, we only collected the indicators of the first blood collection of the patients on admission to the hospital, and more than half of the patients were treated by an outside hospital, which may have a certain impact on the collected indicators, and we did not monitor the related indicators dynamically to learn the changing trend of the related

indicators during the hospitalization. Moreover, we did not monitor the relevant indicators dynamically to know the trend of the relevant indicators during the hospitalization of the patients and failed to conduct a more in-depth assessment. Second, some studies have reported that viral load is related to prognosis [19], but we did not perform relevant tests in the data collected, and more advanced technical support is still needed in the future. Finally, in this study, although the patient was diagnosed with SFTS, co-infection with other pathogens could not be excluded, and according to previous studies, viral hemorrhagic fevers often cause similar changes in laboratory indicators, so this point needs to be emphasized and considered in future studies.

In summary, admission combined with hemorrhagic manifestations, impaired consciousness, lymphopenia, elevated lipase index, and TT delay were independent influences on patient death in this study, and the accuracy of prognostic judgment by elevated lipase index was better than that of lymphopenia and TT delay by constructing ROC curves. However, due to our limited data and the lack of dynamic monitoring, in-depth multicenter studies with large samples are still needed in the future to obtain more accurate clinical manifestations and indicators at different stages of the patient's disease course, to detect critically ill patients at an early period, and to make timely and good clinical judgments on the changes in the patient's condition.

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Author contributions
MYY and JLW designed the experiment, MYY and LJZ engaged in data collection, MYY and BMH performed statistical analysis of the data, MYY and MY finished writing the first draft, and JLW and ZHZ made critical revisions to the paper. All authors contributed to the article.

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Data availability
The datasets generated and analyzed during the current study are not publicly available because the individual privacy of patients is being compromised.

Declarations

Ethics approval and consent to participate
This research was authorized by the Ethics Committees of the Second People's Hospital of Hefei and The First Affiliated Hospital of USTC. As this was a retrospective study, the researchers collected data mainly by reviewing the electronic medical record system and using blood specimens discarded during clinical visits, and would not use medical records and specimens that the patients had previously explicitly refused to use, and would not adversely affect the patients' rights and health, the Ethics Committees of the Second People's Hospital of Hefei and The First Affiliated Hospital of USTC waived the requirement for patients' informed consent. (Ethics Approval No. 20240111191800015689 7, 2024-Scientific research-124)

Conflict of interest
All authors declare no competing interests.

Consent for publication
Not applicable.

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