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Original Article

Serum IL-6 and IL-10 levels are associated with fatal outcomes in patients with SFTS in China

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Abstract

Introduction: Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease with a high mortality rate and is a public health concern. This study aimed to investigate the associations of serum interleukin 6 (IL-6) and interleukin 10 (IL-10) levels with the prognosis of SFTS patients.

Methodology: A total of 95 patients with confirmed SFTS were included. Clinical and laboratory data were compared between the survival and non-survival groups. Multivariate logistic regression analysis was used to assess independent risk factors for mortality. The predictive efficacies of laboratory markers were evaluated using receiver operating characteristic (ROC) curves. Survival analysis was performed using Kaplan–Meier curves based on the log-rank test.

Results: The levels of IL-6 and IL-10 at admission were significantly greater in the non-survival group than in the survival group ($p < 0.05$). Multivariate logistic regression analysis indicated that the IL-6 and IL-10 levels, estimated glomerular filtration rate, and activated partial thromboplastin time (APTT) were independent risk factors for a poor prognosis in patients with SFTS. ROC curve analysis revealed that the IL-6 and IL-10 levels and the APTT had a greater predictive value than other measured laboratory markers. Kaplan–Meier survival analysis demonstrated that SFTS patients with IL-6 > 39.5 pg/mL or IL-10 > 45.2 pg/mL had significantly lower survival within a 30-day follow-up period.

Conclusions: The levels of IL-6 and IL-10 at admission are the best markers for predicting in-hospital mortality of SFTS patients and have potential prognostic value in patients with SFTS.

Key words: SFTS; interleukin 6; interleukin 10; prognosis.

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease caused by the SFTS virus (SFTSV), which has currently been renamed Dabie bandavirus [1]. The disease was first identified in 2009 in rural regions of central China and has since become an epidemic across 20 provinces in China. It has also been observed in Japan and Korea [2–4].

SFTS is characterized by thrombocytopenia and leukopenia following the onset of fever, as well as by neural disorders and gastrointestinal symptoms, and multiple organ failure can develop in severe cases [5]. The case fatality rate has been reported to be 2.5–33.3% in China, and is even higher in Japan and Korea [6,7].

However, the pathogenic mechanism of rapid disease progression has not been well studied in SFTS. Previous studies have suggested that a cytokine storm might be associated with the development of this disease [8]. Interleukin 6 (IL-6) is a proinflammatory cytokine that plays a pivotal role in inflammation and serves as a crucial mediator of cytokine storm-induced mortality. Interleukin 10 (IL-10) is an important immunoregulatory cytokine with pleiotropic roles in the immune system. Systemic hyperproduction of both IL-6 and IL-10 can induce a cytokine storm, which contributes to disease pathology and is strongly associated with fatal outcomes [9].

Although many serum markers have been previously tested for their ability to predict disease severity and mortality in patients with SFTS, determining their exact impacts on disease progression remains challenging. In this study, we aimed to evaluate the potential of IL-6 and IL-10 as prognostic markers

for disease progression and in-hospital mortality among patients with SFTS.

Methodology

Patients and samples

This retrospective study enrolled 95 hospitalized patients who were diagnosed with SFTS at the First Affiliated Hospital of Anhui Medical University between September 2019 and June 2023. Diagnosis was confirmed by testing for SFTSV RNA or SFTSV IgM/IgG in blood samples collected upon admission. The patients were subsequently divided into two groups based on clinical outcomes: the non-survival group, with 25 patients, and the survival group, with 70 patients. This study was approved by the research ethics committee of the First Affiliated Hospital of Anhui Medical University and was performed in accordance with the principles of the Declaration of Helsinki. The patient information was anonymized, nonidentifiable, and treated confidentially. The patients and their families were informed about this study and signed the relevant informed consent forms.

Data collection

Information, including demographic information, comorbidities, clinical features, laboratory indicators, and outcomes, was collected from the electronic medical records. The laboratory is certified by ISO 15189. The laboratory indicators were assessed within 24 hours of patient admission and included routine blood tests using an XN-9000 automatic hematology analyzer (Sysmex, Kobe, Japan), coagulation function tests using an STA-R Max automatic coagulometer (Stago, Paris, France), biochemical marker and C-reactive protein (CRP) analyses using a VITROS-5600 automatic biochemical analysis system (Ortho, USA), procalcitonin (PCT) tests using a mini VIDAS (bioMérieux, Lyon, France), SFTSV RNA tests using a high-purity viral RNA kit (Qiagen, Dusseldorf, Germany) and IL-6 and IL-10 tests using a Roche c6000 automatic immune analyzer (Roche, Basel, Switzerland). The primary outcome was 30-day mortality. Moreover, we followed the patients by telephone if they were discharged within 30 days. Mortality refers to patients who died during the course of the disease.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) for normally distributed data, or as the median (M) and interquartile range (IQR) for skewed data, and categorical variables are described as frequencies. A Student's t test or the Mann–Whitney U test was used to compare differences between the two groups. The Chi-square test was used to determine differences in categorical variables between the groups. Receiver operating characteristic (ROC) curve analysis was used to calculate the optimal cut-off values for the risk factors. The area under the curve (AUC) with the highest Youden index was used to determine the predictive efficacies of the risk factors. Survival analysis was performed using Kaplan–Meier curves based on the log-rank test. Multivariate logistic regression analysis was used to assess independent risk factors for mortality. The Statistical Package for Social Sciences (SPSS) 21.0 software (IBM Corp, Armonk, NY, USA) and the GraphPad Prism 9 software (GraphPad Software, San Diego, CA, USA) were used for statistical analysis, and two-sided p values < 0.05 were considered to indicate statistical significance.

Table 1. Comparison of clinical characteristics in the survival and non-survival groups.

Characteristics	Survivors (n = 70)	Non survivors (n = 25)	*p* value
Gender, male (%)	33 (47.00)	11 (44.00)	0.787[c]
Age (years)	62.06 ± 12.68	65.00 ± 10.84	0.774[b]
Hospital stay (days)	11.00 (9.00, 16.00)	4.00 (2.00, 8.00)	< 0.001[a]
Onset to admission (days)	5.00 (4.00, 7.00)	5.00 (4.50, 7.00)	0.777[a]
Highest body temperature (°C)	38.80 (38.40, 39.00)	38.70 (38.00, 39.10)	0.848[a]
Fever, N (%)	70 (100.00)	25 (100.00)	-
Vomit, N (%)	21 (30.00)	17 (68.00)	0.001[c]
Headache, N (%)	14 (20.00)	12 (48.00)	0.007[c]
Conscious disturbance, N (%)	0	25 (100.00)	< 0.001[c]
Diarrhea, N (%)	20 (28.60)	9 (36.00)	0.489[c]
Hemorrhage of digestive tract, N (%)	12 (17.10)	10 (40.00)	0.020[c]
Pulmonary infection, N (%)	11 (15.70)	11 (44.00)	0.004[c]
Acute pancreatitis, N (%)	21 (30.00)	9 (36.00)	0.580[c]
Oral candidiasis, N (%)	0	1 (4.00)	0.093[c]
MODS, N (%)	0	15 (60.00)	< 0.001[c]
DIC, N (%)	0	2 (8.00)	0.017[c]

Data are presented as the median (IQR), mean ± SD, or N (%). *p* values were calculated using [a]Mann–Whitney U test, [b]Student's t test, or [c]Chi-square test. DIC: diffuse intravascular coagulation; MODS: multiple organ dysfunction syndrome.

Results

Demographic and baseline characteristics of patients with SFTS

A total of 95 patients diagnosed with SFTS were included in this study, with an average age of 62.83 ± 12.23 years. Among them, 51 (53.68%) were females, and 44 (46.32%) were males. Seventy-five patients were assigned to the survival group, and 25 patients were allocated to the non-survival group based on the clinical outcome. The demographic and baseline characteristics of the patients in the non-survival and survival groups are summarized in Tables 1 and 2. There were no significant differences in the age or gender between the two groups ($p > 0.05$). The patients in the non-survival group had shorter hospital stays than did those in the survival group ($p < 0.05$). Patients with fatal outcomes had increased incidences of vomiting, headache, consciousness disorders, hemorrhage of the digestive tract, pulmonary infection, multiple organ dysfunction syndrome (MODS), and diffuse intravascular coagulation (DIC).

The prothrombin time (PT); activated partial thromboplastin time (APTT); and levels of D-dimer (D-D), CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea nitrogen (UREA), creatinine (CRE), cardiac troponin I (TnI), PCT, viral RNA, IL-6, and IL-10 were significantly greater in the non-survival group than in the survival group within 24 hours of hospitalization ($p < 0.05$). Conversely, the estimated glomerular filtration rate (eGFR) was significantly lower in the non-survival group than in the survival group ($p < 0.05$). No significant differences were detected between the two groups for the remaining biomarkers ($p > 0.05$).

IL-6, IL-10, and the APTT as putative markers for predicting mortality in patients with SFTS

To assess the prognostic usefulness of the laboratory markers for predicting mortality in patients with SFTS, ROC curves were drawn for the 95 patients with SFTS. The IL-6 concentration had a sensitivity of 80% and a specificity of 84.3% for predicting SFTS mortality. The cut-off value for predicting mortality was assumed to be 39.5 pg/mL, and the AUC was 0.885 (95% CI: 0.807–0.963, $p < 0.001$). The ROC curve of IL-10 concentrations for predicting SFTS mortality was

Table 2. Comparison of laboratory indicators between patients in the survival and non-survival groups.

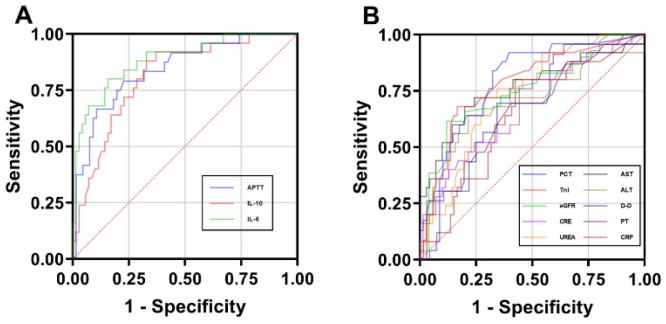
	Normal range	Survivors (n = 70)	Non-survivors (n = 25)	*p* value
Viral load (copies/mL)	0	583.50（116.75, 2357.50）	26200.00 (1352.00, 545750.00)	0.001
Coagulation function				
PT (s)	11.00–16.00	13.30 (12.80, 14.00)	13.70 (13.10, 15.50)	0.018
APTT (s)	28.00–42.00	50.30 (42.60, 57.50)	66.10 (59.10, 84.80)	< 0.001
Fibrinogen (g/L)	2.00–4.00	2.71 (2.23, 3.23)	2.41 (1.87, 3.25)	0.188
D-D (mg/ml)	0.00–0.50	2.56 (1.31, 6.72)	6.53 (2.45, 12.90)	0.007
Blood routine				
White blood cell ($\times10^9$/L)	3.50–9.50	2.29 (1.40, 4.58)	2.39 (1.35, 3.38)	0.524
Neutrophil ($\times10^9$/L)	1.80–6.30	1.36 (0.90, 2.53)	1.37 (0.85, 2.01)	0.488
Lymphocyte ($\times10^9$/L)	1.10–3.20	0.65 (0.43, 1.07)	0.70 (0.35, 0.96)	0.914
Monocyte ($\times10^9$/L)	0.10–0.60	0.12 (0.06, 0.28)	0.09 (0.06, 0.16)	0.683
Hemoglobin (g/L)	130.00–175.00	128.00 (115.00, 139.00)	131.00 (119.00, 138.00)	0.585
Platelet count ($\times10^9$/L)	125.00–350.00	48.00 (35.00, 67.00)	39.00 (31.00, 50.00)	0.125
Biochemical markers				
Total bilirubine (g/L)	3.00–22.00	11.10 (8.00, 13.40)	10.00 (8.90, 16.50)	0.648
ALT (U/L)	0–35.00	71.00 (43.00, 92.00)	137.00 (64.00, 261.00)	0.003
AST (U/L)	14.00–36.00	156.00 (91.00, 246.00)	460.00 (201.00, 1098.00)	< 0.001
ALP (U/L)	38.00–126.00	70.00 (57.00, 87.00)	82.00 (60.00, 169.00)	0.077
UREA (mmol/L)	2.50–6.10	5.55 (4.40, 8.04)	8.20 (6.45, 10.81)	0.001
CRE (umol/L)	46.00–92.00	69.00 (60.20, 90.40)	90.60 (70.90, 160.30)	0.007
eGFR (ml/min)	> 90.00	95.00 (71.00, 105.00)	66.00 (40.00, 85.00)	< 0.001
CK (U/L)	50.00–310.00	517.00 (158.00, 1097.00)	574.00 (264.00, 1500.00)	0.373
CKMB (U/L)	0-24.00	15.00 (6.00, 35.00)	21.00 (8.00, 59.00)	0.251
TnI (ng/ml)	0-0.019	0.040 (0.010, 0.083)	0.170 (0.060, 0.331)	< 0.001
Amylase (U/L)	30.00–110.00	99.00 (63.00, 174.00)	104.00 (82.00, 283.00)	0.137
Lipase (U/L)	23.00–300.00	580.00 (314.00, 889.00)	541.00 (349.00, 919.00)	0.773
Infection-related biomarkers				
CRP (mg/L)	0.00–10.00	2.05 (0.69, 10.77)	5.87 (2.68, 17.68)	0.039
PCT (ng/mL)	0.00–0.50	0.13 (0.06, 0.33)	0.60 (0.25, 1.53)	< 0.001
Cytokine				
IL-6 (pg/mL)	0–5.40	12.70 (5.30, 28.90)	104.00 (44.40, 211.60)	< 0.001
IL-10 (pg/mL)	0–12.90	20.20 (8.00, 52.90)	97.90 (50.50, 236.50)	< 0.001

Data are presented as the median (IQR). *p* values were calculated using the Mann–Whitney U test. ALP: alkaline phosphatase; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CK: creatine kinase; CKMB: creatine kinase-MB; CRE: creatinine; CRP: C-reactive protein; D-D: D-dimer; eGFR: estimated glomerular filtration rate; IL-6: interleukin 6; IL-10: interleukin 10; PCT: procalcitonin; PT: prothrombin time; TnI: cardiac troponin I; UREA: urea nitrogen.

also analyzed. The AUC of IL-10 concentrations for predicting mortality was 0.813 (95% CI: 0.720–0.906, $p < 0.001$), with a cut-off value of 45.15 pg/mL. The IL-10 concentration had a sensitivity of 88% and a specificity of 67.1%. The AUC and cut-off value were also determined for the APTT, with values of 0.85 and 58.6 seconds, respectively (Table 3 and Figure 1A).

The results also showed that the AUCs with the best performance in predicting mortality were those for the IL-6 and IL-10 concentrations, and the APTT at admission. The details of the ROC curve characteristics for other measured laboratory markers indicated their limited abilities to predict mortality, as shown in Table 3 and Figure 1B.

Figure 1. ROC curve analysis of (A) IL-6, IL-10, and APTT and (B) PCT, TnI, eGFR, AST, ALT, D-D, CRE, UREA, PT, and CRP values to predict 30-day mortality in SFTS patients.



The ROC curve plots were created with GraphPad Prism 9. The SFTS patients were divided into survival and non-survival groups based on their survival status according to the ROC curve analysis. ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CRE: creatinine; CRP: C-reactive protein; D-D: D-dimer; eGFR: estimated glomerular filtration rate; IL-6: interleukin 6; IL-10: interleukin 10; PCT: procalcitonin; PT: prothrombin time; ROC: receiver operating characteristic; SFTS; severe fever with thrombocytopenia syndrome; TnI: cardiac troponin I; UREA: urea nitrogen.

Independent risk factors for death in patients with SFTS

Based on our assignment of the corresponding indicators (Table 4), multivariate binary logistic regression analysis was performed to predict the risk of mortality in patients with SFTS. After adjusting for age, the PT, APTT, D-D, CRP, ALT, AST, UREA, CRE, eGFR, TnI, PCT, IL-6 and IL-10 variables were used in the model as prognostic factors to predict mortality and to discriminate between non-survivors and survivors. Forward conditional analysis revealed that four incremental degrees of adjustment in multivariate binary logistic regression models were significantly associated with death. We found that IL-6 (OR = 18, 95% CI: 5.415–59.829, $p < 0.001$) in model 1; IL-6 (OR = 12.041, 95% CI: 3.19–45.448, $p < 0.001$) and APTT (OR = 10.199, 95% CI: 2.573–40.419, $p = 0.001$) in model 2; IL-6 (OR = 11.679, 95% CI: 2.624–51.972, $p = 0.001$), APTT (OR = 13.56, 95% CI: 2.811–65.418, $p = 0.001$), and the eGFR (OR = 10.971, 95% CI: 1.883–63.904, $p = 0.008$) in model 3; and IL-6 (OR = 10.339,

Table 4. Variables and assignments of SFTS risk factor analysis.

Variables	Assignment description	
PT (s)	≥ 13.60 = 1	< 13.60 = 0
APTT (s)	≥ 58.60 = 1	< 58.60 = 0
D-D (mg/ml)	≥ 3.80 = 1	< 3.80 = 0
CRP (mg/L)	≥ 2.58 = 1	< 2.58 = 0
ALT (U/L)	≥ 94.00 = 1	< 94.00 = 0
AST (U/L)	≥ 312.00 = 1	< 312.00 = 0
UREA (mmol/L)	≥ 7.25 = 1	< 7.25 = 0
CRE (umol/L)	≥ 72.20 = 1	< 72.20 = 0
eGFR (ml/min)	< 89.50 = 1	≥ 89.50 = 0
TnI (ng/ml)	≥ 0.102 = 1	< 0.102 = 0
PCT (ng/ml)	≥ 0.175 = 1	< 0.175 = 0
IL-6 (pg/mL)	≥ 39.50 = 1	< 39.50 = 0
IL-10 (pg/mL)	≥ 45.20 = 1	< 45.20 = 0

ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CRE: creatinine; CRP: C-reactive protein; D-D: D-dimer; eGFR: estimated glomerular filtration rate; IL-6: interleukin 6; IL-10: interleukin 10; PCT: procalcitonin; PT: prothrombin time; SFTS; severe fever with thrombocytopenia syndrome; TnI: cardiac troponin I; UREA: urea nitrogen.

Table 3. ROC curve analysis of serum laboratory markers for predicting mortality in patients with SFTS.

Variable	AUC	*p* value	95% CI	Cut-off value	Sensitivity	Specificity
PT	0.685	0.009	0.556-0.814	13.550	69.60	61.90
APTT	0.850	< 0.001	0.757-0.943	58.600	82.60	76.20
D-D	0.686	0.008	0.560-0.813	3.785	69.60	65.10
CRP	0.640	0.040	0.516-0.764	2.580	80.00	57.60
ALT	0.699	0.003	0.565-0.832	94.000	64.00	78.60
AST	0.762	< 0.001	0.639-0.885	312.000	68.00	80.00
UREA	0.734	0.001	0.628-0.84	7.245	72.00	71.40
CRE	0.682	0.007	0.557-0.806	72.200	76.00	55.70
eGFR	0.751	< 0.001	0.142-0.357	89.500	88.00	61.40
TnI	0.780	< 0.001	0.671-0.889	0.102	68.00	83.30
PCT	0.782	< 0.001	0.682-0.883	0.175	92.00	60.30
IL-6	0.885	< 0.001	0.807-0.963	39.500	80.00	84.30
IL-10	0.813	< 0.001	0.720-0.906	45.150	88.00	67.10

ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; AUC: area under the curve; CI: confidence interval; CRP: C-reactive protein; CRE: creatinine; D-D: D-dimer; eGFR: estimated glomerular filtration rate; IL-6: interleukin 6; IL-10: interleukin 10; PCT: procalcitonin; PT: prothrombin time; ROC: receiver operating characteristic; SFTS; severe fever with thrombocytopenia syndrome; TnI: cardiac troponin I; UREA: urea nitrogen.

95% CI: 2.019–52.951, $p = 0.005$), APTT (OR = 8.547, 95% CI: 1.607–45.444, $p = 0.012$), eGFR (OR = 13.549, 95% CI: 1.964–93.461, $p = 0.008$) and IL-10 (OR = 9.141, 95% CI: 1.559–53.592, $p = 0.014$) in model 4 were significantly linked to mortality in patients with SFTS. The lack of improvement in the explanatory power by other parameters, such as PT, D-D, CRP, ALT, AST, UREA, CRE, TnI, and PCT, led to their exclusion from the forward conditional analysis, as shown in Table 5.

Survival analysis

We hypothesized that patients with higher levels of IL-6 and IL-10 on admission were more likely to have a poor prognosis. The patients were divided into two groups, namely, IL-6low and IL-6high, based on the optimal cut-off value of the IL-6 concentration (39.5 pg/mL). Similarly, the patients were divided into IL-10low and IL-10high groups according to the optimal cut-off value of the IL-10 concentration (45.2 pg/mL). Kaplan–Meier survival analysis demonstrated that SFTS patients with IL-6 > 39.5 pg/mL (log-rank test; $\chi^2 = 33.17$, $p < 0.001$) or IL-10 > 45.2 pg/mL (log-rank test; $\chi^2 = 23.42$, $p < 0.001$) had a significantly shorter survival within the 30-day follow-up period (Figure 2).

Discussion

The rapid onset and high fatality rate of SFTS make it a significant health concern in China. However, no effective treatment options are currently available for this disease. It is imperative to accurately identify patients who require intensive treatment upon admission. Consequently, we propose the use of IL-6 and IL-10 concentrations at the time of admission as a means to assess the prognosis of SFTS patients.

In this study, the incidences of clinical symptoms such as vomiting, headache and consciousness disorders were greater among patients with fatal outcomes than among the survivors. The primary causes of mortality in the patients with fatal outcomes were gastrointestinal hemorrhage, pulmonary infection, MODS, and DIC; which was consistent with the majority of previous studies [10,11]. We also observed significant increases in the levels of multiorgan injury biomarkers, including coagulation function markers (PT, APTT, and D-D), infection-related biomarkers (CRP and PCT), hepatocyte injury markers (AST and ALT), renal injury markers (UREA and CRE), and a myocardial injury marker (TnI), in deceased individuals compared with those in survivors. Furthermore, the non-survival group exhibited significantly lower eGFRs than did the survival group. These findings suggest that patients in the non-survival group experienced earlier and more severe onset of multiorgan failure than did those in the survival group, which is consistent with the findings of previous studies [12,13].

It is well known that excessive release of cytokines by activated immune cells and infected cells is involved in immunopathology and the development of organ dysfunction [9]. Therefore, the assessment of serological markers associated with a cytokine storm may aid in predicting disease severity and mortality. Our findings in this study, namely, that there are high plasma concentrations of IL-10, IL-6, and viral RNA in

Figure 2. Kaplan–Meier survival curves within 30 days of follow-up according to the cut-off values of the IL-6 and IL-10 levels at admission. **A**: IL-6, interleukin 6, cut-off value = 39.5 pg/mL; **B**: IL-10, interleukin 10, cut-off value = 45.2 pg/mL.

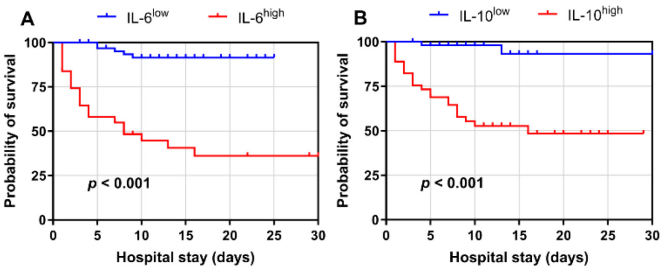


Table 5. Results of binary logistic regression analysis of serum markers to predict SFTS mortality.

Variables		B	*p* value	OR	95% CI
Model 1	IL-6	2.890	< 0.001	18.000	5.415–59.829
Model 2	APTT	2.322	0.001	10.199	2.573–40.419
	IL-6	2.488	< 0.001	12.041	3.190–45.448
Model 3	APTT	2.607	0.001	13.560	2.811–65.418
	eGFR	2.395	0.008	10.971	1.883–63.904
	IL-6	2.458	0.001	11.679	2.624–51.972
Model 4	APTT	2.146	0.012	8.547	1.607–45.444
	eGFR	2.606	0.008	13.549	1.964–93.461
	IL-6	2.336	0.005	10.339	2.019–52.951
	IL-10	2.213	0.014	9.141	1.559–53.592

Adjusted for age. In forward conditional binary logistic regression, model 1 (IL-6), model 2 (IL-6 and APTT), model 3 (IL-6, APTT and eGFR), and model 4 (IL-6, APTT, eGFR, and IL-10) were considered predictors of mortality in SFTS patients. APTT: activated partial thromboplastin time; B: regression coefficient; CI: confidence interval; eGFR: estimated glomerular filtration rate; IL-10: interleukin-10; IL-6: interleukin-6; OR: odds ratio; SFTS; severe fever with thrombocytopenia syndrome.

non-surviving patients with SFTS, suggest that excessive cytokine release and uncontrolled viremia are critical determinants of the fatal outcome. IL-6 is a proinflammatory cytokine and a key cytokine in cytokine release syndrome-induced mortality [14]. Serum IL-10 is an important anti-inflammatory cytokine that protects the host from tissue damage resulting from excessive proinflammatory responses during infection. However, IL-10 can also be an immune-activating and proinflammatory cytokine in some autoimmune diseases, cancer, and severe COVID-19 [15,16]. Several studies have consistently reported that the serum IL-10 concentration is significantly greater in patients with fatal SFTS, severe COVID-19, and Ebola and H5N1 infections [17–20]. In this study, similar to the IL-6 concentration, the concentration of IL-10 could predict poor outcomes in SFTS patients.

Multivariate logistic regression analysis revealed that IL-6, IL-10, APTT, and eGFR could be used as independent factors to predict poor outcomes in SFTS patients. Yoo *et al*. [18] noted that the peripheral blood IL-6 and IL-10 levels could be used as independent factors to predict the progression of SFTS, which is consistent with the results of this study; therefore, the role of IL-6 and IL-10 in this disease deserves special attention. It was reported that SFTS patients with APTT prolongation of 60 seconds had a 4-fold greater mortality rate than those with less marked prolongation. However, the mechanisms underlying the prolongation of APTT in SFTS patients remain largely unknown [21]. Wang *et al*. reported that the eGFR was an independent risk factor in the early stage of the disease, which is consistent with our data [10]. Interestingly, the ROC curve analysis revealed that the abilities of IL-6, IL-10, and APTT to predict clinical fatality among SFTS patients were superior to those of the other measured laboratory markers. Furthermore, in the survival analysis, hospitalized patients who exhibited increased serum concentrations of IL-6 and IL-10 had a significantly decreased likelihood of 30-day survival. Consequently, healthcare professionals should diligently monitor SFTS patients with elevated levels of IL-6 and IL-10, and promptly implement appropriate management strategies to optimize their prognosis.

However, this study also has several limitations. First, this was a retrospective, single-center study with a relatively small cohort size, and the number of deaths was also low, which might have led to a possible statistical bias. Second, we tested IL-6 and IL-10 only at the time of admission and lacked continuous measurements for assessing disease progression. All these limitations need to be addressed in the future.

Conclusions

The levels of IL-6 and IL-10 at admission were the best markers for predicting in-hospital mortality of SFTS patients and have potential prognostic value for SFTSV infection. In addition, determination of the levels of these cytokines in SFTS patients upon hospital admission may help in treatment-related decision making to prevent disease complications and death, because these markers are prognostic variables for poor outcomes.

Authors contributions

WH, FZ, XL, and JQ: study design, data analysis, manuscript writing. All authors reviewed the manuscript.

Ethical approval and consent to participate

This study was approved by the Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University and was performed in accordance with the principles of the Declaration of Helsinki. The patient information was anonymized, nonidentifiable, and treated confidentially. The patients and their families were informed about this study and signed the relevant informed consent forms.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of interests

No conflict of interests is declared.

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