

## Original Article

# Identification and treatment of severe fever with thrombocytopenia syndrome

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**Abstract:** *Objective:* This study aimed to investigate the affecting factors and early warning indicators of severe fever with thrombocytopenia syndrome (SFTS) to develop clinical triage criteria and corresponding treatment protocols. *Methods:* The data were collected from 166 SFTS patients, who were admitted in our hospital from August 2009 to June 2017. The clinical characteristics of these patients were retrospectively analyzed. These patients were divided into two groups, according to their survival: survival group and death group. The clinical manifestations and laboratory findings obtained from these two groups were then compared and the related risk factors of critically ill patients and death patients were screened using *t*-test and Spearman's correlation analysis. *Results:* The average age, levels of aspartate aminotransferase, alanine aminotransferase, creatine kinase, prothrombin time, activated partial thromboplastin time, and novel bunyavirus nucleic acid were significantly higher in patients in the death group than in the survival group, while platelet count was significantly lower in patients in the death group than in the survival group. The differences were statistically significant ( $P < 0.01$ ). *Conclusion:* Advanced age, underlying diseases, obnubilation, high levels of lactate dehydrogenase and creatine kinase, prolonged prothrombin time, and activated partial thromboplastin time can be used as diagnostic indicators of critical SFTS. If these critical indicators appear, these patients should be transferred into the intensive care unit in a timely manner, and undergo intensive treatment with large doses of antiviral drugs and bedside blood filters. This approach should improve survival rates.

**Keywords:** Severe fever with thrombocytopenia syndrome, critical, early stage, identification, treatment

### Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an infectious disease characterized by fever and thrombocytopenia that appeared in eastern China in recent years. At present, it is known that severe fever results from the thrombocytopenia syndrome bunyavirus (SFTSV), which is also referred to as "novel bunyavirus" [1, 2]. At present, SFTS cases have also been reported in Japan and South Korea [3, 4]. The fatality rate of this disease is approximately 12.2%. Some patients become seriously ill with progression of the disease, while some patients die of multiple organ failure, and the fatality rate of critically ill patients is approximately 50% [5]. There have been continuous reports of cases of human transmission. Therefore, this disease greatly endangers the life and health of people [6, 7]. However, to date, very

effective therapies have not been found. Furthermore, there is also the problem of whether the warning factors for severe patients can be found at the early stage and an appropriate strengthened treatment can be given according to the severity of the disease, in order to improve the prognosis of these patients. In the present study, the data of 166 SFTS patients, who were admitted in our hospital from August 2009 to June 2017, were analyzed to summarize the early identification and treatment options for severe and critically ill patients.

### Materials and methods

#### General information

A total of 166 SFTS patients admitted in Xinyang Central Hospital of Henan Province from August

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2009 to June 2017 were included into this study. Among these patients, 132 patients were assigned into the survival group and 34 patients were assigned into the death group. In the survival group, 121 patients were male and 45 patients were female, and the age of these patients ranged within 32-80 years old, with an average age of  $52.3 \pm 7.8$  years old. In the death group, 13 patients were male and 21 patients were female, and the age of these patients ranged within 41-89 years old, with an average age of  $66.5 \pm 8.9$  years old. The difference in age between these two groups was statistically significant ( $t = -3.501$ ,  $P < 0.01$ ). In the survival group, 35 patients had underlying diseases (coronary heart disease, chronic obstructive pulmonary disease, etc.), accounting for 26.5%. In the death group, 34 patients had underlying diseases (coronary heart disease, chronic obstructive pulmonary disease, etc.), accounting for 100%. Seriously ill patients who gave up treatment were followed-up by phone call, and recorded as dead patients after their death was confirmed. All patients met the diagnostic criteria for the Guidelines for the Prevention and Treatment of Severe Fever with Thrombocytopenia Syndrome (2010 Edition) [8].

### Research methods

The clinical data of 166 patients, including symptoms and signs, laboratory test results, imaging data, treatment and outcomes, were retrospectively analyzed. The age, underlying disease status, blood routine test, liver function, blood coagulation function, viral nucleic acid load, and other factors that could influence the prognosis and thus were analyzed. Furthermore, according to early warning indicators, clinical grouping was carried out, and corresponding treatment programs were developed. The virus nucleic acid detection was performed using a SFTSV nucleic acid quantitative detection kit (fluorescence probe PCR method; the kit was provided by Zhongshan University David gene Limited by Share Ltd, product number: YZB/State 5627-2011). The lower limit of detection was 100 TCID<sub>50</sub>/mL (TCID<sub>50</sub> refers to 50% tissue culture infective dose).

### Statistics analysis

Data were statistically analyzed using statistical software SPSS 20.0. Count data were

expressed as percentage. Normally distributed measurement data are expressed as the mean  $\pm$  standard deviation (SD), and evaluated using *t*-test. The correlation between laboratory test results and the prognosis of patients was analyzed using Spearman's correlation analysis, and indicators related to the prognosis were analyzed by multivariate binary logistic regression analysis.  $P < 0.05$  was considered statistically significant.

## Results

### *Comparison of clinical manifestations between the survival group and death group*

All 166 patients had fever, asthenia, superficial lymph node enlargement, and other clinical manifestations. Their body temperature ranged from 37.6°C to 41.00°C, with an average temperature of 39.10°C. The majority of patients (89 patients, 53.6%) had high fever, which mainly manifested as continued fever; while moderate fever occurred in 42 patients, accounting for 25.3%, and low fever occurred in 35 patients, accounting for 21.1%. Fifty-nine patients had a history of chronic obstructive pulmonary disease (COPD), hypertension, coronary heart disease, and diabetes, accounting for 35.54% (36 patients were from the death group, accounting for 61%, and 23 patients were from the survival group, accounting for 39%). Ninety-one patients (54.82%) had mental symptoms such as unconsciousness, slow reaction, and impaired consciousness, among which 20 patients were from the survival group and 34 patients were from the death group. Eighty-nine patients had digestive symptoms such as nausea, vomiting, and diarrhea, among which 55 patients were from the survival group and 34 patients were from the death group. Seventy-five patients had cough, expectoration, and chest tightness, among which 43 patients were from the survival group and 32 patients were from the death group. Fifty-two patients had skin mucosal ecchymosis, oral bleeding, and hematuria, among which 18 patients were from the survival group and 34 patients were from the death group.

### *Comparison of laboratory examination results between the survival group and death group*

White blood cell count and platelet count decreased in both two groups, and the differ-

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**Table 1.** Comparison of clinical indicators and prognosis in patients with fever and thrombocytopenia syndrome with survival and death

Clinical data	Survival group	Death group	t	P
Age (year, $\bar{x} \pm s$ )	52.3±7.8	66.5±8.9	t=-0.307	<0.01
Number of underlying diseases (n, %)	35 (26.5%)	34 (100%)	t=-0.612	<0.01
White blood cell ( $\times 10^9/L$ )	3.51	2.69	t=-0.623	<0.01
Platelet ( $\times 10^9/L$ )	46.3	35.6	t=-2.011	<0.01
AST (U/L)	66	121	t=-2.031	<0.01
ALT (U/L)	103	165	t=-0.607	<0.01
Cr (ummol/L)	59.2	93.8	t=-0.307	<0.01
CK (U/L)	395	1350	t=-3.546	<0.01
LDH (U/L)	653	1522	t=-4.290	<0.01
PT (s)	12.1	15.3	t=-4.635	<0.01
APTT (s)	45.3	68.1	t=-5.369	<0.01
FIB (g/L)	2.98	2.13	t=-3.12	<0.01
Viral nucleic acid (IgTCID50/mL)	3.83	5.91	t=-8.26	<0.01
CRP	35.8	123.5	t=-3.36	<0.01

**Table 2.** Relationship between patients with stage and sftsv nucleic acid quantitative

	Light	Combined basic disease	Severe	Critically Severe
Viral nucleic acid quantification ( $\times 10^4$ IgTCID50/mL)	0.52±0.36	3.98±2.1	5.03±2.8	8.35±3.2

ence in platelet count was statistically significant ( $P<0.05$ ). Differences in alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (CR), and lactate dehydrogenase (LDH) between these two groups were statistically significant ( $P<0.05$ ). Differences in prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen (FIB) between these two groups were statistically significant ( $P<0.05$ ). The difference in C-reactive protein (CRP) between these two groups was statistically significant ( $P<0.01$ ). SFTSV nucleic acid detection results: The level of SFTSV nucleic acid in patients in the death group was  $5.92\pm 1.20$  IgTCID50/mL, which was higher than that in patients in the survival group ( $3.82\pm 1.20$  IgTCID50/mL), and the difference was statistically significant ( $P<0.01$ , **Table 1**).

### *Characteristics and prognosis of the disease*

These patients were divided into four types, according to their characteristics and prognosis (**Table 2**).

*Mild or occult type:* This type mainly occurred in children and young adults. These patients had

a body temperature of  $<38^\circ\text{C}$ , and presented with mild asthenia, nausea, and discomfort. Their leukocyte and platelet levels were slightly decreased or normal, and AST, ALT, CR, CK, and LDH levels were normal or slightly higher. Furthermore, their SFTSV nucleic acid was  $<1$  IgTCID50/ml, and the patient's condition was mild. In addition, these patients usually visited a doctor after tick bites, and the patient's condition was self-limited. Therefore, no special treatment was required. The patients generally achieved self-healing within one week. Hence, the disease was easily neglected.

*Underlying diseased-combined type:* This type usually occurred in middle-age and elderly patients with underlying diseases. These patients had a body temperature of  $<39^\circ\text{C}$ , had obvious asthenia and muscle soreness, and had obvious nausea, vomiting, diarrhea, and other symptoms, but had no change in consciousness and cavity bleedings. Their platelet count was  $>50\times 10^9/L$ , AST, ALT, CR, CK, and LDH levels were below five times of the normal value, SFTSV nucleic acid was  $<5$  IgTCID50/ml, the course of the disease was within 10-14 days, and the prognosis was satisfactory.

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**Table 3.** Comparison of prognosis between two groups (with or without treatment)

	Light		Combined basic disease		Severe		Critically Severe	
	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group
Survival group	51	25	41	18	11	10	8	2
Death group	0	0	6	9	3	7	7	2
P	>0.05		<0.01		<0.01		>0.05	

**Severe type:** This type usually occurred in middle-age and elderly patients with underlying diseases. These patients had a body temperature of 39-40°C, and had mental symptoms such as apathy and somnolence on the above bases, or complicated by bleedings of the digestive tract, lungs, uterus, and other cavities. Their platelet count was 30-50×10<sup>9</sup>/L, AST, ALT, CR, CK, and LDH levels were 5-10 times of normal level, SFTSV nucleic acid was <10 IgTCID50/ml, and the course of the disease was >2 weeks. Most patients were able to improve after treatment, while few patients progressed into the critical type.

**Critical type:** The following conditions occurred on the basis of the severe type: (1) Patients developed coma, delirium, or systemic convulsions, and other altered mental status; (2) Patients were complicated with other organ failures; (3) Patients were complicated with cerebral hemorrhage or massive hemorrhage in the digestive tract, lungs and uterus; (4) The conditions of patients rapidly progressed, platelet level rapidly decreased to <30×10<sup>9</sup>/L, AST, ALT, CR, CK, and LDH levels rapidly increased, which were more than 10 times of the normal levels, and SFTSV nucleic acid was >10 IgTCID50/ml; (5) Patients had exacerbations of underlying diseases; (6) Patients were complicated with severe infections.

### *Comparison of treatment options between the survival group and death group*

Two groups of patients were treated with intravenous drip of 0.5-1.0 g/times of ribavirin, twice a day, before and after the diagnosis, and received a subcutaneous or intravenous injection of 2-5 µg/kg of recombinant human granulocyte stimulatory factor, once a day. Patients in the severe group were additionally treated with an intravenous drip of 1×10<sup>5</sup> units of ulinastatin three times a day, an intravenous drip of 450 mg/time of magnesium isoglycyr-

rhizinate, once a day, and 0.5 g/kg/d of immunoglobulin for three days. Patients in the critical group were treated with platelet transfusion, bedside blood filtration, ventilator-assisted respiration and other organ supportive treatment as soon as possible on the basis of the above details. According to the above treatment methods, all patients were divided into two groups: treatment group and control group. In the severe type, the difference in mortality rate between these two groups was statistically different (*P*<0.01, **Table 3**).

### **Discussion**

SFTS is a group of clinical syndromes caused by SFTSV infection, which is mainly characterized by fever and thrombocytopenia. In the early stage, this disease is characterized by influenza-like symptoms, such as fever, fatigue, and systemic ache, thrombocytopenia, and leucopenia, which can be detected by laboratory examination. With the progress of this disease, excessive inflammatory response and organ dysfunction mediated by viremia can occur in the patient due to individual differences and underlying diseases, and severe patients would finally die of multiple organ dysfunction. This disease is mostly self-limited, and most patients recover within one week. However, if a patient progresses once into a severe status, the disease will present difficulties in treatment, complications, and high mortality rate [9, 10]. Our hospital has a designated unit that admits critical SFTS patients in Xinyang city. In the present study, the proportion of patients with severe and critical diseases was relatively high (18.67%), the mortality rate of patients with underlying disease-combined type was 25.42%, the mortality rate of severe type patients was 47.6%, and the mortality rate of critical type patients was 90%. The key to the treatment of this disease is to closely attend to patients complicated with this underlying disease, and it should be noted that

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this type of patient is prone to progressing into severe type patients. It is a key to improve the prognosis of patients. Therefore, severe patients should be detected at the early stage and sent to the intensive care unit (ICU) early to receive intensive treatment in order to prevent the deterioration of the underlying disease. This will permit carrying out early functional supportive treatment for various organs.

The present study revealed that patients with this disease were dominated by middle-age and elderly populations. Furthermore, the average age in the death group was significantly higher than that in the survival group, and the proportion of patients with underlying diseases in the heart, lung, and other important organs were also significantly higher in the death group than in the survival group. This suggests that advanced age and underlying heart and lung diseases are risk factors for the poor prognosis of SFTS [11, 12]. In addition, the levels of AST, ALT, CK, PT, APTT, and LDH were significantly higher in the death group than in the survival group, while platelet count was significantly lower in the death group than in the survival group, and the differences between these two groups were statistically significant ( $P < 0.01$ ). This suggests that the elevations of the above indicators were positively correlated to the severity of the disease [13].

Quantitative detection of SFTSV directly reflects viral replication in patients, and the viral load shows dynamic changes in the progression of the disease. Viral nucleic acid can generally be detected in serum in SFTS patients within two weeks after onset. A recent paper reported that fluorescent-probe PCR was more favorable for the early diagnosis of this disease [14]. The level of SFTSV nucleic acid was higher in the death group ( $5.92 \pm 1.20$  IgTCID<sub>50</sub>/ml) than in the survival group ( $3.82 \pm 1.20$  IgTCID<sub>50</sub>/ml) and the difference was statistically significant ( $P < 0.01$ ). This suggests that viral load is of great clinical significance to evaluate the prognosis of patients. In the present study, we attempted to add a viral nucleic acid load to the clinical classification criteria, because it is necessary to evaluate its function in future work.

In the present study, according to the characteristics of the disease, laboratory test results and outcomes, these SFTS cases were divided

into four types: mild or occult type, underlying disease-combined type, severe type, and critical type. Among the SFTS patients admitted in our hospital, mild or occult type patients accounted for 45.78%, underlying disease-combined type patients accounted for 35.54%, severe type patients accounted for 12.65%, and critical type patients accounted for 6.02%. Through typing, clinicians can early detect and diagnose severe and critical SFTS patients, allowing practical and effective intensive treatment to be performed, which would reduce complications and the fatality rate in the greatest possibility.

The levels of CRP in these two groups were compared, and it was found that this was significantly higher in the death group than in the survival group. These results reveal that inflammatory reactions play a very important role in the progression of this disease. Since severe and critical SFTS patients presented with virus-mediated excessive inflammatory reactions and organ dysfunction on the basis of these underlying diseases, in the present study, the main treatments were antiviral therapy, anti-inflammatory response therapy, and organ function supportive treatment. Antiviral treatment should first select an intravenous drip of 0.5-1.0 g/time of ribavirin, two times per day. Ribavirin belongs to nucleoside drugs, which can effectively inhibit the replication of RNA and DNA viruses and its antiviral ability is very strong. Moreover, the patient's tolerance to this drug is relatively good, its onset time is short, and the adverse reactions are few [15, 16]. Anti-inflammatory reaction therapy comprised of the application of  $1 \times 10^5$  units of ulinastatin, three times a day. Ulinastatin is a refined glycoprotein extracted from human urine, which belongs to proteases inhibitor. This can inhibit the activities of trypsin and other pancreatic enzymes, stabilize lysosome membranes, inhibit the release of lysosomal enzymes, inhibit the production of myocardial inhibitory factors, and improve the circulatory state during shock. A study reported that immunoglobulin combined with hormones was effective in patients with SFTS complicated with consciousness disorder, and the reason was considered to be correlated to the inhibition of inflammatory response [17]. For patients with abnormal liver function, we chose an intravenous drip of 450 mg/time of magnesium isoglycyrrhizinate, once

a day. This drug has anti-inflammatory effects, which can protect liver cell membranes and improve liver function, and reduce liver fibrosis [18]. For patients with obvious bleeding tendency or a significant decrease in platelets, 300 U/kg of recombinant human thrombopoietin was given, once a day; while patients with massive hemorrhage were treated with transfusion of platelets and plasma. Most of the patients presented with type I respiratory failure when the oxygenation index was <200. Patients who present with altered consciousness, endotracheal intubation mechanical ventilation should be given as soon as possible, and respiratory support according to the ventilation strategy for acute respiratory distress syndrome (ARDS) should be performed. For patients with low urinary output and continuous elevation of serum creatinine, continuous renal replacement therapy (CRRT) should be performed as soon as possible. This method not only functions in kidney replacement, but also reduces viremia-related inflammatory mediators such as IL-6, IL-8, IL-10, and TNF- $\alpha$ . However, intermittent hemodialysis is not recommended [19, 20]. Recently, a study reported that plasmapheresis for severe patients complicated with impaired consciousness achieved good clinical outcomes, but the sample size was too small. Hence, this result should be confirmed through further studies.

Most patients with SFTS had mild symptoms, do not require treatment, or merely need antiviral therapy alone, and disease spontaneously resolves. However, if the disease progresses into severe and critical stages, the fatality rate is high. Therefore, early identification, early diagnosis, early intensive care, and early anti-inflammatory treatment and organ function support are particularly important. On the basis of the treatment for severe or critical SFTS patients, intensive care should be given, and the combination of immunoglobulin, ulinastatin and CRRT treatment should be given as soon as possible, which can improve the success rate of rescue.

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### Disclosure of conflict of interest

None.

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