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Analysis of the laboratory indexes and risk factors in 189 cases of severe fever with thrombocytopenia syndrome

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Abstract

The current study aimed to analyze the clinical characteristics of severe fever with thrombocytopenia syndrome (SFTS) and to explore the risk factors of critical patients. From 2016 to 2018, we collected the hospitalized diagnosed cases with SFTS in Jinan infectious disease hospital of Shandong University and analyzed by the descriptive epidemiological method. According to the prognosis, they were divided into general group and severe group. The epidemiological characteristics, clinical features, and laboratory indexes of these 2 groups of patients were compared and analyzed at the first visit. The risk factors related to the severity of the disease were analyzed by univariate Logistic regression. In total, 189 cases of SFTS were treated during the period and 33 deaths occurred in the severe group, with the fatality rate of 17.46%. The patients' age ($\chi^2=8.864$, $P<.01$), ALT ($Z=-2.304$, $P=.03$), AST ($Z=-3.361$, $P<.01$), GLU ($t=-4.115$, $P<.01$), CK ($Z=-3.964$, $P<.01$), CK-MB ($Z=-2.225$, $P=.03$), LDH ($Z=-3.655$, $P<.01$), α-HBDH ($Z=-2.040$, $P=.04$), APTT ($t=-3.355$, $P<.01$), BUN ($Z=-2.040$, $P=.04$), Cr ($Z=-3.071$, $P=.01$), and D-dimer ($Z=-2.026$, $P=.04$) in the severe group were higher than that in the normal group, but the blood platelet (PLT) counts were significantly lower ($Z=-2.778$, $P<.01$) than that in the normal group. With the neuropsychiatric symptoms (OR = 24.083, 95% CI = 6.064–95.642), skin bleeding point (OR = 30.000, 95% CI = 6.936–129.764), multiple organ dysfunction (OR = 34.048, 95% CI = 7.740–149.782), past medical history (OR = 3.792, 95% CI = 1.284–11.200), and fasting glucose elevation (OR = 1.359, 95% CI = 1.106–1.668) could predict the severity of the SFTS. In summary, the abnormality of the laboratory index, the special clinical manifestations, and the past medical history of SFTS patients were the important basis for judging the patient's serious condition.

Abbreviations: ALB = albumin, ALT = alanine aminotransferase, AMS = amylase, APTT = activated partial thromboplastin time, AST = aspartate transaminase, BUN = urea nitrogen, CI = confidence intervals, CK = creatine kinase, CK-MB = creatine kinase isoenzyme, Cr = creatinine, CRP = C-reactive protein, FIB = fibrinogen, GLU = glucose, HBDH = hydroxybutyrate dehydrogenase, LDH = lactate dehydrogenase, LPS = lipase, OR = odds ratios, PCT = procalcitonin, PLT = blood platelet, PT = prothrombin time, SFTS = severe fever with thrombocytopenia syndrome, SFTSV = severe fever with thrombocytopenia syndrome virus, TT = thrombin time, WBC = white blood cell, WHO = World Health Organization.

Keywords: laboratory index, retrospective analysis, risk factors, severe fever with thrombocytopenia syndrome

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an acute, infectious, hemorrhagic disease caused by SFTSV. In 2007, the SFTS was first discovered in Xinyang county of Henan province, the virus was isolated in Henan province, China, reported in 2011.[1] It was retrospectively identified in South Korea in 2012 and the western regions of Japan in 2013.[2,3] The clinical manifestation of SFTS is characterized by fever, thrombocytopenia, and leukocytopenia, as well as vomiting, diarrhea, and multisystem organ failure often accompanied by hemorrhage. The mortality rates for SFTS were exceeding 12% to 30%.[1–3] The disease is widely expanding at global level. Until 2016, over 7000 SFTS cases were reported from 23 provinces in China. Laboratory-confirmed SFTS cases were recorded in 19 provinces in Central and Eastern China.[4] Moreover, similar viruses have recently been found to circulate in the United States, South Korea, and Japan.[2,3,5] Although SFTS is a tick-borne disease, person-to-person transmission caused by direct contact with blood has also been reported.[6–8] Currently, there is no effective clinical treatment for this infection, and the development of an inactivated vaccine is still under way. Therefore, the World Health Organization (WHO) has included SFTSV in its list of priority target pathogens requiring urgent attention.[9]

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In recent years, the number of SFTS patients in Shandong Province has been increased, and the clinical characteristics and laboratory indexes have also changed. The laboratory indexes and clinical characteristics of 189 patients with SFTS were analyzed retrospectively to provide guidance for improving the cure rate of critical patients.

2. Materials and methods

2.1. Clinical samples

There were 189 SFTS patients admitted from Jinan Infectious Disease Hospital affiliated to Shandong University from July 2016 to November 2018. All the 189 laboratory-confirmed SFTSV patients, who met the criteria that a positive result for SFTSV RNA detected by real-time RT-PCR assay, were used for the analysis. The patients were divided into 2 groups according to their clinical manifestation and prognosis: 148 patients in the general group (clinically cured and improved patients) and 41 patients in the critical group (critically ill and dead patients who are discharged from hospital automatically). This study had been approved by the medical ethics committee of Jinan Infectious Disease Hospital affiliated to Shandong University. All patients in the study have signed an informed consent and agreed with publication of data.

2.2. Statistical analysis

SPSS was used to analyze the data. The measurement data satisfying normal distribution were expressed in $\overline{x} \pm s$, and the independent sample t test was used in the comparison between groups. The measurement data of non-normal distribution were expressed in the median [*M (P25, P75)*]. The comparison between the 2 groups was performed by the Mann–Whitney U test. The counting data were expressed as examples and percentages, and analyzed by using the χ^2 test. Univariate logistic regression analysis was used to determine the critical variables of SFTS patients.

3. Results

3.1. Epidemiological data

3.1.1. Sex and age distribution. Among the 189 subjects in this study (84 males and 105 females), the age ranged from 26 to 88 years (60.3 ± 10.5). There were 147 patients aged 50 years or older, accounting for 77.8%. The mean ages in the general group and in the severe group were 58.2 ± 10.7 years and 65.9 ± 11.2 years, respectively. Significant difference was found in age and sex between the 2 groups ($t = 3.869$, $P < .01$; $\chi^2 = 2.809$, $P < .01$). The distribution of age group is presented in Table 1.

3.1.2. Season, occupation, geographical distribution. One hundred sixty-eight cases, which account about 88.9%, were concentrated from May to October, and the peak period was from June to September. One hundred seventy-two cases (91.0%) were mainly farmers. All the included cases were distributed throughout the province, and 7 counties (districts) existed cases in Jinan. The top 3 numbers of cases were Licheng District (48 cases), Zhangqiu City (31 cases), and Changqing District (15 cases), accounting for 49.7% of the total number of cases.

Table 1

Distribution of SFTS patients in different ages in general group and severe group [case (%)].

Age (year)	Frequency (%)	General group (%)	Severe group (%)
20–39	12(6.3)	12(8.1)	0(0.0)
40–59	85(45.0)	74(50.0)	11(26.8)
60–88	92(48.7)	62(41.9)	30(73.2)

SFTS = severe fever with thrombocytopenia syndrome.

3.1.3. Contact history and past medical history. All the cases were sporadic, 58 cases had a history of tick bite within 1 month before onset, 119 cases had a history of field work within half a month before onset, and 12 cases had a history of living in mountainous areas. There were 87 cases (46.0%) complicated with basic diseases, 58 cases (39.2%) in the common group, including 22 cases of hypertension, 12 cases of diabetes, 7 cases of sequelae of cerebral infarction, 6 cases of coronary heart disease, and 11 cases of other diseases; 29 cases (70.7%) in severe group, including 10 cases with hypertension, 6 cases with sequelae of cerebral infarction, 5 cases with diabetes, 3 cases with coronary heart disease, 3 cases after tumor operation, and 2 cases with psoriasis.

3.2. Clinical symptom and sign of patients

3.2.1. Clinical symptom. There was a different degree of fever in 189 patients. The peak of fever was 39.07 ± 0.56°C in the general group and 39.05 ± 0.61°C in the severe group. No significant difference was found in peak of fever between these 2 groups ($P > .05$). The number of patients with muscle soreness, neuropsychiatric symptoms, skin bleeding spots, and multiple organ dysfunctions in the severe group was significantly higher than that in the normal group, the difference in all the above mentioned factors was statistically significant ($P < .01$). The common clinical symptoms and signs of SFTS patients are shown in Table 2.

3.2.2. Clinical sign. There were 136 patients with superficial lymphadenopathy (110 cases of unilateral inguinal lymph node enlargement, 4 cases of axillary lymph node enlargement, 3 cases of neck lymph node enlargement, 14 cases of bilateral inguinal lymph node enlargement, 5 cases of bilateral anterior neck complicated with inguinal lymph node enlargement) in the 2 groups, and no significant difference was detected between the 2 groups ($P > .05$). Skin ecchymosis was found in 25 critical patients, most of them were found in venipuncture, intramuscular injection. Nervous symptoms such as indifference of expression, slow reaction, disturbance of consciousness in 34 critical patients, accompanied by involuntary tremor of tongue body, mandible and extremities, and convulsions were analyzed. The detailed are shown in Table 2.

3.2.3. Laboratory index. The 2 groups of patients with SFTS infection had abnormal blood routine indexes, manifested by different degrees of thrombocytopenia and leukopenia. In some cases, liver, myocardium, pancreas, and coagulation function were damaged, including ALT, AST, LDH, GLU, CK, CK-MB, α HBDH, APTT, TT, and LPS increased abnormally in varying degrees. Compared with the normal group and the severe group, it was found that BUN, Cr, AMS, PT, FIB, D-dimer, and CRP was normal in the general group. The WBC and ALB decreased in both groups, and the PCT had a slight increase in the 2 groups, and there was no significant difference between the 2 groups ($P > .05$). Analysis was performed on the laboratory index of the first diagnosis in the 2 groups, significant differences were found in blood PLT, ALT, GLU, AST, LDH, CK, CK-MB, HBDH,

Table 2

Cases of clinical symptoms and signs in patients with SFTS [case (%)].

Symptom and sign	Total (N = 189)	General group (N = 148)	Severe group (N = 41)	χ^2 value	*P* value
Fever	189(100.0)	148 (100.0)	41 (100.0)		
Fatigue	171 (90.5)	134 (90.5)	37 (90.2)	0.0033	.95
Anorexia	179 (94.7)	139 (93.9)	40 (97.6)	0.278	.60
Chilly	86 (45.5)	68 (45.9)	18 (43.9)	0.054	.82
Ague	47 (24.9)	39 (26.4)	8 (19.5)	0.803	.37
Muscle soreness	123 (65.1)	88 (59.5)	35 (85.4)	9.48	<.01
Nausea	93 (49.2)	75 (50.7)	18 (43.9)	0.589	.44
Vomit	44 (23.3)	32 (28.4)	12 (29.3)	1.051	.31
Abdominal pain	36 (19.0)	29 (19.6)	7 (17.1)	0.132	.72
Ventosity	25 (13.2)	18 (12.2)	7 (17.1)	0.675	.41
Diarrhea	56 (29.6)	46 (31.1)	10 (24.4)	0.689	.41
Dizziness headache	110 (58.2)	89 (60.1)	21 (51.2)	1.049	.31
Cough	72 (38.1)	53 (35.8)	19 (46.3)	1.509	.22
Expectoration	64 (33.9)	49 (33.1)	15 (36.6)	0.1733	.68
Chest tightness	45 (23.8)	31 (20.9)	14 (34.1)	3.084	.08
Superficial Lymphadenopathy	136 (72.0)	109 (73.6)	27 (65.9)	0.967	.33
Skin bleeding point	31 (16.4)	6 (4.1)	25 (61.0)	75.87	<.01
Neuropsychiatric Symptoms	57 (30.2)	22 (14.9)	35 (85.4)	75.76	<.01
Symptoms Multiple organ dysfunction (n ≥ 5)	35 (18.5)	8 (5.4)	27 (65.9)	77.75	<.01

SFTS = severe fever with thrombocytopenia syndrome.

APTT, D-dimer, BUN, and Cr level, respectively (all $P < .05$). Detailed data are given in Table 3.

3.2.4. Treatment and prognosis. After admission to hospital, patients with SFTS were treated with ribavirin if there was no contraindication. Patients with bacterial and fungal infections were treated with sensitive antibiotics. Physical cooling for patients with high fever, and the drug was used for fever if necessary. If there is obvious bleeding or significant decrease of platelet ($<30 \times 10^9$/L), fresh plasma and platelet were transfused. Patients were given albumin if serum albumin was less than 25 g/L. The granulocyte colony stimulation factor was used when absolute neutrophil count decreased. The basic treatment was also paid attention to the protection of important organs such as liver, brain, and kidney to prevent the occurrence of multiple organ dysfunctions. Of the 189 cases in this study, 148 patients in

Table 3

Analysis of laboratory indexes on admission to first diagnosis of SFTS patients.

Laboratory index	Total (N = 189)	General group (N = 148)	Severe group (N = 41)	value	*P* value
	$\bar{x} \pm s$				*t* value
ALB (g/L)	31.98 ± 5.25	32.14 ± 3.80	31.58 ± 8.02	0.405	0.69
GLU (mmol/L)	7.70 ± 3.60	6.69 ± 1.93	10.23 ± 5.32	−4.115	<0.01
APTT (s)	40.77 ± 11.85	37.84 ± 9.72	48.11 ± 13.69	−3.355	<0.01
FIB (g/L)	2.70 ± 0.86	2.77 ± 0.84	2.52 ± 0.91	1.063	0.29
	M (P25,P75)				Z value
WBC ($\times 10^9$/L)	3.7 (2.1,5.7)	3.6 (2.1,5.8)	3.9 (2.2,5.8)	−0.694	0.49
PLT ($\times 10^9$/L)	66.5 (41,85.3)	66.5 (42.0,87.3)	43.0 (34.3,68.8)	−2.778	<0.01
ALT (U/L)	79.5 (36.8,143.0)	63.5 (33.8,139.3)	98.0 (65.0,144.5)	−2.304	0.03
AST (U/L)	153.0 (65.8,310.5)	107.5 (58.0,266.8)	284.0 (112.5,548.3)	−3.361	<0.01
CK (U/L)	367.0 (153,916.5)	256 (130.9,671.5)	824 (415,2124.5)	−3.964	<0.01
CK-MB (U/L)	20.2 (13.1,34.5)	18.5 (11.9,31.8)	32.1 (18.1,38.0)	−2.225	0.03
LDH (U/L)	532.0 (331.0,923)	482.1 (302,792.2)	927 (467.5,1663.5)	−3.655	<0.01
HBDH (U/L)	336.5 (243.3,561)	315 (211.0,523.8)	436 (286.8,708.8)	−2.040	0.04
PT (s)	11.9 (10.8,12.9)	11.6 (10.8,12.5)	12.8 (11.6,13.7)	−2.609	0.01
TT (s)	17.6 (15.5,22.0)	17.3 (15.3,22.3)	18.2 (16.4,20.9)	−0.736	0.46
D dimmer (mg/L)	0.7 (0.4,2.3)	0.6 (0.4,1.3)	1.1 (0.6,3.9)	−2.026	0.04
BUN (μmol/L)	4.6 (3.6,6.2)	4.5 (3.6,5.6)	6.5 (3.3,9.9)	−2.040	0.04
Cr (μmol/L)	59.0 (53.5,73.0)	46.5 (49.1,70.0)	77.5 (63.8,120.5)	−3.071	0.01
LPS (U/L)	85.0 (52.1,136.0)	72.0 (44.1,131.5)	99.0 (68.2,183.5)	−1.474	0.14
AMS (U/L)	75.0 (53.1,118.0)	64.0 (51.8,115.0)	83.2 (69.3,120.1)	−1.796	0.07
CRP (mg/L)	6.7 (0.6,12.1)	5.1 (0.4,8.2)	11.2 (9.6,12.2)	−1.464	0.14
PCT (ng/mL)	0.2 (0.1,0.7)	0.1 (0.1,0.3)	0.7 (0.5,4.2)	−1.937	0.05

ALB = albumin, ALT = alanine aminotransferase, AMS = amylase, APTT = activated partial thromboplastin time, AST = aspartate transaminase, BUN = urea nitrogen, CK = creatine kinase, CK-MB = creatine kinase isoenzyme, Cr = creatinine, CRP = C-reactive protein, FIB = fibrinogen, GLU = glucose, HBDH = hydroxybutyrate dehydrogenase, LDH = lactate dehydrogenase, LPS = lipase, PCT = procalcitonin, PLT = blood platelet, PT = prothrombin time, SFTS = severe fever with thrombocytopenia syndrome, TT = thrombin time, WBC = white blood cell.

Table 4

Analysis of other factors affecting the prognosis of SFTS.

Factor	General group (N = 148)	Severe group (N = 41)	T/χ^2 value	*P* value
Sex			$\chi^2 = 8.64$	<.01
Males	57	27		
Females	91	14		
Age			$\chi^2 = 12.573$	<.01
(<60)	86	11		
(≥60)	62	30		
First visit days	7.68 ± 3.25	6.93 ± 2.33	t = 1.185	.24
Hospital stay	11.87 ± 4.48	5.40 ± 5.11	t = 5.436	<.01
Coinfection	43	19	$\chi^2 = 4.35$	.04
Past medical history	58	29	$\chi^2 = 12.86$	<.01
Peak of fever	39.07 ± 0.56	39.05 ± 0.61	t = 0.365	.72
Skin bleeding points	6	25	$\chi^2 = 75.87$	<.01
Neurological manifestations	22	35	$\chi^2 = 75.76$	<.01
symptoms Multiple organ dysfunction (n≥5)	8	27	$\chi^2 = 77.74$	<.01

SFTS = severe fever with thrombocytopenia syndrome.

the general group had a good prognosis, and 33 patients died, all of which occurred in critical recombination, with a mortality rate of 17.46%.

3.2.5. Other factor analysis. In addition, we also analyzed other factors affecting the prognosis of SFTS, including age (<60, ≥60), sex, past medical history, first visit days, hospital stay, coinfection, and heating peak. Univariate logistic regression analysis was performed between these factors and 23 other factors, including neurological manifestations, skin bleeding points, multiple organ dysfunction, PLT, ALT, AST, LDH, CK, CK-MB, HBDH, PT, APTT, D-dimer, fasting glucose, urea nitrogen, creatinine, etc. The results showed that the severity of the disease could be predicted by neurological manifestations and skin bleeding points, multiple organ dysfunctions, and previous medical history and fasting glucose elevation. The results showed that patients with neuropsychiatric symptoms, skin bleeding spots, multiple organ dysfunction, previous medical history, and elevated fasting blood glucose had predictive effects on the severity of the disease (all the $P < .05$) (Tables 4 and 5).

4. Discussion

SFTS is a new infectious disease and it is not specific in its clinical symptoms and signs. It is usually with unknown fever as the first symptom, attention should be paid to differentiate it from human granulocyte anaplasmosis, thrombocytopenic purpura, hemorrhagic fever with renal syndrome, etc.[2] It is found that the incidence of the disease has been increasing year by year in Shandong Province, and the incidence and mortality of severe cases have also increased when collecting the cases of SFTSV infection in Jinan Infectious Diseases Hospital affiliated to Shandong University in recent years. According to relevant data, the mortality of SFTS was as high as 13% to 24%,[10] which was consistent with the fatality rate of this study.

The onset of SFTS was urgent. According to the clinical occurrence process, development process, and dynamic changes of laboratory examination, the clinical course of SFTS was divided into 4 periods: latent period (approximately 1 wk), fever period (days 1–7 of onset), multiple organ dysfunction period (days 7–13 of onset), and decubation.[11] The multiple organ dysfunction periods, which may overlap with the fever period, is very important to the prognosis of the patient. The platelets will continue to decrease, liver, kidney, brain, heart, blood system, and other systemic organs can be involved during this period. It may be due to shock, respiratory failure, DIC and multiple organ failure died if it is not treated in time. Most cases of death occur at multiple organ dysfunction period, and the nondeath cases usually last 3 to 5 days and enter the recovery period.[12] The prognosis of the patients in decubation was good, which was consistent with the clinical report.

In laboratory examination, all patients were accompanied by leukocyte and platelet reduction in varying degrees. The results of liver function examination in some cases showed that AST was significantly higher than ALT, suggesting that there was serious liver function damage on admission. Compared with the 2 groups, the liver function in the common group returned to normal after liver protection treatment, and the ALT, AST, LDH, and other indexes in the severe group were significantly higher than those in the common group, and the rising speed was fast and the recovery was slow.[13] The decrease of ALB in both groups may be related to the injury of liver and kidney. BUN and Cr were normal in the general group, and increased in different degrees in the critical group, suggesting that mild and ordinary cases rarely cause renal parenchyma damage. In addition, SFTS as a disease caused by viral infection, CRP as the most commonly used inflammatory index was normal in the general group, slightly increased in the critical group, but less than 50 mg/L; PCT, as an early indicator of bacterial infection and viral infection, was slightly increased in both groups, and there was no significant difference. It may be related to interferon-γ blocking the production of PCT during virus infection.

Table 5

Logistic regression analysis of prognostic risk factors in 189 patients with SFTS.

Variable	OR value	*P* value	(95% CI)
Multiple organ dysfunction	34.048	<.01	7.740–149.782
Skin bleeding points	30.000	<.01	6.936–129.764
Neurological manifestations	24.083	<.01	6.064–95.642
Past medical history	3.792	.02	1.284–11.200
Fasting glucose	1.359	<.01	1.106–1.668

CI = confidence intervals, OR = odds ratios, SFTS = severe fever with thrombocytopenia syndrome.

The study showed that SFTS patients were mainly farmers (90.4%) which might be related to the field work, more exposure to ticks, and consistent with the epidemic season of arthropods. The patients with SFTS were more than 50 years old (79.5%), because the elderly were often associated with basic diseases, organ aging, and hypofunction that occurred with the increase of age; dysfunction of organs could occur in a short time when SFTS occurred.[14] Of the 189 confirmed cases, 84 were males and 105 were females. In the death cases, 21 (63.6%) of 33 patients were males, which was significantly higher than females, suggesting that the prognosis of older males (> 60 years old) was worse than that of older females. Moreover, SFTS have a pan-tropism that can destroy various tissues and cells of the human body and cause damage to the multiorgan system.[12] The more the number of affected organs, the more serious the condition, the prognosis was worse.[15] The results of this study also showed that the prognosis was very poor when multiple organ dysfunction (≥ 5 damaged organs) occurred in critical group.

The pathogenesis of SFTSV is not clear, existing studies have shown that SFTS viral load, ALT, AST, LDH, CK, T cell subsets and other laboratory parameters are related to the progression and severity of the disease. The degree of descent of T-lymphocytes, helper T-cells, and cytotoxic T-cells in the peripheral blood of patients with SFTS is of great significance for clinical treatment and prognosis.[13] The role of immune response in the course of SFTS virus infection and its effect on prognosis need to be further studied.[16]

At present, there are no specific drugs and methods for the treatment of SFTS, mainly using comprehensive therapy and symptomatic treatment. Most patients have a good prognosis, but once neuropsychiatric symptoms, bleeding tendency, and multiple organ dysfunctions were found in the elderly patients with basic diseases, the progress was rapid and the prognosis was poor. Therefore, it is of great significance for the treatment and prognosis of the patients to master the clinical characteristics, the changes of laboratory indexes, and the risk factors of the critically ill case.

Author contributions

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