MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2021; 27: e932836
DOI: 10.12659/MSM.932836

Received: 2021.04.22
Accepted: 2021.08.06
Available online: 2021.08.18
Published: 2021.11.08

Risk Factors of Neurological Complications in Severe Fever Patients with Thrombolytic Syndrome: A Single-Center Retrospective Study in China

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Financial support: This study was supported by the Medical and Health Science and Technology Development Program of Shandong Province (grant no. 202003081074)
Conflict of interest: None declared

Background: Severe fever with thrombocytopenia syndrome is a serious insect-borne infectious disease caused by the Huaiyangshanbanyang virus. We conducted a retrospective study to identify risk factors for neurological complications caused by the virus.

Material/Methods: We included 121 patients who had severe fever with thrombocytopenia syndrome and were admitted to our hospital from 2013 to 2020. Patients' laboratory test results and clinical data were collected. Univariate and multivariate regression were used for statistical analysis.

Results: Patients with neurological complications had higher mortality rates and longer hospital stays and disease duration than did patients without neurological complications. The neurological symptoms with the highest incidence rates were involuntary tremors (tongue and mandible), cognitive disorder, and limb tremors. Patients with neurological complications had a higher incidence of abnormal heart rhythms. Subcutaneous bleeding, pulmonary rales, percentage of neutrophils, increased lactate dehydrogenase and C-reactive protein levels, and decreased chloride ion concentration were closely related to the occurrence of neurological complications. The significant decrease in chloride ion concentration within 1 to 5 days of disease onset may be a risk factor for predicting the occurrence of neurological complications in patients with severe fever with thrombocytopenia syndrome.

Conclusions: Early monitoring of subcutaneous bleeding, pulmonary rales, electrocardiogram changes, and biochemical indicators in patients with severe fever with thrombocytopenia syndrome can predict the occurrence of neurological complications.

Keywords: Central Nervous System • Retrospective Studies • SFTS Phlebovirus

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/932836

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Background

Severe fever with thrombocytopenia syndrome (SFTS) is an acute fatal infectious disease caused by the Huaiyangshanbanyang virus (BHAV), a *Bandavirus* from the genus of the *Phenuiviridae* family [1,2]. *Haemaphysalis longicornis* and *Rhipicephalus microplus* are possible vectors of SFTSV and could transmit the pathogen through tick bites [3-5]. Direct contact with the blood of a sick person can also transmit the virus [6,7]. *Haemaphysalis longicornis* was found to be present in 10 countries, predominantly in eastern Asia, the United States, Australia, and New Zealand. At least 30 human pathogens, including BHAV, were associated with *Haemaphysalis longicornis* [8]. Previous studies reported that the incidence of SFTS is related to temperature, precipitation, land cover, vegetation, and other factors [9]. Most patients with SFTS work in shrublands and farmlands [10]. The virus can be found in the serum of animals such as dogs, sheep, chickens, pigs, and bats [11-13]. The presence of ticks in the environment or contact with tick-carrying livestock or bats also increases the risk of the disease. The peak incidence of SFTS is from April to June (in the Northern Hemisphere), and sporadic cases also occur in summer and autumn.

In humans, the clinical manifestations include fever, chills, anorexia, nausea, vomiting, abdominal pain, diarrhea, lymphadenopathy, and reduced leucocyte and platelet counts; the disease duration could be up to 49 days [14]. A previous meta-analysis reported a case mortality rate of 5% to 40% and an average mortality rate of 12.2% [15,16]. Relevant studies have been conducted in more than 20 provinces in China, with more than 5000 cases reported from 2009 to 2016 [17]. Patients with SFTS have also been reported in Japan, South Korea, Vietnam, and the United States [18-21]. Because of the heavy burden, lack of vaccines and effective therapies, and high mortality rates, the disease has become an important health issue.

The pathogenesis of neurological symptoms induced by BHAV is still unclear. Studies have shown that cytokines such as monocyte chemotactic protein-1 and interleukin-8 play an important role in the pathogenesis of viral invasion in the nervous system [22]. It has been confirmed that high mortality is closely related to neurological complications [23]. Early diagnosis and treatment of neurological complications may help to reduce mortality. There are many studies on the death-related risk factors of SFTS, but there are few studies on the risk factors of neurological complications. Therefore, we collected the clinical information of patients with SFTS to analyze the risk factors for neurological complications with the goal of detecting the neurological complications as soon as possible.

Material and Methods

Sample Size

A total of 121 patients with SFTS who were admitted to Weifang Yidu Central Hospital, Shandong, between 2013 and 2020 were enrolled in our study. Patients with suspected cases of SFTS were diagnosed with the disease if they fulfilled the following 2 criteria: (1) history of working, living, or traveling in hilly, forested, and mountainous areas during the epidemic season (from April to June) or with a history of being bitten by ticks 2 weeks before the disease onset, and (2) patients with the above mentioned epidemiological history who exhibited fever (armpit temperature above 37°C) and decreased peripheral blood platelet (reference range: 100-400×10^9/L) and white blood cell counts (reference range: 4-10×10^9/L). Blood samples were obtained from patients with suspected cases, and those who tested positive for the novel Bunyavirus nucleic acid were diagnosed with SFTS. The SFTS nucleic acid quantitative detection kit was used, and the polymerase chain reaction fluorescence probe method was used for detection, which was performed in the Weifang Center for Disease Control and Prevention. Using the presence or absence of neurological complications as a guide, patients with confirmed infection were divided into a group with neurological complications and a group without neurological complications. The experimental procedure is shown in **Figure 1**.

Data Collection

The demographic factors, date of illness onset, admission date, death date, disease outcome, clinical presentations, physical examination, and laboratory parameters of these patients were retrospectively collected. Their case data were entered into the designed EpiData database, and were exported into an Excel spreadsheet.

Statistical Validation

Statistical analysis included the use of the chi-squared test and *t* test (SPSS version 26, IBM, Armonk, NY, USA). Univariate logistic regression was performed on test indicator variables to select the indicators with statistical significance, and then a correlation analysis was performed on these indicators. The correlation was greater than 60%, and only 1 of the 2 indicators with statistical significance was retained. The variables of the best model were selected, and binary multivariate logistic regression was performed. The input method was selected. The inclusion and exclusion criteria were <0.05 and >0.1, respectively, and the number of iterations was 20.

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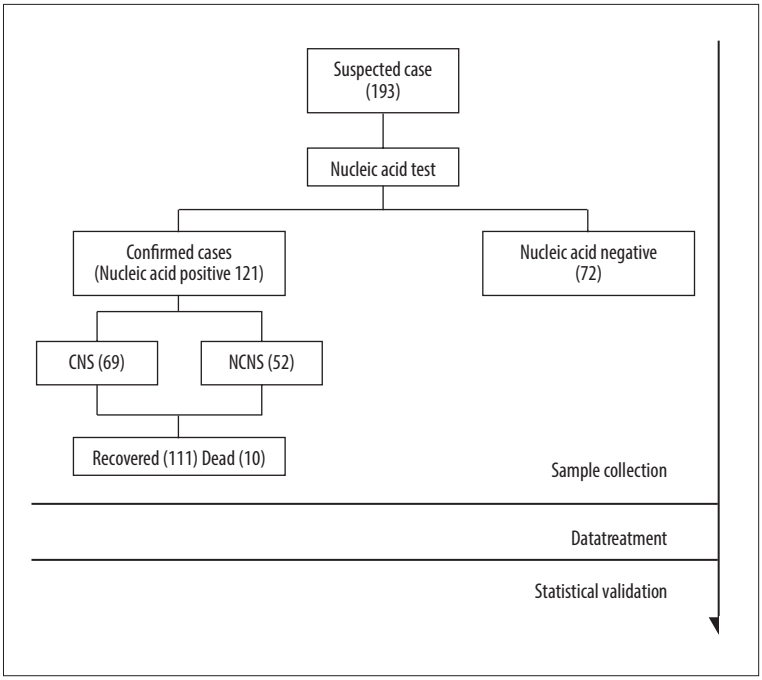

Figure 1. Research flowchart. Severe fever with thrombocytopenia syndrome nucleic acid tests were performed on the first or second day of admission. During hospitalization, ECG monitoring was performed daily and blood pressure and pulse were recorded. Clinical symptoms and signs of patients were recorded daily, with the focus on the observation of neurological symptoms. During the first and second weeks of hospitalization, routine blood, biochemical, urine, coagulation, and inflammatory indexes were checked daily. During the third and fourth weeks of hospitalization, laboratory tests were performed according to the patient's condition. (Made by Microsoft office Word 2007, Microsoft USA).

Table 1. Demographic characteristics of patients with severe fever with thrombocytopenia syndrome.

	CNS (n=69)	WCNS (n=52)	*P*
Male/Female	30/39	22/30	0.9
Age (min/max)	65 (39, 95)	57 (15, 83)	<0.01
Location (Qingzhou/Linqu)	21/46	14/38	0.6
Disease course, mean (min/max)	18.3 (4,34)	17.3 (8,30)	0.33
Hospital stay, mean (min/max)	12.5 (1, 27)	11.6 (5, 21)	0.31
Death	10 (14.5%)	0 (0)	0.01
History of tick bites	5 (7.2%)	9 (17.3%)	<0.01
Hypertension	18 (26.1%)	9 (17.3%)	0.23
Diabetes	9 (13.0%)	2 (3.8%)	0.73
Heart disease	10 (14.5%)	5 (9.6%)	0.19
Cerebrovascular disease	6 (8.7%)	2 (3.8%)	0.25

NC – group with neurological complications; WNC – group without neurological complications

Results

Demographic Characteristics

From 121 patients aged between 15 and 95 years, a total of 69 patients were diagnosed with neurological complications, of which 10 patients died from the disease, while the remaining 52 had less severe conditions. The mean age of the patients with neurological complications was significantly higher than that of patients without neurological complications; however, there was no significant difference in sex between the 2 groups. Patients in the neurological complications group had the disease between 4 and 34 days, but hospitalization ranged from 1 to 27 days. The median time to onset of neurological symptoms was 7.4 days. The later the neurological complications appeared, the longer the patient's hospital stay and course of disease ($P<0.01$). The number of patients with a confirmed history of tick bites in the group without neurological complications was significantly higher than that in the neurological complication group ($P<0.01$). It appeared that there was no significant difference in the manifestation of neurological disorders in patients having comorbidities, such as hypertension, type 2 diabetes, heart disease, or cerebrovascular disease (**Table 1**).

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Table 2. Clinical symptoms and signs in patients with severe fever with thrombocytopenia syndrome.

	Total (n=121)	CNS (n=69)	WCNS (n=52)	*P*
Headache	49 (40.5)	26 (37.7)	23 (44.2)	0.47
Chills	82 (67.8)	47 (68.1)	35 (67.3)	0.93
Muscle soreness	78 (64.5)	41 (59.4)	37 (71.2)	0.18
Joint pain	50 (41.3)	30 (43.5)	20 (38.5)	0.58
Nausea and vomiting	81 (66.9)	51 (73.9)	30 (57.7)	0.06
Lack of appetite	118 (97.5)	68 (98.6)	50 (96.2)	0.40
Abdominal pain	24 (19.8)	15 (21.7)	9 (17.3)	0.55
Diarrhea	40 (33.1)	29 (42.0)	11 (21.2)	0.02
Cough	44 (36.4)	34 (49.3)	10 (19.2)	<0.01
Expectoration	35 (28.9)	29 (42.0)	6 (11.5)	<0.01
Pulmonary rales	54 (44.6)	41 (59.4)	13 (25.0)	<0.01
Subcutaneous bleeding	91 (75.2)	58 (84.1)	33 (63.5)	<0.01
Superficial lymphadenopathy	46 (38.0)	40 (58.0)	6 (11.5)	0.01
Hemoptysis	3 (2.5)	2 (2.9)	1 (1.9)	0.73
Gastrointestinal bleeding	5 (4.1)	5 (7.2)	0 (0.0)	0.05
Sinus tachycardia	7 (5.8)	6 (8.7)	1 (1.9)	0.11
Sinus bradycardia	16 (13.2)	13 (18.8)	3 (5.8)	0.04
Premature beat	13 (10.7)	11 (15.9)	2 (3.8)	0.03
Conduction block	4 (3.3)	3 (4.3)	1 (1.9)	0.46
Atrial fibrillation	12 (9.9)	10 (14.5)	2 (3.8)	0.05
Abnormal T wave	19 (15.7)	17 (24.6)	2 (3.8)	<0.01

CNS – group with neurological symptoms; NCNS – group with no neurological symptoms.

Clinical Symptoms, Signs, and Electrocardiogram Results

Patients with neurological complications specifically refer to those who developed one or more of the following symptoms: (1) muscle and limb tremors (involuntary muscle tremors of the tongue, jaw, or limbs); (2) cognitive impairment, including decrease in directional force, memory, and computing power, unresponsiveness, inability to answer questions accurately, inability to cooperate with a simple command, inability to perform fine motor movement and aphasia, and verbal communication barriers (such as difficulty speaking, finding words, and naming objects); (3) consciousness-related problems, including drowsiness, lethargy, coma, and delirium; and (4) convulsions or seizures. Among all patients in this study with neurological disorders, 58 (84.1%) had muscle tremors, 49 (71%) had limb tremors, 28 (40.6%) had restlessness, 50 (72.5) had cognitive impairment, 26 (37.7%) had confusion, 5 (7.2%) had convulsions, 16 (23.2%) had drowsiness, 3 (4.3%) had lethargy, 18 (26.1%) had delirium, and 13 (18.8%) had coma. Ten (8.3%) patients with neurological complications died.

Among other clinical symptoms, gastrointestinal symptoms and subcutaneous bleeding commonly occurred in both groups. The gastrointestinal symptoms were gradually relieved 2 weeks after onset. Subcutaneous bleeding was manifested as petechiae or petechiae at the injection site, which gradually disappeared after the patients were discharged from the hospital.

Electrocardiogram (ECG) abnormalities, such as sinus bradycardia, premature beats, atrial fibrillation, and T-wave abnormalities, were observed in a greater number of patients with neurological complications than in those without neurological complications. These abnormalities were mainly manifested as cardiac rhythm abnormalities.

The probability of patients with neurological complications of having diarrhea, cough, sputum, subcutaneous bleeding, lymph node enlargement, pulmonary rale, gastrointestinal bleeding, sinus bradycardia, premature beats, atrial fibrillation, and T-wave abnormalities was significantly higher than

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Table 3. Associations of clinical manifestation and laboratory parameters with neurological symptoms by multivariate logistic regression analysis.

	Univariate analysis			Multivariate analysis		
	OR	*P*	95% CI	OR	*P*	95% CI
Diarrhea	2.7	0.02	1.19, 6.13	2.67	0.07	0.94, 7.64
Cough	4.08	<0.01	1.77, 9.41	0.74	0.75	0.11, 4.84
Expectoration	5.56	<0.01	2.10, 14.75	5.38	0.11	0.68, 42.83
Subcutaneous bleeding	4.39	<0.01	1.99, 9.68	3.18	0.02	1.16, 8.71
Superficial lymphadenopathy	3.04	0.01	1.29, 7.15	1.5	0.48	0.49, 4.62
Pulmonary rales	10.58	<0.01	3.99, 28.06	5.71	<0.01	1.76, 18.48
Gastrointestinal bleeding	4.11	1	2.14, 7.64	1.1	1	0.98, 1.18
Sinus tachycardia	3.79	0.05	1.02, 14.09	2.37	0.33	0.42, 13.32
Premature beat	4.74	0.05	1.00, 22.42	0.82	0.86	0.10, 6.94
Atrial fibrillation	4.24	0.07	0.89, 20.25	1.52	0.7	0.19, 12.20
Abnormal T wave	8.17	<0.01	1.80, 37.21	4.38	0.11	0.70, 27.25
N%	1.02	<0.01	1.01, 1.03	1	0.01	1.01, 1.10
M	1	0.05	0.97, 1.02	3.3	0.42	0.18, 61.27
PLT	0.99	<0.01	0.98, 1.00	1	0.33	0.99, 1.00
LDH	1	<0.01	1.00, 1.00	1.01	<0.01	1.00, 1.01
CK	1	<0.01	1.00, 1.00	1	0.15	1.00, 1.00
CRP	1.11	<0.01	1.07, 1.16	1.29	0.01	1.08, 1.55
Cl	0.93	<0.01	0.90, 0.96	0.82	0.01	0.70, 0.95
PT	1.23	0.05	1.00, 1.50	1.36	0.2	0.85, 2.16
TT	1.22	0.01	1.05, 1.43	1.36	0.2	0.85, 2.16
ALB	0.94	<0.01	0.91, 0.97	1.09	0.45	0.88, 1.34

N – neutrophile granulocyte; M – mononuclear leucocytes; PLT – platelet count; LDH – lactic dehydrogenase; CK – creatinine kinase; CRP – C-reactive protein; Cl – chloride; PT – prothrombin time; TT – thrombin time; ALB – albumin.

that of patients without neurological complications (**Table 2**). Subcutaneous bleeding and pulmonary rale were closely related to the occurrence of neurological complications (**Table 3**).

Laboratory Indicators

Significant differences were observed between the 2 groups in routine laboratory results, including percentage of lymphocytes, erythrocyte count, platelet count, percentage of neutrophils and monocytes, biochemical measurements, such as aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme, sodium (Na), chloride (Cl), calcium (Ca), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), direct bilirubin, and serum globulin. Significant differences were also observed in coagulation, including prothrombin time (PT), activated partial prothrombin time (APTT), and thrombin time (TT) and in other laboratory test results, such as C-reactive protein (CRP), procalcitonin, and brain natriuretic peptide (**Table 4**). Among them, the decrease in chloride (Cl) and increase in neutrophil percentage, LDH, CRP were significant (**Table 3**).

We selected several routine blood, inflammatory, myocardial enzyme, liver function, renal function, electrolyte, and routine blood coagulation indexes and drew a line chart (**Figure 2**). The red broken line represents the group with neurological complications, while the blue line represents the group without neurological complications. The 2 groups showed similar trends in the results of routine blood tests. In the routine blood test results, the neutrophil count increased 1 to 15 days after disease onset, while the lymphocyte count increased 15 days after disease onset. The platelet count decreased significantly 1 to

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Table 4. Laboratory parameters of patients with severe fever with thrombocytopenia syndrome.

	CNS (mean±SD)	NCNS (mean±SD)	*P*
WBC	4.92±2.72	4.61±2.81	0.12
N%	62.65±16.77	57.21±17.89	<0.01
N	3.2±2.16	2.92±2.54	0.11
LY%	26.36±12.72	31.34±14.22	<0.01
LY	1.21±0.86	1.28±0.65	0.25
M	0.53±0.56	0.46±0.33	0.03
M%	10.31±6.15	10.48±6.03	0.71
RBC	4.06±0.59	4.2±0.52	<0.01
HGB	126.05±18.61	124.45±18.82	0.24
PLT	95.56±88.2	116.94±75.11	<0.01
AST	239.2±549.51	144.05±231.75	<0.01
LDH	673.21±694.88	398.57±198.93	<0.01
CK	602.23±1017.12	266.66±441.93	<0.01
CK-MB	36.1±44.36	24.22±25.94	<0.01
CRP	16.48±26.94	3.18±5.64	<0.01
PCT	0.37±0.67	0.18±0.39	<0.01
K	3.87±0.52	3.89±0.46	0.45

	CNS (mean±SD)	NCNS (mean±SD)	*P*
Cl	98.35±5.21	100.13±4.17	<0.01
Na	136.83±5.41	138.57±4.1	<0.01
Ca	2.09±0.19	2.72±8.85	0.26
BUN	4.15±2.22	5.57±28.27	0.43
CR	57.78±36.31	56.92±11.84	0.65
UA	183.44±91.65	214.92±92	<0.01
PT	11.43±2.76	10.62±1.21	0.01
APTT	47.5±18.18	39.77±7.81	<0.01
TT	17.51±3.66	15.88±3.06	<0.01
ALT	101.28±142.27	104.89±132.7	0.71
TBIL	15.86±8.37	14.63±8.25	0.06
DBIL	6.98±4.84	5.17±3	<0.01
ALB	34.69±6.11	36.72±4.96	<0.01
GLO	31.15±5.94	30.1±6.1	0.03
GGT	86.46±113.01	69.79±72.54	0.02
ALP	100.51±70.22	77.89±47.47	<0.01
BNP	3020.91±6040.79	1007.84±2749.43	<0.01

CNS – group with neurological symptoms; NCNS – group with no neurological symptoms; WBC – white blood cells; N – neutrophile granulocytes; L – lymphocytes; M – mononuclear leucocytes; RBC – red blood cells; HGB – hemoglobin; PLT – platelet count; AST – aspartate aminotransferase; LDH – lactic dehydrogenase; CK – creatinine kinase; CK-MB – creatine kinase-MB; CRP – C-reactive protein; PCT – procalcitonin; K – potassium; Na – sodium; Cl – chloride; Ca – calcium; BUN – blood urea nitrogen; CREA – creatinine; UA – uric acid; PT – prothrombin time; APTT – activated partial thromboplastin time; TT – thrombin time; ALT – alanine aminotransferase; TBIL – total bilirubin; DBIL – direct bilirubin; TP – total protein; ALB – albumin; GLO – globulin; GGT – gamma-glutamyl transferase; ALP – alkaline phosphatase; BNP – brain natriuretic peptide.

15 days after disease onset and gradually returned to normal. Among myocardial enzymes, the level of CK increased earlier than the level of LDH and AST in the group with neurological complications, and the levels of liver enzymes increased later than those of myocardial enzymes. The concentrations of Na, Cl, and Ca in both groups decreased significantly within 1 to 15 days after disease onset and then gradually returned to normal. The decrease in Cl concentration within 1 to 5 days after disease onset was closely related to the occurrence of neurological complications (**Table 5**). Among the coagulation indexes, the APTT and TT in patients with neurological complications were significantly higher than those in patients without neurological complications within 1 to 15 days of disease onset, suggesting that the coagulation function was affected. No significant difference was observed in blood urea nitrogen and creatinine levels between the 2 groups; however, the creatinine level in the group with neurological complications was significantly lower than that in the group without neurological complications 15 days after disease onset.

Discussion

SFTS was first reported in 2008 in Huaiyang Mountain, Henan Province, China [24]. The pathogen was isolated from the patient's serum in 2010 and was then named as SFTS virus, which has since been renamed Huaiyangshanbanyang virus [2]. In addition to indirect effects induced by a cytokine storm, autopsy results in patients with SFTS with neurological symptoms suggested that SFTSV nucleocapsid protein-positive immunoblasts were detected in all organs examined, including in the central nervous system and vascular lumina of each organ. This indicates that the deterioration of central nervous system function can also be directly caused by BHAV infection [25].

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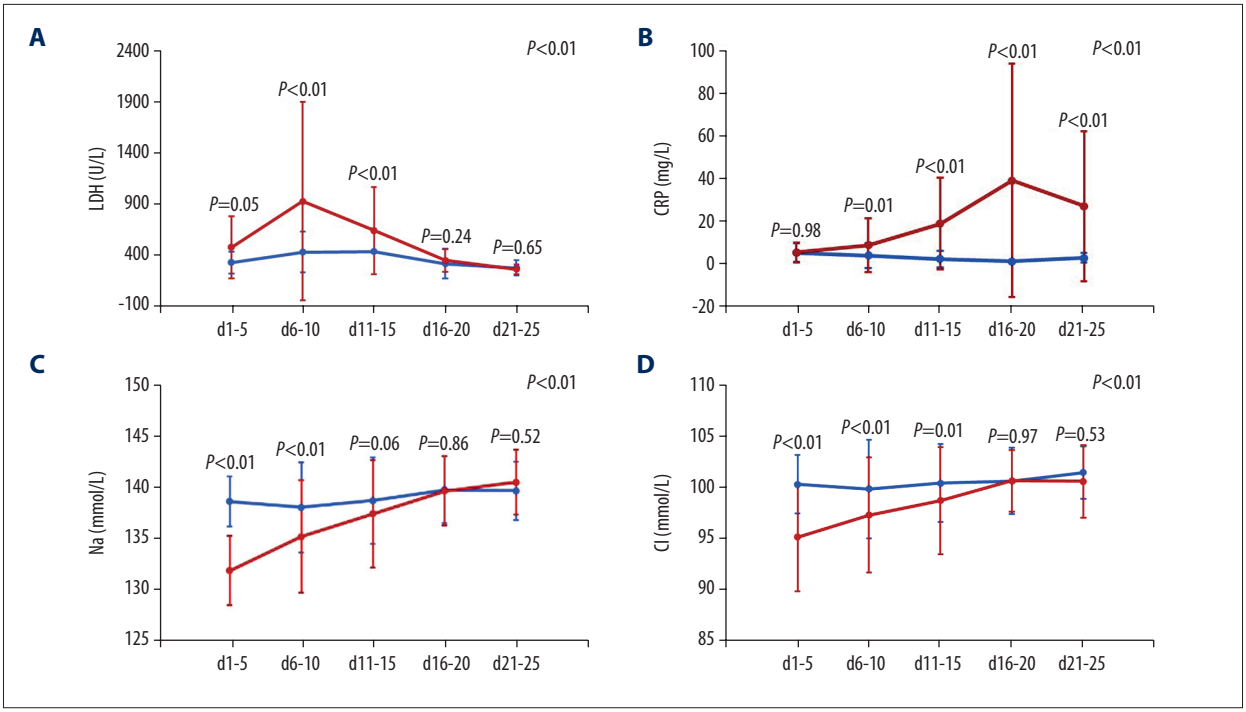

Figure 2. (**A-D**) The broken-line graph of lactic dehydrogenase, C-reactive protein, sodium, and chloride in confirmed cases of patients with severe fever with thrombocytopenia syndrome. The red broken line represents the group with neurological complications, and the blue line represents the group without neurological complications. (Made by Microsoft office Excel 2007, Microsoft USA).

Table 5. Association between laboratory parameters in 1 to 5 days of disease onset with neurological symptoms by multivariate logistic regression analysis.

	Univariate analysis			Multivariate analysis		
	OR	*P*	95% CI	OR	*P*	95% CI
M%	0.85	0.04	0.73, 0.99	1.19	0.5	0.72, 1.94
PLT	0.99	0.05	0.97, 1.00	1	0.93	0.97, 1.03
AST	1	0.14	1.00, 1.01	1.02	0.58	0.99, 1.02
LDH	1	0.16	0.99, 1.01	1	0.82	0.99, 1.02
Cl	0.77	0.02	0.62, 0.97	0.7	0.02	0.52, 0.96
Na	0.74	0.02	0.59, 0.94	0.77	0.51	0.35, 1.69
Ca	0	0.05	0.00, 0.89	0	0.09	0.00, 3.15
CREA	1.06	0.04	1.00, 1.02	1.14	0.12	0.97, 1.33
APTT	1.22	0.11	0.95, 1.57	1.42	0.33	0.71, 2.85
TT	2.52	0.05	0.99, 6.41	4.13	0.41	0.14, 121.15

CI – confidence interval; OR – odds ratio; M – mononuclear leucocyte; PLT – platelet; AST – aspartate aminotransferase; LDH – lactic dehydrogenase; Na – sodium; Cl – chloride; Ca – calcium; CREA – creatinine; APTT – activated partial thromboplastin time; TT – thrombin time.

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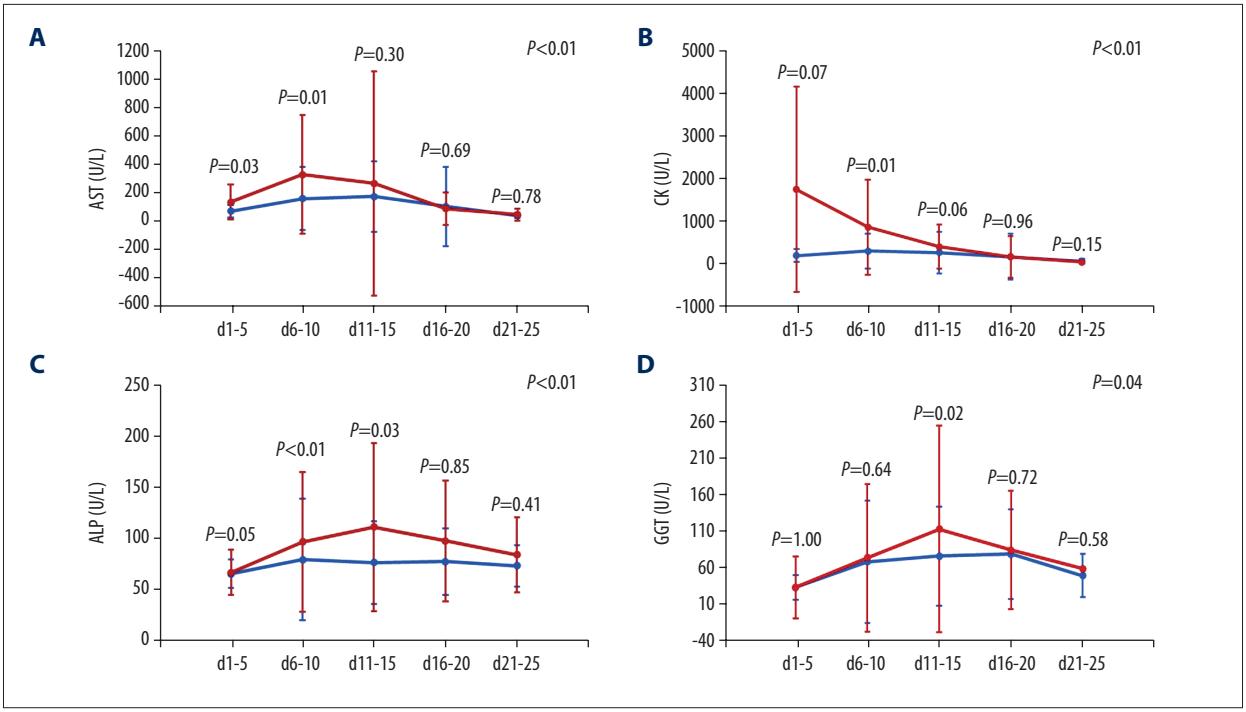

Figure 3. (**A-D**) The broken-line graph of aspartate aminotransferase, creatinine kinase, alkaline phosphatase, and gamma-glutamyl transferase in confirmed cases of patients with severe fever with thrombocytopenia syndrome. The red broken line represents the group with neurological complications, and the blue line represents the group without neurological complications. (Made by Microsoft office Excel 2007, Microsoft USA).

The incidence of neurological complications associated with SFTS was 57.02% in the present study. The estimated percentage of neurological complications has been reported to range between 19% and 76% [22,26,27], which was consistent with the results of our study. We found that the neurological symptoms with the highest incidence rates were involuntary tremors (tongue and mandible), cognitive disorders, and limb tremors. In addition, there were consciousness disorders, epilepsy, coma, and other more serious symptoms. The symptoms of muscle limb tremors in patients with SFTS have been found by many researchers, and these symptoms often occur before the severe disturbance of consciousness [23,28]. In the present study, the incidence of these symptoms was more than 70%, so we added the above contents in the diagnosis of neurological complications, which was conducive to the early detection of neurological damage. Cui et al found that 19.1% of patients were clinically diagnosed with encephalitis during hospitalization, and the common mental abnormalities recorded included mental vagueness, irritability, convulsion, lethargy, and coma, excluding muscle and limb tremors; therefore, the incidence of neurological complications in their study was lower than that in our study [26]. However, we believe that encephalitis is not a neurological complication but is a kind of nervous system damage syndrome caused by systemic multiple organ damage.

Previous studies have showed that cerebrospinal fluid samples of patients, craniocerebral magnetic resonance imaging, and electroencephalogram have limited value in clinical application in the diagnosis of neurological complications [26,28]. Moreover, patients with disturbance of consciousness are often unable to complete these examination methods. We suggest that the onset of muscle tremors, limb tremors, cognitive impairment, and other symptoms should be considered as neurological complications, rather than waiting for a patient to develop serious symptoms or loss of consciousness. We also suggest that the basis of diagnosis cannot completely rely on examinations.

On the other hand, we found that patients with neurological complications were more likely to have lymph node enlargement, diarrhea, cough, expectoration, pulmonary rale, subcutaneous bleeding, and gastrointestinal bleeding. These symptoms mainly involved the respiratory system and the blood clotting system. Additionally, we found that spots of subcutaneous bleeding and pulmonary rales may indicate neurological complications, findings that have not been mentioned in previous studies. Thus, if a patient is suspected of having neurological complications, observing the extent of subcutaneous bleeding and pulmonary rales may be helpful in the diagnosis.

In addition, we also found that patients with neurological complications had a higher rate of sinus bradycardia, premature

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beats, atrial fibrillation, and T-wave abnormalities on ECG during hospitalization. Among them, sinus bradycardia, premature beats, and atrial fibrillation were all abnormal cardiac rhythms. All patients with abnormal ECG findings had no previous history of heart disease before they developed SFTS, and their ECG parameters gradually returned to normal after they recovered from SFTS, without any sequelae. This suggests that damage to the nervous system may affect changes in heart rhythm.

Similarly, liver enzyme, myocardial enzyme, and coagulation indexes also changed significantly in patients with neurological complications in the present study. Cl, LDH, and CRP were observed to be closely related to the occurrence of neurological complications, which was not completely consistent with the conclusions of previous studies [26]. According to previous research, the clinical course of SFTS is divided into 4 periods: a latent period (approximately 1 week), fever period (days 1-7 of onset), multiple organ dysfunction period (days 7-13 of onset), and decubation [29]. In the present study, the LDH of patients with neurological complications reached the peak at the multiple organ dysfunction period and return to normal at decubation, while the difference in LDH in the other group was mild (**Figure 2**). Similar differences can be seen in levels CK, AST, ALP, and GGT (**Figure 3**), and all of these indicators are risk factors associated with the severity of SFTS [30]. Contrarily, we found that CRP, which is commonly seen in acute infections or trauma, increased gradually and reached a peak at decubation in the neurologic complications group (**Figure 2**). This indicated that infection occurred in the recovery period of SFTS. The decrease in Na, Cl, and Ca occurred during the fever period and returned to the normal range during the recovery period (**Figure 2**). As for electrolyte disorders caused by SFTS, previous studies have confirmed that patients with SFTS usually have hyponatremia [31], which agrees our results. Of note, we also pointed out hypocalcemia and hypochloremia and when these changes took place. Furthermore, hypochloremia can be used as an indicator for early prediction of neurological complications, and this can provide a laboratory diagnostic basis for early diagnosis of the occurrence of nervous system complications.

Current treatments for SFTS include convalescent plasma [32], favipiravir [33,34], and ribavirin [35]. There is no specific drug for the treatment of nervous system symptoms. Gamma globulin is the first choice for the treatment of acute and chronic neuropathy [36]. Moreover, gamma globulin can affect the differentiation process of Schwann cells in the nervous system and improve their regenerative potential [37]. Studies have also shown that gamma globulin is effective in treating encephalitis caused by various viruses, such as the West Nile virus [38]. Therefore, gamma globulin may have a certain therapeutic effect on the neurological complications induced by BHAV, which needs to be confirmed in future studies.

Relatively mild symptoms, such as muscle tremors, limb tremors, and cognitive impairment, have been overlooked in many studies of neurological complications. However, these are actually the most common neurological symptoms of SFTS. We included these symptoms in the scope of neurological complications, and this is where we differed from previous studies. In previous studies, neurological complications were only diagnosed when patients suffered from disturbances of consciousness, coma, or convulsions. In addition, we found abnormalities in the cardiac rhythm in patients with neurological complications and that hypochloremia can be used as an early predictor of neurological complications.

Limitations of our study were that it was a retrospective study and lacked a rigorous experimental design. The diagnosis of neurological symptoms depended entirely on the judgment of the clinician, which may have resulted in delays in the detection of neurological symptoms in some patients.

Conclusions

In conclusion, the early diagnosis of SFTS with neurological complications cannot rely only on the observation of muscle tremors, limb tremors, and cognitive impairment. The occurrence of nervous system complications should also be indicated by the manifestations of subcutaneous bleeding points and lung rales. In addition, a change of ECG rhythm, increase of LDH, and significant decrease of Cl can be used as a basis for the early diagnosis of neurological complications.

Acknowledgements

The authors gratefully acknowledge the laboratory technical support for the SFTS antibody detection by the Shandong Center for Disease Control and Prevention as well as the Qingzhou Center for Disease Control and Prevention. Useful suggestions provided by Professor Jie Li of the Department of Infectious Diseases, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University are also acknowledged.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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