MAJOR ARTICLE

Clinical Progress and Risk Factors for Death in Severe Fever with Thrombocytopenia Syndrome Patients

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Background. Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by the SFTS virus (SFTSV) with an average fatality rate of 12%. The clinical factors for death in SFTS patients remain unclear.

Methods. Clinical features and laboratory parameters were dynamically collected for 11 fatal and 48 non-fatal SFTS cases. Univariate logistic regression was used to evaluate the risk factors associated with death.

Results. Dynamic tracking of laboratory parameters revealed that during the initial fever stage, the viral load was comparable for the patients who survived as well as the ones that died. Then in the second stage when multi-organ dysfunction occurred, from 7–13 days after disease onset, the viral load decreased in survivors but it remained high in the patients that died. The key risk factors that contributed to patient death were elevated serum aspartate aminotransferase, lactate dehydrogenase, creatine kinase, and creatine kinase fraction, as well as the appearance of CNS (central nervous system) symptoms, hemorrhagic manifestation, disseminated intravascular coagulation, and multi-organ failure. All clinical markers reverted to normal in the convalescent stage for SFTS patients who survived.

Conclusions. We identified a period of 7–13 days after the onset of illness as the critical stage in SFTS progression. A sustained serum viral load may indicate that disease conditions will worsen and lead to death.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by severe fever with thrombocytopenia virus (SFTSV) in China [1]. The clinical presentations of SFTS patients are fever, thrombocytopenia, leukocytopenia, gastrointestinal symptoms, neural symptoms, and bleeding tendency. Liver and cardiac enzymes are commonly elevated in SFTS patients, indicating impairments in the liver and heart, respectively [1, 2]. In critically ill SFTS patients, clinical conditions can deteriorate rapidly and end in multi-organ failure and death [2]. However, there has been a lack of a systemic analysis of the disease progression of SFTS. More importantly, this disease has a mortality rate of up to 30% [1], but only limited data exist on the possible risk factors for death [3].

To better understand the disease progression of SFTS and identify the clinical features that are related to the fatal outcome of severely ill patients, a dynamic study was conducted on 59 SFTS cases, including 11 patients who died and 48 survivors, to track clinical signs and laboratory findings along the entire disease course, from the onset of illness to the endpoints of death or full recovery. Risk factor analysis was performed to reveal important clinical features statistically associated with the fatal outcome of SFTS patients.

MATERIALS AND METHODS

Identification of SFTS Patients

All 59 confirmed SFTS patients involved in this study were admitted to the Infectious Diseases Hospital affiliated with Shandong University in China from 1

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May 2008 to 31 July 2011. All SFTS cases were clinically defined according to the presence of the following 2 conditions: (1) acute fever of ≥e38°C with thrombocytopenia, and (2) laboratory-confirmed SFTSV infection by the use of a certified clinical SFTS real-time PCR diagnosis kit (SFDA Registration No. 340166, China). In this study, multiple organ dysfunction (MOD) is defined by the existence of two or more of the following conditions: (1) hypoxia requiring respirator-assisted ventilation for at least 3–5 days; (2) serum bilirubin ≥2–3 mg/dL or liver function tests ≥twice normal; (3) oliguria ≤479 mL/24 hours or rising creatinine (≥2–3 mg/dL); (4) ileus with intolerance to enteral feeding >5 days; (5) PT (prothrombin time) and PTT (partial thromboplastin time) increase >25% or platelet counts <50–80 000; (6) confusion, mild disorientation; and (7) decreased ejection fraction or capillary leak syndrome [4, 5]. Multiple organ failure (MOF) is defined by the existence of two or more of the following conditions: (1) progressive ARDS (adult respiratory distress syndrome) requiring PEEP (positive end-expiratory pressure) > 10 cm H_2O and $FIO_2 > 0.50$; (2) clinical jaundice with bilirubin ≥8–10 mg/dL; (3) renal dialysis; (4) stress ulcers requiring transfusion, acalculus cholecystitis; (5) disseminated intravascular coagulation (DIC); (6) progressive coma; and (7) hypodynamic response refractory to inotropic support [4, 5].

Dynamic Collection of Sera Samples

A series of blood samples was collected from clinically diagnosed SFTS patients every other day from the time of hospital admission. The onset of illness was determined as the date when the patients had an acute fever of ≥38°C and thrombocytopenia. Platelet counts and white blood cell counts were determined by automatic blood cell analysis. Serum biological parameters were acquired with automated analytical instruments. The results of dynamic blood and serum analyses were presented according to the days after the onset of the disease, which is useful when observing the entire course of the disease.

Real-Time RT-PCR Detection of Serum Viral Load

Viral RNA was extracted from serum samples using a QIAamp viral RNA kit (Qiagen) according to the manufacturer's instructions. A one-step, multiplex, real-time RT-PCR assay was performed using a certified, real-time PCR kit for the clinical diagnosis of SFTS patients (SFDA Registration No 340166, China). The kit is based on the detection of the viral S genomic segment, which encodes the nucleocapsid protein (N) of SFTSV, and viral RNA copies were determined according to the manufacturer's instructions based on the methods we described previously [6].

Statistical Analysis

Categorical variables were described using frequencies and percents, while continuous variables were described using mean, median, range, and interquartile range (IQR) values. The Pearson χ^2 test was used to compare qualitative variables and a 2-sample t test was implemented to compare continuous variables. Univariate analyses (continuity correction χ^2 test) were performed to evaluate the risk factors associated with death. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) v.13.0 software (SPSS Inc). For unadjusted comparisons, $P < .05$ was considered statistically significant.

RESULTS

Patient Description

All SFTS patients in this study, including 11 fatal cases and 48 non-fatal cases, were laboratory diagnosed as described in the Methods section. The 59 SFTS patients consisted of 29 males and 30 females with ages ranging from 40 to 83 years and a mean age of 61 years. Of these patients, there were 48 patients who survived, including 25 males and 23 females, with an average age of 61 years; 11 patients died, including 6 males and 5 females, with an average age of 64 years. When taking into account age and gender, there was no significant difference between the 2 groups. Except for 1 doctor and 1 retired teacher, the other 57 SFTS patients were farmers. All SFTS patients described a history of field exposure at mountainous or hilly areas within 2 weeks of the disease onset. In our study, fatalities occurred within 7–14 days after the onset of illness, and surviving SFTS patients commonly recovered 2–3 weeks after the disease onset.

Clinical Presentations in Fatal and Non-Fatal SFTS Cases

Dynamic monitoring of the disease course showed that SFTS patients initially developed flu-like symptoms, such as fever, fatigue, headache, and myalgia. Over 70% of the survivors and 80% of the deceased patients had a high fever over 39°C. Gastrointestinal symptoms, such as lack of appetite, nausea, vomiting, and diarrhea, were present in 85% of the survivors and in 90% of the deceased patients. For SFTS patients, fever persisted for 5–11 days and gastrointestinal symptoms lasted for a median of 12 days. However, in comparison to the non-fatal cases, the fatal cases did not show a significant difference in the fever temperature, fever duration, and the incidence of other flu-like symptoms and gastrointestinal symptoms (Table 1). Lymphadenopathy, hemorrhagic signs, and central nervous system (CNS) symptoms commonly occurred approximately 5 days after the onset of illness, and persisted for 1–2 weeks. In our study, the incidence rate of lymphadenopathy was 75% in survivors and 72.7% in deceased patients (Table 1), which was higher than previously reported [1]. It

Table 1. Clinical Features in Fatal and Non-fatal SFTS Cases

Symptoms and Signs[a]	Fatal (N = 11)[a] No. (%)	Non-fatal (N = 48)[a] No. (%)	*P* value[b]
Fever			
≤39°C	2 (18.2)	14 (29.2)	.462
>39°C	9 (81.8)	34 (70.8)	
Fatigue	8 (72.7)	32 (66.7)	.703
Headache	6 (54.5)	19 (39.6)	.368
Myalgia	6 (54.5)	28 (58.3)	.823
Lack of appetite	10 (90.9)	41 (85.4)	.628
Nausea	8 (72.7)	30 (62.5)	.522
Vomiting	5 (45.5)	13 (27.1)	.231
Diarrhea	4 (36.4)	12 (25.0)	.437
Lymphadenopathy			
Lymphadenopathy	8 (72.7)	36 (75.0)	.882
Unilateral sub-inguinal lymphadenopathy	6 (54.5)	29 (60.4)	.719
Tenderness of lymph nodes	7 (63.6)	31 (64.6)	.953
CNS manifestations			
Apathy	10 (90.9)	18 (37.5)	**.001**
Lethargy	9 (81.8)	11 (22.9)	**<.001**
Muscular tremor	8 (72.7)	13 (27.1)	**.004**
Convulsions	4 (36.4)	1 (2.1)	**.002**
Coma	8 (72.7)	4 (8.3)	**<.001**
Hemorrhagic manifestations			
Petechiae	9 (81.8)	13 (27.1)	**.001**
Pulmonary bleeding	3 (27.3)	1 (2.1)	**.020**
Melena	6 (54.5)	5 (10.4)	**.003**
DIC	7 (63.6)	2 (4.2)	**<.001**
MOD	11 (100)	43 (89.6)	.263
MOF	11 (100)	2 (4.16)	**<.001**

Abbreviatoins: DIC, disseminated intravascular coagulation; MOD, multiple organ dysfunction, defined as progressive physiologic dysfunction in two or more organ systems; MOF, multiple organ failure, defined as organ failure in two or more organs of critically ill patients [4, 5].

[a] Values are listed as a number (percent) unless otherwise noted.

[b] The Pearson χ^2 test was used to compare qualitative variables. Statistical analyses were performed using SPSS v.13.0. $P < .05$ was considered statistically significant.

was revealed after a thorough examination of patients who developed lymphadenopathy that 60.4% of the survivors and 54.5% of the deceased patients had unilateral sub-inguinal lymphadenopathy, and 64.6% of the survivors and 63.6% of deceased patients exhibited tender lymph nodes. Furthermore, >90% of the deceased patients developed CNS manifestations including apathy (99.9%), lethargy (81.8%), muscular tremor (72.7%), convulsions (36.4%), and coma (72.7%) before death, while for survivors, <37% developed these CNS manifestations, which were mainly apathy (37.5%), lethargy (22.9%), and muscular tremor (27.1%) (Table 1). Additionally, >80% of the deceased patients had incidence of hemorrhagic manifestations, such as ecchymosis (81.1%) at the venous puncture site, with progression to DIC (disseminated intravascular coagulation) (63.6%) and accompanying pulmonary and gastrointestinal bleeding, which was much higher than the 4.2% incidence in the survivors (Table 1). Although 89.6% of survivors showed MOD, only 4.2% of the survivors proceeded to the stage of life-threatening MOF. In contrast, all fatal cases showed MOD (100%), and all these patients died of MOF (100%).

Dynamic Profile of Laboratory Findings in SFTS Patients

To determine the major clinical features that appeared during SFTS disease progression and all risk factors associated with fatal outcome, the dynamic changes in 12 clinical laboratory parameters, including virological, hematological and biochemical parameters, were tracked from day 1 to day 19 after the onset of the disease with 2-day intervals (Figure 1). The results showed that there are three stages in the clinical progression of SFTS.

During the first stage of the disease, which is defined as day 1–7 after the onset of illness, the initial serum viral load was high (with an average of 10^{5-6} copies/ mL) and comparable between the patients that died and survived (Figure 1). Most SFTS patients in both groups had marked thrombocytopenia and leukocytopenia in this stage. The platelet counts and peripheral white blood cell counts dropped from day 3 after the onset of illness, and decreased to a minimum on day 7–9 (Figure 1). The lymphocytes substantially decreased during the 3–9 days after the onset of illness (Figure 1), while neutrophils only slightly decreased during the same period (Figure 1). These data suggested that lymphocytes are the major cell types that are involved in leukocytopenia in SFTS patients.

The coagulation tests showed that prolonged aPTT (activated partial thromboplastin time) occurred on day 5–9 during the disease course, while PT rarely extended except for a transient change shown in the group of fatal cases at day 11 (Figure 1). In addition, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase MB fraction (CK-MB) began to elevate later during this stage (Figure 1). Proteinuria was observed in 75.6% of the non-fatal cases and 81.8% of the fatal cases, and urinary occult blood was observed in 60.9% of the non-fatal cases and 63.6% of the fatal cases.

The second stage occurs between day 7–13 after disease onset. As shown in Figure 1, the featured findings in this period are a decreased serum viral load in survivors but a high serum viral load in the patients who died, and average serum viral copies of up to 10^8 copies/mL in deceased patients. The

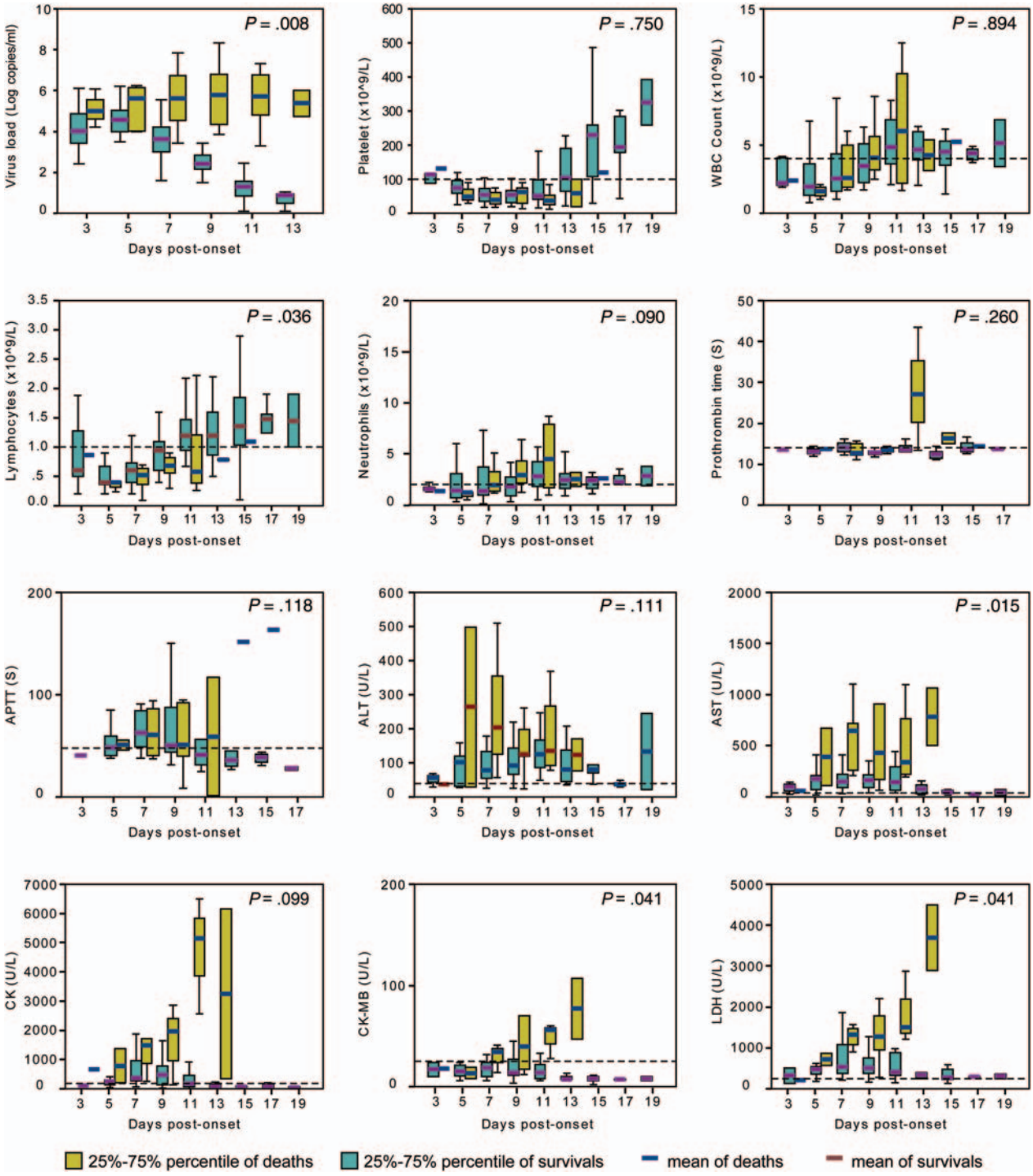

Figure 1. Dynamic profile of laboratory parameters in 59 SFTS patients. Box-and-whisker plots illustrate the laboratory parameters in 59 SFTS patients (11 deceased patients and 48 survivors) every other day based on the days after the onset of illness. Green boxes indicate deceased patients, and blue boxes indicate survivors. Bars indicate the mean values of the study groups. The dashed lines show the normal level of each parameter. *P* values at the corner of each plot show the statistical significance between the averages of the two patient groups calculated over the whole course.

platelet counts reverted to the normal range in survivors, but continued to decline in deceased patients. In SFTS patients who survived, the serum tissue enzymes reached maximal values at day 9 or day 11 and declined thereafter, and the levels almost reverted to normal at day 13. However, in fatal cases, except for ALT (>200 U/L), AST (>400 U/L), LDH (>800 U/L), CK (>1000 U/L), and CK-MB (>50 U/L) appeared to progressively rise during this stage and reached

maximum levels before death. The sustained low platelet counts and high levels of AST, CK, CK-MB, and LDH in the peripheral blood were associated with MOD or MOF that was frequently observed during this stage. After day 13, most clinical parameters converted to normal physical ranges in survivors, and the deaths were commonly attributed to severe MOD and DIC at this stage.

Therefore, considering the dynamic progress of clinical symptoms, the first stage was characterized by fever and high viremia in both deceased and surviving patients and was termed the "fever" stage; the second stage was characterized by a progressive exacerbation of MOD in fatal cases or a MOD self-limiting process in survivors and was then termed the "MOD" stage; the third stage was characterized by recovery progress for patients who survived and was termed the "convalescent" stage, while this stage is not applicable to the patients who died of SFTS.

Risk Assessment of Clinical Features Associated with the Death of SFTS Patients

It was observed that during the period of 7–13 days after the onset of illness, there was an obvious difference between the serum viral load of the surviving and deceased patients. At the same time period, the CNS symptoms and bleeding tendency were further exacerbated, and serum AST, LDH, CK, CK-MB continued to increase in severely ill patients. Therefore, we thought that the period of 7–13 days after the onset of illness was a critical stage for SFTS patients, and identified the clinical risk factors for death in this period by univariate logistic regression analysis (Table 2).

In comparison with SFTS patients who recovered, we found that >88% of the deceased patients developed CNS symptoms and had obvious hemorrhagic tendency; 66% of the deceased patients developed DIC, which only occurred in 3% of survivors. Although 89.6% of the survivors and 100% of the deceased patients had MOD, only 4.16% of the survivors but 100% of the deceased patients finally developed MOF. The analysis of relative risk with 95% confidence intervals revealed that the odds ratio of CNS manifestation, hemorrhagic manifestation, DIC, and MOF was 15.27, 20.44, 62, and 32, respectively, and all these were significant risk factors for the death of SFTS patients. In particular, the logistic regression analysis showed that during the period of 7–13 days after the onset of illness, a viral load $>10^5$ copies/mL was a high risk factor for the death of SFTS patients. Additionally, the incidence of substantially elevated serum AST (>400 U/L), LDH (>800 U/L), CK (>1000 U/L), and CK-MB (>50 U/L) was 21.9%, 40.6%, 25%, and 3.2% for survivors, while it was 77.8%, 88.9%, 77.8%, and 44.4% for deceased patients, respectively. Therefore, risk analysis identified high levels of serum AST (>400 U/L), LDH (>800 U/L), CK (>1000 U/L), and CK-MB (>50 U/L) as risk factors associated with the death of SFTS patients.

The clinical approach for the treatment of SFTS consisted of general supportive measures and the monitoring of the patient's hematologic and coagulation status. Antiviral drugs that block viral replication, such as ribavirin, would most likely be effective for hemorrhagic fever with renal syndrome (HFRS) caused by hantavirus, another member of the Bunyaviradae family [7–9], and thus, all 59 SFTS patients were treated with an intravenous drop of 0.6 g ribavirin once a day. The risk factor analysis during day 7–13 after the onset of illness showed that for 22 of 32 non-fatal cases and 4 of 9 fatal cases that received a late treatment of ribavirin during the MOD stage, there was not a high risk for death (Table 2). Therefore, it seems that the time until the initiation of ribavirin treatment did not affect patient outcome. Additionally, antibiotics were used to prevent or treat secondary bacterial infection. Other supportive care measures included intravenous transfusion of fresh frozen plasma, blood, platelets, albumin or granulocyte colony stimulating factors as necessary.

DISCUSSION

This study systemically described the clinical symptoms and laboratory parameters during the complete course of SFTS disease in fatal and non-fatal SFTS cases. Three distinct clinical stages in the SFTS disease progress were described for the first time. More importantly, we identified critical clinical symptoms and laboratory parameters related to the fatal outcome of SFTS patients.

Viruses in the family *Bunyaviridae* are pantropic viruses that injure various tissues and cells, and they commonly cause symptoms such as fever, bleeding, and multi-organ injury [10–13]. In addition to the fever that is observed in SFTSV infection, other symptoms are hemorrhagic signs and MOF, gastrointestinal symptoms, leukocytopenia, thrombocytopenia, elevated tissue enzymes, proteinuria, and hematuria [1]. However, these medical signs and symptoms also occur in other hemorrhagic fevers. Interestingly, our study found that lymphadenopathy occurred at an unusually high incidence rate of >70% in SFTS patients, with no significant difference in the occurrence rate between the patients who died and those who survived. We carefully examined the data and found that unilateral subinguinal lymphadenopathy could account for most of the incidences of lymphadenopathy, and lymphadenopathy was always accompanied by tenderness of the lymph nodes. Lymphadenopathy is rare in diseases caused by bunyaviruses such as hemorrhagic fever with renal syndrome (HFRS), hantavirus pulmonary syndrome (HPS), rift valley fever (RVF), and Crimean-Congo hemorrhagic fever (CCHF) [11, 14–17]. In addition, although lymphadenopathy is common in infections caused by the Epstein–Barr virus (EBV) [18, 19], rubella virus, and HIV (human immunodeficiency virus) [20–22], unilateral subinguinal lymphadenopathy

Table 2. Risk Factors Associated With the Death of SFTS Patients on Day 7–13 After Disease Onset

	Fatal (N = 9) No. (%)	Non-fatal (N = 32) No. (%)	Odds Ratio (95% Confidence Interval)	*P* Value[a]
Clinical features				
Fever (>39°C)	7 (77.8)	22 (68.8)	1.59 (.28–9.07)	.911
Gastrointestinal symptoms	8 (88.9)	27 (84.4)	1.48 (.15–14.59)	1.000
Lymphadenopathy	6 (66.7)	23 (71.9)	0.78 (.16–3.82)	1.000
CNS manifestations	8 (88.9)	11 (34.4)	15.27 (1.69–138.27)	**.012**
Hemorrhagic manifestations	8 (88.9)	9 (28.1)	20.44 (2.23–187.69)	**.004**
DIC	6 (66.7)	1 (3.1)	62.00 (5.48–701.53)	**<.001**
MOD	9 (100.0)	26 (81.2)	1.23 (1.04–1.45)	.383
MOF	9 (100.0)	1 (3.1)	32.00 (4.65–220.27)	**<.001**
Laboratory parameters[b]				
Viral load (>10^5 copies/mL)	6 (66.7)	7 (25.0)	7.14 (1.41–36.08)	**.032**
WBC (>2×10^9/L)	6 (66.7)	21 (34.4)	1.05 (.22–5.02)	1.000
NEU (>0.5×10^9/L)	9 (100.0)	31 (96.9)	1.03 (.97–1.10)	1.000
LYM (<0.5×10^9/L)	4 (44.4)	12 (37.5)	1.33 (.30–5.96)	1.000
Platelet (<30×10^9/L)	3 (33.3)		4.83 (.78–30.00)	.207
PT (>15 s)	3 (33.3)	8 (25.0)	1.50 (.30–7.43)	.924
APTT (>70 s)	3 (33.3)	10 (31.3)	1.10 (.23–5.31)	1.000
ALT (>200 U/L)	3 (33.3)	5 (15.6)	2.70 (.50–14.53)	.479
AST (>400 U/L)	7 (77.8)	7 (21.9)	12.50 (2.11–74.20)	**.006**
LDH (>800 U/L)	8 (88.9)	8 (40.6)	24.00 (2.59–222.65)	**.002**
CK (>1000 U/L)	7 (77.8)	8 (25.0)	10.50 (1.80–61.24)	**.012**
CK-MB (>50 U/L)	4 (44.4)	1 (3.2)	24.80 (2.28–269.63)	**.006**
Ribavirin treatment				
Day 7–13 after disease onset	4 (44.4)	22 (68.8)	0.364 (.080–1.650)	.344

[a] Univariate analyses (Continuity correction χ^2 test) were performed to evaluate the risk factors associated with death. $P < .05$ is considered statistically significant and noted in bold.

[b] For each parameter, the value in brackets indicates the level to define a substantially altered parameter in SFTS patients based on clinical experiences.

is rare. Therefore, lymphadenopathy with tenderness, especially unilateral subinguinal lymphadenopathy, seems to be a characteristic sign of SFTS; however, further studies are required to clarify this finding.

The dynamic tracking of the disease progress based on 59 SFTS cases enabled us to identify three distinct stages of SFTS: fever, MOD, and convalescence stages. The fever stage is characterized by the sudden onset of fever, headache, and gastrointestinal symptoms. On average, this stage persists for approximately 7 days and is accompanied with thrombocytopenia and leukocytopenia. Lymphadenopathy is commonly noted at this stage. One important marker for clinical diagnosis at this stage is a high viral load detected in the sera of both survivors and deceased patients. The MOD stage, according to the diagnostic criteria of MOD [4, 5], develops rapidly 7–13 days after onset of illness, and may overlap with the fever period. The clinical progress in this phase is key to predicting the disease outcome, as we found that the serum viral load gradually cleared in the survivors, but remained high in the patients that died. The important biomarkers for clinical outcome, AST (>400 U/L, $P = .006$), LDH(>800 U/L, $P = .006$), CK (>1000 U/L, $P = .02$), and CK-MB (>50 U/L, $P = .012$), significantly increased to a high level in fatal cases as compared with non-fatal cases. In addition, the clinical presentations during SFTS progression such as the appearance of hemorrhagic manifestations, neurological symptoms, sustained platelet decline, and the development of DIC and MOF, served as major risk factors associated with death. Therefore, the MOD phase is a critical stage to determine the outcome for SFTS patients, as patient survival through this period was followed by recovery from the SFTSV infection. However, the risk assessment for death from our study did not show significance between patients who survived and died for coagulation factors such as TT ($P = .92$) and APTT ($P = 1.00$), as was reported by Zhang et al [23]. Because the laboratory parameters could quickly change during disease progression (as shown in Figure 1), comparing the different stages may lead to different conclusions. The convalescence stage ranged from 11–19 days after the onset of illness, and during this time, clinical symptoms began to resolve and abnormal laboratory parameters gradually returned to normal.

A remarkable finding from our dynamic tracking study was that the viral load remained high in all fatal cases. A high

serum viral load in fatal SFTS cases has been reported in the case of human-to-human transmission [24], with a serum virus titer of 10^8 copies/mL before patient death. Recently, Zhang et al reported that high viral RNA load in SFTS patients was associated with a fatal outcome [23]. The study examined the host responses of cytokines and acute phase proteins, and showed that IL-6, IL-8, IL-10, G-CSF, and IFN-α were enhanced in fatal cases and correlated with the viral load. However, it is still not clear if this close association between viral load and disease severity is due to the direct or indirect effect of viral infection. Cytokine storm occurring in the acute phase of the disease has been widely hypothesized to be the main cause of mobility and mortality for several viral infections [25], but for SFTSV infection, the correlation between cytokines or chemokines and disease severity, as well as the molecular mechanisms of pathogenesis, have not been well addressed. A large cohort of SFTS patients, a reliable diagnostic method for case confirmation, and systemic bioinformatics analysis will be needed to resolve these issues.

The current clinical approaches to treat SFTS are based on general supportive measures. In this study, the hematologic and coagulation status of patients was closely monitored, and intravenous transfusion of fresh frozen plasma, blood, platelet, albumin, or granulocyte colony stimulating factor was performed as needed. Bacterial superinfection was treated with antibiotics as necessary. All SFTS patients involved in this study were treated with intravenous ribavirin. Although a late treatment with ribavirin was not a risk factor for death (Table 2), it is still inadequate to judge the effect of ribavirin on SFTS patients because of study limitations, and more parameters need to be investigated to make a determination.

In summary, based on a dynamic analysis on 59 SFTS patients including 11 deceased patients and 48 survivors, we defined the clinical course of SFTS as progressing through three stages: fever stage, MOD stage, and convalescent stage. High serum viral load was identified as an important feature of SFTS patients and served as the major laboratory marker for clinical diagnosis and therapy in the first stage, which ranged from 3–7 days after the onset of illness on average. The second stage (day 7–13 after disease onset) is a critical stage for disease outcome, as a sustained high viral load and substantial elevation of serum AST, CK, CK-MB and LDH during this time are major clinical indicators and risk factors associated with fatal outcome. Additionally, if hemorrhagic manifestations, CNS manifestations, DIC, and MOF appear in SFTS patients, they should receive intensive care in clinical monitoring and treatment to avoid a fatal outcome at maximum extent. Our findings will assist physicians in better understanding the disease progression and critical factors associated with disease severity and case fatalities of SFTS patients, and thus aid physicians to immediately initiate prompt and supportive treatment in order to block the rapid development of the illness and avoid fatality.

Notes

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