MAJOR ARTICLE

Case-Fatality Ratio and Effectiveness of Ribavirin Therapy Among Hospitalized Patients in China Who Had Severe Fever With Thrombocytopenia Syndrome

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Background. The wide distribution and high case-fatality ratio of severe fever with thrombocytopenia syndrome (SFTS) have made it a significant public health problem. This study was designed to identify the predictors of fatal outcomes and to evaluate the effectiveness of antiviral therapy in treating SFTS virus (SFTSV)–infected patients.

Methods. A cross-sectional study was performed in a general hospital located in Xinyang city, whereas the largest number of patients with SFTS in China were treated during 2011–2012. The primary outcome for the treatment effect analysis was death. Other outcomes included sequential platelet levels and viral loads observed throughout the hospitalization and the interval between the initiation of ribavirin therapy and the return of the platelet count to a normal level.

Results. A total of 311 SFTSV-infected patients were included in the study. The most frequent clinical presentations were fever, weakness, myalgia, and gastrointestinal symptoms. Each patient had thrombocytopenia, leukopenia, or both. The case-fatality ratio (CFR) was 17.4% (95% confidence interval [CI], 13.1%–21.6%). Older age (odds ratio [OR], 1.061; 95% CI, 1.023–1.099; $P = .001$), decreased level of consciousness (OR, 5.397; 95% CI, 2.660–10.948; $P < .001$), and elevated levels of lactate dehydrogenase (>1200 U/L; OR, 2.620; 95% CI, 1.073–6.399; $P = .035$) and creatine kinase (>800 U/L; OR, 2.328; 95% CI, 1.129–4.800; $P = .022$) were significantly associated with fatal outcome. The CFRs were similar between patients who received ribavirin and those who did not. Ribavirin treatment showed no significant effect on either platelet counts or viral loads during hospitalization of patients with fatal or nonfatal cases.

Conclusions. These findings can improve knowledge about the characteristics of patients with fatal outcomes and the use of antiviral drug for SFTS.

Keywords. case-fatality; ribavirin therapy; severe fever with thrombocytopenia syndrome.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging hemorrhagic fever that was reported recently in rural areas of China. The causative agent of SFTS is a novel bunyavirus named SFTS virus (SFTSV), a novel *Phlebovirus* in the *Bunyaviridae* family. The disease is characterized by fever, thrombocytopenia, and leukopenia, with a reported case-fatality ratio ranging from 2.5% to 30% in different areas of endemicity [1–3]. Since the initiation of national surveillance for SFTS in October 2010, a wide incidence of SFTS has been reported in 11 provinces/municipalities of mainland China [4]. It is also notable that 2 patients with similar clinical and laboratory features were recently described in Missouri. The causal pathogen was

Received 26 April 2013; accepted 1 August 2013; electronically published 20 August 2013.

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Clinical Infectious Diseases 2013;57(9):1292–9

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DOI: 10.1093/cid/cit530

demonstrated to be a new *Phlebovirus* closely related to the SFTSV [5]. The wider distribution [5, 6] and high case-fatality rate have made this emerging infectious disease a significant public health problem not only in China, but possibly in other regions of the world, as well.

For an emerging infectious disease, the understanding of clinical features, the risk factors contributing to disease severity and prognosis, and the evaluation of therapy effectiveness is critical in promoting diagnosis and treatment of the patients in clinical practice. Until recently, the indicators of fatal outcome remained sparsely investigated, with only limited cases analyzed and unfortunately no consistent conclusion derived [3, 7–9]. Reports on clinical observations implied that antibiotics might be effective in treating SFTS [10, 11], which led to disputes regarding drug therapy for a viral disease. Following the guideline released by the Chinese Ministry of Health, ribavirin was administered widely in treating SFTS, based on its active effect in vitro against SFTSV [11, 12]. However, the clinical effectiveness of antiviral therapy has not been established. The lack of this knowledge prohibits us from implementing proper medical care of the patients and from initiating interventions to reduce disease incidence. In this retrospective study, data were analyzed to determine case-fatality ratios (CFRs) and factors that may influence fatal outcome in a cohort of hospitalized patients with SFTSV in China. The possible effectiveness of adding ribavirin to the treatment was also evaluated in these patients.

METHODS

Study Setting

The study was performed in a military hospital (Hospital 154) in Xinyang administrative district of Henan Province in 2011 and 2012. Xinyang is the area of greatest SFTS endemicity in China, where 98.75% of the SFTS cases in Henan Province were reported in 2010 and 2011. The hospital is one of the largest hospitals in Xinyang, providing medical services, especially for infectious diseases, to residents throughout the district. The average monthly patient influx was 18 441 individuals during 2011. The army hospital received 82.2% of the total confirmed patients with SFTS reported in Xinyang since Chinese national surveillance for SFTS was initiated in October 2010 (Supplementary Figure 1).

Participants

We recruited all patients with a clinical diagnosis of SFTS, defined as acute fever (temperature, of ≥37.5°C) with thrombocytopenia (platelet count, $< 100 \times 10^9$ platelets/L) and/or leukopenia (leukocyte count, $< 4.0 \times 10^9$ leukocytes/L). Sequential serum samples were collected from all patients with clinically suspected SFTS on admission and during hospitalization for laboratory diagnosis. Laboratory measurements of SFTSV RNA, by real-time reverse-transcription polymerase chain reaction (RT-PCR), and of SFTSV-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, by enzyme-linked immunosorbent assay (ELISA), were performed as described below. Laboratory-confirmed SFTS was defined as meeting 1 or more of the following criteria: (1) isolation of SFTSV in cell culture, (2) detection of SFTSV RNA by a molecular method, and (3) seroconversion or ≥4-fold increase of antibody titers between 2 serum samples collected at least 2 weeks apart. Patients with laboratory-confirmed are included in this study. Nine patients were excluded because of comorbidities associated with cancer or diabetes (Supplementary Figure 2).

Data Collection

A medical record review was performed to collect information on demographic characteristics, symptoms and signs, laboratory test results, and treatment regimens during hospitalization. For patients who discontinued therapy because of severe clinical progression and left the hospital, we made follow-up visits to determine their final outcome. The research protocol was approved by the human ethics committee of the hospital, and all participants provided written informed consent.

Laboratory Tests

Serum specimens from all patients were analyzed for SFTSV RNA by real-time RT-PCR with specific primers and probes. The virus loads of sequentially acquired serum specimens from patients with confirmed SFTS were determined using quantitative RT-PCR targeting the same gene segments. Whole genomic sequences of SFTSV were obtained from randomly selected patients with fatal or nonfatal SFTS. Phylogenetic analyses were performed using the nucleotide sequences encoding the RNA-dependent RNA polymerase (RdRP), Gn-Gc envelope glycoproteins (GP), nucleocapsid (NP), and nonstructural (NSs) proteins. Neighbor-joining phylogenetic trees were reconstructed with the maximum composite likelihood method and complete deletion of gaps by using MEGA5. For serological testing, IgM and IgG antibodies were detected by ELISA, using the recombinant nucleoprotein of SFTSV as described previously [1]. The levels of 17 cytokines and chemokines in acute serum specimens were measured by the Human BioPlex ProTM Assays 17-Plex Panel (BioRad, USA; Supplementary Materials).

Outcome Measures

The primary outcome for the treatment effect analysis was defined as death. Other outcomes included sequential platelet levels and viral loads observed throughout the hospitalization and the interval between the initiation of ribavirin therapy and the return of the platelet count to a normal level.

Statistical Analysis

Descriptive statistics were calculated for all variables; continuous variables were summarized as means and standard deviations (SD) or as medians and ranges, and categorical variables were summarized as frequencies and proportions. To determine the difference between groups, an independent *t* test, a χ^2 test, a Fisher exact test, or a nonparametric test was used where appropriate.

Logistic regression analysis was performed to identify variables that were associated with fatal outcome of patients with SFTS. All data on demographic characteristics, on clinical manifestations, and from laboratory tests were included in univariate analysis. Biologically plausible variables with a *P* value of < .10 in the univariate analysis were entered into a multivariate logistic regression model by a stepwise method. In the logistic regression analyses on death in patients with SFTSV infection, we prespecified age, sex, days from onset to admission, and lower respiratory tract infection as confounders. To control their confounding effects, we included the above variables that were significant at a *P* value of < .10 in the univariable analyses into the multivariable models. Adequacy of the 2 models was determined with the Hosmer-Lemeshow goodness-of-fit test and by examining the estimated standard errors of the parameters and the estimated coefficients. We have checked for multicollinearity among independent variables when performing the multivariable regression analysis of death in patients. The analyses revealed that the tolerances of all the independent variables were >0.35 (>0.20), and the variance inflation factors were <3.0 (<5.0), indicating no multicollinearity.

For treatment effect analysis, the Kaplan–Meier method was used to analyze time-to-event data using the log-rank test; hazard ratios and 95% confidence intervals (CIs) were calculated on the basis of a Cox regression model. The $\log_{10}$-transformed data on daily platelet counts and viral loads after treatment were analyzed over time with the generalized estimating equation (GEE) models [13], which took into account the correlation between viral loads and platelet counts obtained at baseline and at follow-up points in the same patient. Considering that the variables of age, sex, and interval from disease onset to admission were related to the outcome of SFTS, these variables were adjusted in all multivariate analyses. Odds ratios (ORs) and their 95% CIs were estimated using maximum likelihood methods.

The cytokine/chemokine concentrations were log transformed, ranked, and tested for differences between different groups by generalized linear models when adjusted for age, sex, and interval from onset date to collection date. Cytokine levels below the limit of detection (LOD) were imputed using the formula LOD/$\sqrt{2}$.

A 2-sided *P* value of <.05 was considered to be statistically significant. All analyses were performed using SAS software, version 9.1.3, and SPSS software, version 17.0.

RESULTS

Patients With SFTS

During April–November 2011 and May–September 2012, 311 patients with laboratory-confirmed SFTS were enrolled. The median age was 61 years (range, 7–87 years), and 140 (45.0%) were male. Most patients were agricultural workers. The frequent symptoms among patients with SFTS at hospital admission were fever, weakness, myalgias, and gastrointestinal syndromes (diarrhea, vomiting, nausea, and anorexia). Frequently observed laboratory abnormalities included thrombocytopenia, leukopenia, and elevated levels of serum aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), and creatine kinase (CK; Table 1). Each patient had thrombocytopenia, leukopenia, or both.

Predictors of Fatal Outcome

Fifty-four of 311 patients died, leading to a case-fatality ratio (CFR) of 17.4% (95% CI, 13.1%–21.6%). The median age of patients who died was 66 years (range, 34–85 years), and 32 (59.3%) were male. The high case-fatality ratio among patients with SFTS was associated with older age, male sex, and long duration from the onset of disease to admission. An age-dependent increase in CFR was observed in the patients older than 54 years, with the age group of >74 years having the highest risk of death (Supplementary Table 1).The proximate causes of death were related to multiple organ failure (40 patients), acute renal failure (13 patients), and chronic obstructive pulmonary disease with endometrial malignant tumor (1 patient).

In univariate regression analyses, 14 variables (older age, male sex, time from disease onset to admission, cough, sputum production, decreased level of consciousness, low platelet and hemoglobin levels, and high AST, ALT, alkaline phosphatase, gamma-glutamyl transpeptidase, LDH, and CK levels) were significantly associated with fatal outcome (Table 1).

Multivariate regression analysis revealed that older age (OR, 1.061; 95% CI, 1.023–1.099; *P* = .001), decreased level of consciousness (OR, 5.397; 95% CI, 2.660–10.948; *P* < .001), and elevated levels of LDH (>1200 U/L; OR, 2.620; 95% CI, 1.073–6.399; *P* = .035) and CK (>800 U/L; OR, 2.328; 95% CI, 1.129–4.800; *P* = .022) were significant predictors for fatal outcome (Table 2).

In comparison with patients with SFTS who survived, the patients with a fatal outcome produced higher levels of interferon γ (IFN-γ) and interleukin 10 (IL-10) in the early phase of disease. No significant differences in levels of other cytokines were demonstrated (Supplementary Table 2).

Genetic Analysis

To evaluate whether fatal outcome was possibly related to the virulence of SFTSV strains, whole-genome sequences of SFTSV

Table 1. Selected Characteristics of Patients Hospitalized With Severe Fever With Thrombocytopenia Syndrome on Admission

Characteristic	All Cases (n = 311)	Nonfatal Cases (n = 257)	Fatal Cases (n = 54)	*P*
Demographic feature				
Female sex	171 (55.0)	108 (42.0)	32 (59.3)	.021[a]
Age, y	61 (7–87)	60 (7–87)	66 (34–85)	<.001[b]
Agricultural worker	283 (91.0)	234 (91.1)	49 (90.7)	1.000
Time from onset to admission, d	5 (1–11)	5 (1–11)	6 (2–11)	.038[b]
Clinical manifestation on admission				
Temperature >38°C	311 (100.0)	257 (100.0)	54 (100.0)	1.000[a]
Weakness	297 (95.5)	245 (95.3)	52 (96.3)	1.000[a]
Myalgias	257 (82.6)	212 (82.5)	45 (83.3)	.882[a]
Headache	54 (17.4)	47 (18.4)	7 (12.5)	.289[a]
Cough	99 (31.8)	72 (28.0)	27 (50.0)	.002[a]
Sputum production	75 (24.1)	52 (20.2)	23 (42.6)	<.001[a]
Dizziness	60 (19.3)	49 (19.1)	11 (20.4)	.825[a]
Lymphadenopathy	132 (42.4)	105 (40.9)	27 (50.0)	.217[a]
Decreased level of consciousness[d]	82 (26.4)	46 (17.9)	36 (66.7)	<.001[a]
Gastrointestinal syndromes	305 (98.1)	253 (98.4)	52 (96.3)	.297[a]
Diarrhea	80 (25.7)	63 (24.5)	17 (31.5)	.287[a]
Vomiting	114 (36.7)	94 (36.8)	20 (37.0)	.949[a]
Nausea	158 (50.8)	131 (51.0)	27 (50.0)	.897[a]
Anorexia	302 (97.1)	250 (97.3)	52 (96.3)	.656[a]
Overt and subclinical coagulopathy	22 (7.1)	15 (5.8)	7 (13.0)	.078[a]
Laboratory feature on admission				
WBC count, $\times 10^9$ cells/L	2.9 ± 2.2	2.9 ± 2.2	2.1 ± 1.8	.698[b]
Platelet count, $\times 10^9$ platelets/L	66 ± 33	69 ± 34	51 ± 29	<.001[b]
Neutrophils, %	62.9 ± 16.9	62.8 ± 16.6	63.7 ± 16.9	.718[b]
Lymphocytes, %	27.2 ± 12.9	27.8 ± 13.2	24.4 ± 10.6	.077[b]
Hb level, g/L	128 ± 20	127 ± 19	134 ± 21	.018[b]
AST level, U/L	290 (12–1807)	101 (12–1739)	250 (33–1807)	<.001[c]
ALT level, U/L	65 (10–800)	57 (10–800)	121(18–560)	<.001[c]
ALB level, g/L	36 (22–50)	36 (22–50)	35 (23–45)	.209[c]
ALP level, U/L	75 (34–422)	75 (34–398)	90 (43–422)	<.001[c]
GGT level, U/L	26 (1–600)	26 (1–600)	52 (14–565)	<.001[c]
LDH level, U/L	473 (14–3354)	428 (14–2374)	799 (250–3354)	.003[c]
CK level, U/L	373 (26–7000)	371 (26–6120)	917 (28–7000)	<.001[c]

Data are No. (%) of patients, mean value ± standard deviation, or median (range).

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT; alanine transaminase; AST, aspartate aminotransferase; CK, creatine kinase; GGT, gamma-glutamyl transpeptidase; Hb, hemoglobin; LDH, lactate dehydrogenase; WBC, white blood cell.

[a] By means of the χ^2 test.

[b] By means of the *t* test.

[c] By means of a nonparametric test.

[d] Includes presence of apathetic facial expressions, blurred mind, or coma.

were obtained from 16 patients who died and 11 who survived (GenBank accession numbers are provided in Supplementary Table 3). No obvious SFTSV mutant was identified in the fatal cases. Phylogenetic analysis based on the nucleotide sequences of RdRP, GP, NP, and NSs revealed that the SFTSV sequences identified in the fatal and nonfatal cases were evenly distributed in 3 lineages (Supplementary Figure 3).

Effect Evaluation of Therapy

A total of 302 patients were included in the analysis of treatment effect. Nine patients with immunocompromise due to underlying conditions were excluded (Supplementary Figure 2). All 302 patients were treated intravenously with doxycycline (100 mg every 12 hours), among whom 138 (45.7%) recruited in 2012 additionally received intravenous therapy with ribavirin

Table 2. Multivariate Logistic Regression Analysis of Variables Associated With Fatal Outcome Among Patients With Severe Fever With Thrombocytopenia Syndrome

Variable	OR (95% CI)	*P*
Age (continuous)	1.061 (1.023–1.099)	.001
Decreased level of consciousness	5.397 (2.660–10.948)	<.001
LDH level, U/L		
≤400	Reference	
400–800	2.214 (.780–6.286)	.571
800–1200	2.310 (.526–10.148)	.563
>1200	2.620 (1.073–6.399)	.035
CK level, U/L		
≤400	Reference	
400–800	0.688 (.215–2.203)	.918
>800	2.328 (1.129–4.800)	.022

Abbreviations: CI, confidence interval; CK, creatine kinase; LDH, lactate dehydrogenase; OR, odds ratio.

(500 mg daily) after release of the Guideline for the Treatment of SFTS by Chinese Ministry of Health. Demographic characteristics, baseline clinical features and laboratory tests, and administration of other drugs were similar for the patients who received ribavirin (ribavirin group) and those who received no ribavirin (nonribavirin group; Supplementary Table 4).

The CFRs were similar between the ribavirin and nonribavirin groups after adjustment for age, sex, and duration from disease onset to admission (24/138 [17.4%] and 28/164 [17.1%], respectively; $P = .910$), displaying no effect of ribavirin on fatality. The Kaplan–Meier analysis showed that the survival curves for the 2 groups were approximately superimposable (hazard ratio, 0.880; 95% CI, .673–1.150; $P = .348$; Supplementary Figure 4).

For the fatal cases, the GEE model using the daily $\log_{10}$- transformed data revealed that ribavirin had no significant effect on either platelet count recovery ($P = .055$; Figure 1*A* and Table 3) or viral load reduction ($P = .416$; Figure 1*B* and Table 3).

Among 250 nonfatal cases, the median time for platelet counts to return to normal levels after treatment was 8 days (range, 1–16 days) and 7 days (range, 1–18 days) for the patients who received ribavirin (n= 114) or no ribavirin (n = 136), respectively. The mean platelet count (±SD) at admission was similar between the cases with and those without ribavirin treatment (63 ± 32 vs 69 ± 35 $\times 10^9$ platelets/L; $P = .166$). The GEE model demonstrated that the ribavirin group did not experience a more rapid increase in the platelet count, compared with the nonribavirin group ($P = .065$; Figure 1*C* and Table 3), after adjustment for age, sex, and time from disease onset to admission. Prespecified subgroup analysis showed no beneficial effect of ribavirin on platelet recovery in any subgroups (Table 3), with patients stratified according to age (≤64 years and >64 years), sex, and time from disease onset to admission (<4 days, 4–6 days, and ≥7 days; Supplementary Figures 5–7).

Upon hospital admission, the mean viral load was 2.5×10^3 copies/mL (range, 1.0×10^2 to 8.7×10^5 copies/mL) among ribavirin recipients who survived and 6.5×10^3 copies/mL (range, 1.0×10^2 to 1.1×10^8 copies/mL; $P = .110$) among nonrecipients who survived. At follow up, there was no statistically significant difference in the decrease of viral loads between the ribavirin and nonribavirin groups ($P = .191$; Figure 1*D* and Table 3). No beneficial effect of ribavirin on viral load reduction was observed in any stratification subgroup (Table 3).

DISCUSSION

In the current study, a verified CFR among hospitalized patients with SFTS was obtained. Clinical indicators were identified as independently related to case fatality and may be indicative of disease severity. The addition of ribavirin to doxycycline therapy was found not to impact CFR or viral loads.

To our knowledge, this study represented the largest sample size of SFTS cases. Until now, 4 previous studies described the indicators of a fatal outcome, but they showed conflicting results because of their limitations, including small sample sizes (9–15 fatal and 32–48 nonfatal cases), limited data from various medical institutions, retrospective study design, and no consideration of etiological aspect [3, 7–9]. In the current study, we recruited 54 patients who died and 257 who survived from a single hospital and performed prospective follow-up observation, revealing a higher CFR than previously reported.

The implementation of multivariate analysis identified 4 variables (older age, decreased level of consciousness, and high LDH and CK levels) as independent predictors for fatal outcome of SFTS after adjustment for possible confounding effects. These parameters were routinely evaluated in clinical practice, thus yielding a highly predictive value for discriminating the patients at higher risk of death, who should get more attention in treatment. In addition, higher levels of serum IFN-γ and IL-10 were observed in fatal cases, which were consistent with previous studies reporting high levels of interleukin 6, IL-10, and IFN-γ in fatal SFTS cases [3, 8], and suggested that proinflammatory response might play a role in disease progression. Moreover, whole genomic sequences of SFTSV strains were analyzed in the study, and the possible role of variation in SFTSV virulence in fatal cases was excluded.

Ribavirin is a synthetic nucleoside antiviral agent with inhibitory activity against both DNA and RNA viruses [14]. It has broad-spectrum antiviral activity and has been used to treat

Table 3. Multivariable Analyses of Ribavirin Therapy on Platelet Counts and Severe Fever With Thrombocytopenia Syndrome Viral Loads, by Generalized Estimating Equation Models

	Platelet Counts (Ribavirin vs Nonribavirin)			Viral Loads (Ribavirin vs Nonribavirin)		
Variable	Patients, No.[a]	OR (95% CI)	*P*	Patients, No.[a]	OR (95% CI)	*P*
Models, by outcome[b]						
Fatal cases (n = 52)	24/28	0.903 (.813–1.002)	.055	16/9	0.606 (.181–2.027)	.416
Nonfatal cases (n = 250)	114/136	0.957 (.913–1.003)	.065	82/43	0.781 (.540–1.131)	.191
Models for nonfatal cases, by prespecified subgroup[c](n = 250)						
Age, y						
≤64	83/97	0.950 (.898–1.004)	.070	60/31	0.850 (.540–1.338)	.484
>64	31/39	0.974 (.899–1.055)	.514	23/12	0.635 (.326–1.236)	.181
Sex						
Male	49/56	0.981 (.886–1.044)	.346	35/20	0.818 (.537–1.248)	.282
Female	65/80	0.950 (.899–1.003)	.066	47/23	0.730 (.412–1.300)	.527
Time from disease onset to admission, d						
<4	28/28	0.761 (.478–1.210)	.247	21/9	0.761 (.478–1.210)	.247
4–6	57/57	1.094 (.613–1.955)	.761	41/18	1.094 (.613–1.955)	.761
≥7	29/51	0.607 (.287–1.281)	.190	20/16	0.607 (.287–1.281)	.190

The $\log_{10}$- transformed data on daily platelet counts and viral loads after treatment were analyzed over time, using repeated-measures analysis with a generalized estimating equation (GEE) model.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Data are No. of patients (ribavirin/nonribavirin) included in the analysis.

[b] The GEE model was built to estimate the mean difference in platelet count and viral load changes from baseline between the ribavirin and nonribavirin groups. Explanatory variables included in the models were age (continuous variable), sex, therapy delay (continuous variable), and ribavirin use.

[c] In the age subgroup, ORs were evaluated by adjusting for sex and time from disease onset to admission; in the sex subgroup, ORs were evaluated by adjusting for age and time from disease onset to admission; in the time from disease onset to admission subgroup, ORs were evaluated by adjusting for age and sex.

various virus infections [15]. High-dose intravenous ribavirin has been administered in the treatment of Lassa fever and hemorrhagic fever with renal syndrome, while conflicting results were demonstrated with regard to the efficacy of ribavirin in treating Crimean-Congo hemorrhagic fever [14, 16–19]. The effectiveness of ribavirin in treating SFTS has not been reported, despite its extensive use as clinical treatment in China. Our observational study found no evidence of beneficial effect of ribavirin on reducing the fatality rate. Receipt of ribavirin therapy could neither increase the platelet counts nor reduce the viral loads, compared with nonreceipt. These results suggest that ribavirin might not have clinical efficacy in treating SFTSV infection. As reported previously, SFTSV could bind to platelets and then enhance phagocytosis of platelets by macrophages [20]. The active effect of ribavirin in vitro against SFTSV has been proven. Therefore, treatment with ribavirin is assumed to reduce viral load, further resulting in an increased platelet count. It was unexpected that the ribavirin group had lower platelet levels than the nonribavirin group throughout the observation period, although the differences were not statistically significant at any time point.

Our study had several important limitations. The primary limitation is that the effect evaluation of patient treatment was based on an observational design rather than on a randomized, controlled design, such that physicians' decisions regarding the choice of therapy might have been influenced by the initial illness severity. A well-designed prospective study is needed to evaluate the predictive values of the identified factors and the effectiveness of ribavirin therapy. In fact, patients were naturally grouped with regard to the year they were infected, and the demographic and clinical characteristics and drug use patterns were comparable between the 2 groups. Thus, our findings have clinical significance, because the ethical concerns about the high fatality rate of SFTS preclude the possibility of placebo administration. Another limitation is that the effect of doxycycline was not evaluated, because this drug is routinely performed, making a designed effect evaluation study less likely. Further controlled studies to evaluate the effect of ribavirin, doxycycline, and other therapy regimens are warranted in patients with SFTS. We are also aware that, although we have described the largest case series of patients with SFTS to date, more cases need to be evaluated to attain adequate statistical power for a multivariable analysis of fatal outcome, especially after adjustment for multiple testing.

In conclusion, our study identified clinical indicators that were associated with fatal outcome. However, our study found

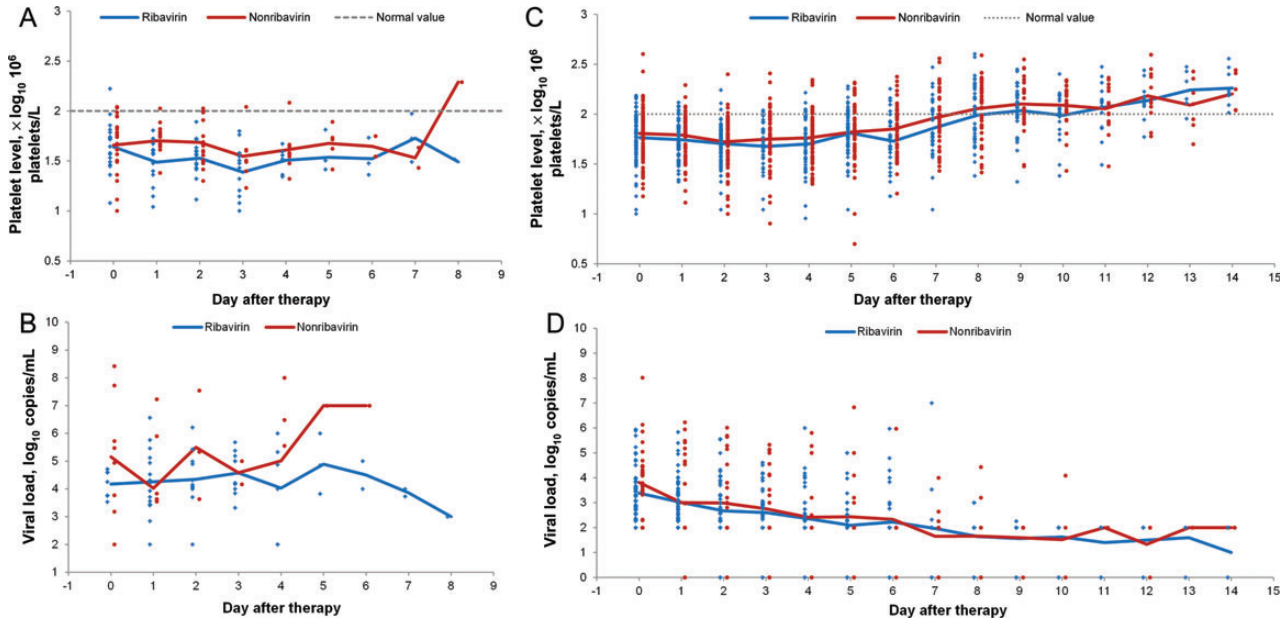

Figure 1. Effect of ribavirin on platelet counts and viral loads over time. Ribavirin's effect on platelet counts over time was shown with $\log_{10}$-transformed data for 52 patients with fatal disease (*A*) and 250 with nonfatal disease (*C*). Ribavirin's effect on viral loads over time was shown with $\log_{10}$-transformed data for 25 patients with fatal disease (*B*) and 125 with nonfatal disease (*D*). For analysis of platelet counts, 87 data points from the ribavirin group and 81 data points from the nonribavirin group were included for the patients who died (*A*); 608 data points from the ribavirin group and 684 data points from the nonribavirin group were included for the patients who did not die (*C*). For analysis of viral loads, 59 data points from the ribavirin group and 25 data points from the nonribavirin group were included for the fatal patients (*B*); 487 data points from the ribavirin group and 175 data points from the nonribavirin group were included for the nonfatal patients (*D*).

no evidence to support the use of ribavirin in the treatment of individuals with SFTS. These findings have a significant potential to alter clinical practice, potentially reducing costs and lowering the risks of ribavirin-associated adverse events.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. All authors contributed to the critical review and revision of the manuscript and have seen and approved the final version of the paper. W.-C. C. and W. L. have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer. The funding agencies had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Financial support. This study was supported by the Natural Science Foundation of China (grants 81222037, 81290344, 81130086, 81072250), the China Mega-Project for Infectious Diseases (grant 2013ZX10004-202), and the Chinese Basic Research Project (grant 2010CB530201). Regarding this report, the authors do not have any commercial or other association that would be considered a conflict of interest.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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