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Clinical progression and predictors of death in patients with severe fever with thrombocytopenia syndrome in China

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ABSTRACT

Background: Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease of which the clinical progression and factors related to death are still unclear.
Objective: To identify the clinical progression of SFTS and explore predictors of fatal outcome throughout the disease progress.
Study design: A prospective study was performed in a general hospital located in Xinyang city during 2011–2013. Confirmed SFTS patients were recruited and laboratory parameters that were commonly evaluated in clinical practice were collected. The clinical progression was determined based on analysis of dynamic profiles and Friedman's test. At each clinical stage, the laboratory features that could be used to predict fatal outcome of SFTS patients were identified by stepwise discriminant analysis.
Results: Totally 257 survivors and 54 deceased SFTS patients were recruited and the data of 11 clinical and laboratory parameters along their entire disease course were consecutively collected. Three clinical stages (day 1–5 post onset, day 6–11 post onset and day 12 to hospital discharge) were determined based on distinct clinical parameters evaluations. Multivariate discriminant analysis at each clinical stage disclosed the indicators of the fatal outcome as decreased platelet counts at early stage, older age and increased AST level at middle stage, and decreased lymphocyte percentage and increased LDH level at late stage.
Conclusions: The significant indicators at three clinical stages could be used to assist identifying the patients with high risk of death. This knowledge might help to perform supportive treatment and avoid fatality.

1. Background

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease first identified in central China in 2009. Its etiological cause is a novel bunyavirus classified as a new member of genus Phlebovirus, family *Bunyaviridae*. The major clinical symptoms include fever, thrombocytopenia, leukocytopenia and gastrointestinal symptoms [1–3]. By July 2013, SFTS cases had been reported in at least 12 provinces of mainland China, after the expanded surveillance was initiated [4–7]. Outside China, SFTS like or confirmed SFTS patients had been reported in Dubai, United Arab Emirates [8], Missouri, United States [9] and Korea [10]. In Japan, four fatal cases with SFTSV infection were reported recently and none of them had overseas travel history [11], suggesting the wider distribution of this disease than previously thought. Moreover, recent findings of the potential person-to-person transmission through blood contact made this newly emerged zoonosis a severe threat to public health [12–16].

SFTS patients had an extensively wide clinical spectrum, with some experiencing self-limiting clinical course, while approximately 14% of the cases developing fatal outcome. Life-threatening complications that were found to forecast fatal outcome included neurological manifestations, pulmonary hemorrhage,

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disseminated intravascular coagulation (DIC) and multiple organ failure (MOF). According to the clinical data, no consensus was obtained as to when these severe complications might develop. However, the emergency of these complications were accompanied by elevated levels of the laboratory parameters that were commonly tested in clinical practice. For example, aspartate aminotransferase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH) were markers of liver damage, decreased platelet and increased blood coagulation times (activated partial thromboplastin time (APTT) and thrombin time (TT)) were indicative of the coagulation disturbances, while early organ failure could be forecasted based on elevated serum levels of the albumin (ALB), creatine kinase (CK) and LDH. The close monitoring of these laboratory parameters could help to recognize the severe complications in early phase to attain an intensive treatment in clinical practice.

To our knowledge, there is only one study focusing on the clinical progression of SFTS [17]. Previous cross-sectional research [18–20], as well as our recent study [21] have been performed to identify the risk factors that might be correlated with disease severity. Incongruent conclusions were obtained due to the limited samples size and the lack of adjustment for potential confounding effects by multivariate analysis in certain studies.

2. Objective

The current prospective study was performed on 357confirmed SFTS patients to identify the clinical progression that SFTS patients experienced and to explore predictors of fatal outcome, which could assist clinicians to identify patients with high risk of death in a real time manner.

3. Study design

3.1. Study sites and patients inclusion

The study was performed in a hospital designated for SFTS treatment (154 Hospital) in Xinyang administrative district of Henan Province in 2011 and 2012. Xinyang is the most severely endemic area of SFTS in China, where 98.75% of the SFTS cases in Henan Province were reported from 2010 and 2012. The detailed information of the hospital and procedure of recruiting patients had been described in the previous study [21]. Briefly, all clinically diagnosed patients admitted into 154 Hospital were defined by an acute fever with thrombocytopenia and/or leukopenia [4]. Serum samples were collected from all clinically diagnosed patients on admission for laboratory detection. Laboratory measurements of SFTSV RNA by real-time RT-PCR and SFTSV-specific IgM and IgG antibodies by enzyme-linked immunosorbent assay (ELISA) were performed as following described [1]. A laboratory-confirmed SFTS patient was defined as meeting one 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 two serum samples collected at least 2 weeks apart. All laboratory-confirmed SFTS patients were included in this study.

3.2. Source of information and data collection

A medical record review was performed to collect the information on demographic characteristics, symptoms and signs, laboratory test results and treatment regimens during the entire hospitalization. Eleven clinical and laboratory parameters that were most frequently tested and biologically related to the complications of fatal SFTS patients were evaluated prospectively, including body temperature, white blood cell (WBC), lymphocyte percentage, platelet, ALT, AST, LDH, CK, ALB, alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT). The research protocol was approved by the Human Ethics Committee of the hospital, and all participants provided written informed consent.

3.3. Statistical analysis

Descriptive statistics were performed with continuous variables estimated as median and range, and categorical variables summarized as frequencies and proportions. To determine the difference between the fatal and non-fatal group, categorical variables were compared with χ^2 or Fisher exact tests and continuous variables with two-sample Wilcoxon rank-sum test.

In order to determine the distinct disease phases that manifested with the most diversified characteristics, the dynamic data of the eleven parameters mentioned above were tracked from disease onset till hospital discharge. Briefly, three clinical phases were randomly categorized and each evaluated parameter was compared among three phases by Friedman's test for fatal and non-fatal cases, respectively. The grouping modes which produced highest number of significant differences among three clinical phases were determined as the clinical phases.

After the clinical phases were determined, the $\log_{10}$-transformed data were tested by univariate discriminant analysis which included all the demographic characteristics and clinical data for analysis at each clinical stage. Significant variables in the univariate analysis ($P < 0.10$) were entered into a multivariate discriminant model to determine the appropriate parameters that could classify the subjects into the fatal and non-fatal group with the highest discriminating power; stepwise selection method was used to retain all selected variables in the model. Adequacy of the discriminant model was determined by examining resubstitution error rates and leave-one-out cross-validation error rates at each clinical stage [22].

All statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC) and $P < 0.05$ was considered statistically significant.

4. Results

4.1. Patient information

During April 2011 to July 2013, 357 laboratory-confirmed SFTSV infected patients were enrolled. The median age was 61 years old (range 7–87), and 202 (56.6%) were female. Fifty-four patients died. The age and gender distribution, as well as the duration from disease onset to admission were significantly different between the fatal and non-fatal patients. Regarding clinical therapy, ribavirin and doxycycline administration composed major therapies, which were highly comparable between two groups (Table 1).

4.2. Laboratory parameters profile and clinical phases defining

The dynamic patterns of 11 clinical and laboratory parameters were derived for the fatal and non-fatal group, respectively (Fig. 1). When we divided the clinical stages into 0–5, 6–11 and >11 days, a distinct pattern among stages could be observed. As displayed in Fig. 1, at early stage (0–5 days), most of the laboratory parameters deviated slightly from normal value ranges, while lymphocyte percentage, ALB, ALP and GGT remained at normal levels. At middle stage (6–11 days), all laboratory parameters began to deviate from normal level progressively. The ALT, AST, LDH and CK kept the increasing trend, attaining the peaking level at about day 11, while the platelet sustained the decreasing trend, declining to a nadir level at day 11. The original normal ALB, ALP and GGT levels deviated slightly in fatal cases. In the late stage (>11 days), all of the