Journal of Clinical Virology 78 (2016) 123–128

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

The prospective evaluation of viral loads in patients with severe fever with thrombocytopenia syndrome

Zhen-Dong Yang[a,1], Jian-Gong Hu[b,1], Qing-Bin Lu[c,**], Chen-Tao Guo[b,d], Ning Cui[a], Wei Peng[e], Li-Yuan Wang[b,d], Shu-Li Qin[a], Hong-Yu Wang[b,d], Pan-He Zhang[b], Xiao-Ai Zhang[b], Wei Liu[b,*], Wu-Chun Cao[b]

[a] The 154 Hospital, Peoples Liberation Army, Xinyang 464000, PR China
[b] State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Beijing 100071, PR China
[c] School of Public Health, Peking University, Beijing 100191, PR China
[d] Graduate School of Anhui Medical University, Hefei 230032, PR China
[e] The Shangcheng County People's Hospital, Shangcheng, PR China

ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form 14 March 2016
Accepted 16 March 2016

Keywords:
Severe fever with thrombocytopenia syndrome
Viral loads
Prospective study
SFTSV
RT-PCR

ABSTRACT

Background: Severe fever with thrombocytopenia syndrome (SFTS), caused by novel bunyavirus (SFTSV) is a potentially fatal disease that was first identified in China. Person to person transmission through contact with blood or body fluids was considered as an important infection route.
Objectives: The study is designed to investigate the longitudinal viral loads following SFTSV infection and to identify factors affecting viral shedding in SFTS patients.
Methods: A prospective, observational study was performed on 208 laboratory-confirmed SFTSV infected patients in Xinyang, Henan Province. Sequential serum samples were collected on admission and during the hospitalization for quantification of SFTSV RNA by real-time RT-PCR.
Results: The viral RNA was undetectable in 55.6% of the patients on admission into the hospital, becoming detectable in most cases until three days and attained maximum level on six days after disease onset. This was followed by an obvious decrease thereafter, but maintained detectable for over 20 days. Viral load was independently predictable of severe disease outcome throughout the hospitalization. Viral load of $>10^7$ copies/mL was predictable of fatal outcome. The serum levels of PLT, WBC, LDH, AST and CK were significantly associated with viral loads level.
Conclusions: The diagnosis of SFTSV infection based on PCR test should be performed at least three days after disease onset. Peaking viral loads were attained around six days after disease, posing a highest risk of human-to-human transmission.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS), caused by novel bunyavirus (SFTSV), is a potentially fatal infection that was first identified in China, subsequently found in Japan and Korea [1–3]. The overall mortality rate of SFTSV infection is about 12%, ranging from 6.3% to 30.0% in various studies [4,5]. SFTSV is thought to circulate in an enzootic tick-vertebrate cycle, with most of cases acquiring infection through tick bites. Person to person transmission through contact with blood or body fluids was considered as another important infection route [6,7]. Multiple nosocomial infection events had been reported from health-care workers and relatives of patients, who acquired second infection during the process of caring for patients [8,9]. Measurement of viral load has become an integral part of disease management, from the confirmation of SFTSV, guiding the disease prevention, monitoring of antiviral treatment effects and prediction of disease progression and outcome. Here we measured the viral load in SFTS patients and assessed its correlation with other laboratory parameters and disease outcomes.

* Corresponding author at: State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, 20 Dong-Da Street, Fengtai District, Beijing 100071, PR China.
** Corresponding author at: School of Public Health, Peking University, No. 38 Xue-Yuan Road, Haidian District, Beijing 100191, PR China.
E-mail addresses: qingbinlu@bjmu.edu.cn (Q.-B. Lu), lwbime@163.com (W. Liu).
[1] These authors contributed equally to the study.

http://dx.doi.org/10.1016/j.jcv.2016.03.017
1386-6532/© 2016 Elsevier B.V. All rights reserved.

2. Material and methods

A prospective, observational study was conducted in the PLA 154 hospital and the Shangcheng County People's Hospital, Xinyang, Henan Province in 2013, using the same protocol as previously described [10]. The disease onset was defined as the day when the initial SFTS like symptoms were observed. For close monitor of their clinical progression, serum samples were sequentially collected once every 1–2 days during the early stage after hospitalization and every 3 days after achievement of a stable illness state. Patients were recruited into the study once laboratory diagnosis of SFTSV infection was established by real-time RT-PCR [10] and the sampling was continued until their discharge from the hospital. The criteria for patients discharge was resolve of clinical syndromes. All samples were subjected for SFTSV RNA detection and quantification by real-time RT-PCR as previously described [10]. In brief, the copy number of viral cDNA in copies/mL sera samples was determined by comparison with a serially diluted plasmid standard of known concentration. Standard curves included 5 dilutions and 3 replicate wells for each dilution. All samples were quantified in at least duplicate wells. The real-time PCR reactions were carried out using the ABI7500 machine (Applied Biosystems). The lower detection limit for this SFTSV real-time PCR assay is 10^2 copies/mL.

Clinical manifestations, hematological and biochemical indicators, details of antiviral treatment received were prospectively collected from the recruited patients by reviewing the medical records and entered into a standard form by trained epidemiological group. The clinical outcome was categorized into fatal, severe or mild. Severe cases were defined by presenting any one of the following: hemorrhagic manifestations, one or more organ failure, and encephalopathy development.

The research protocol was approved by the human ethics committee of the PLA 154 Hospital. All participants provided informed consent.

2.1. Statistical analysis

Descriptive statistics were performed 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. SFTSV RNA concentrations (copies/mL) were log-transformed before statistical analyses were performed. Initial and maximum viral concentration was compared for their difference regarding the demographic information by student's *t* test. Thereafter all the variables were entered into multiple generalized linear regression models to identify independent factors, and the odds ratio (OR) and 95% confidence interval (CI) were calculated for each explanatory variable. The generalized estimating equation (GEE) was applied to evaluate the factors impacting on the viral accumulation and viral clearance, which took into account the correlation between viral loads obtained at baseline and at follow-up points in the same patient [11]. For longitudinal measurements, spearman's rank correlation coefficient was calculated to assess correlations between viral concentration and laboratory evaluation. A two-sided P value of <0.05 was considered to be statistically significant. All analyses were performed using SAS software, version 9.1.3.

3. Results

3.1. Patient recruit and sample collection

From April to November 2013, a total of 268 patients with confirmed SFTSV infection were hospitalized, among whom 208 were included into the study. Sixty patients were excluded due to incomplete information collection or sample collection. The mean (±SD) age of the recruited patients was 58.4 (±12.6) years old and 86 (41.4%) were male; 51 (24.5%) patients had coexisting medical conditions. Altogether 74 (35.6%) patients developed severe disease. Age, gender and disease severity were comparable between the recruited patients and non-recruited patients who were hospitalized during the study period (Supplemental Table 1). The median duration of hospitalization was 9 days (range 3–23 days). A median of 5 (range 4–12) serial measurements were obtained from each patient and the initial viral concentration measurement was obtained on median day 4 (rang 1–13) post disease onset.

3.2. The dynamic pattern of viral RNA concentrations

Time-dependent viral concentration was demonstrated to follow an invert "V" shape. The initial viral loads averaged to be 3.79 ± 2.38 Log_{10} copies/mL at day 3 post-infection, which sharply increased, reaching maximum level of 4.29 ± 2.59 Log_{10} copies/mL at day 6, and returned to 2.13 ± 2.16 Log_{10} copies/mL at day 15 post infection (Fig. 1). A correlation between viral RNA concentration and time elapsed from symptom onset, was observed, indicating spontaneous decrease (Spearman's correlation analysis; $P < 0.001$). The PCR positive rate for SFTSV was calculated to be 44.4% (4/9) on one day after disease onset, peaking at 82.5% (33/40) on three days,

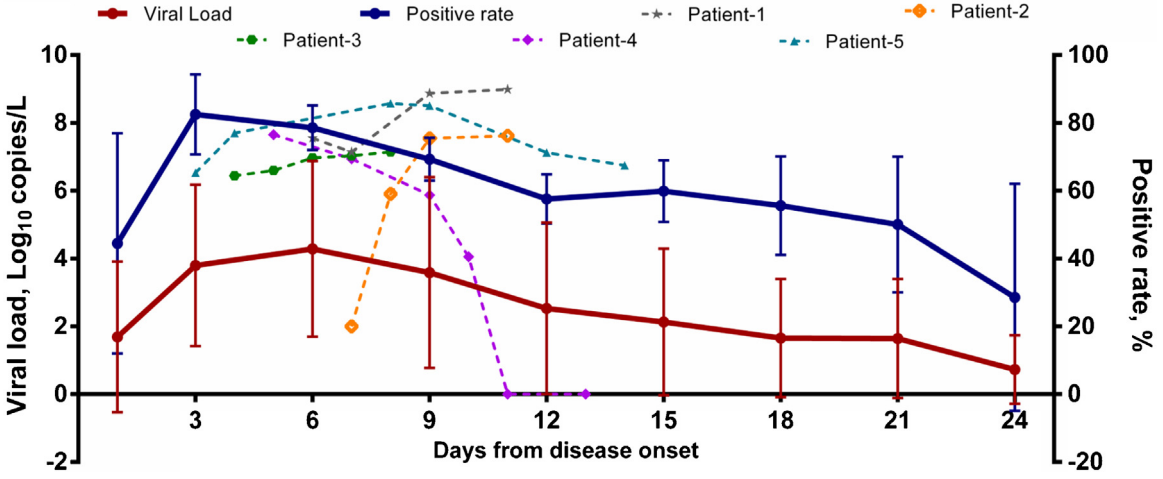

Fig. 1. The profiles of viral RNA concentration and positive rate of SFTSV infection. The upper solid lines represent the log 10-transformed viral RNA concentration. The lower solid lines represent the positive rate of SFTSV infection. The dotted lines represent the viral RNA concentrations of fiver fatal cases with SFTSV infection.

Download English Version:

https://daneshyari.com/en/article/3368740

Download Persian Version:

https://daneshyari.com/article/3368740

Daneshyari.com