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Short Communication

# Common adverse events associated with ribavirin therapy for Severe Fever with Thrombocytopenia Syndrome

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ABSTRACT

Severe Fever with Thrombocytopenia Syndrome (SFTS) is associated with high mortality rate, for which antiviral therapy with ribavirin was recommended. Based on our previous study, no visible effect of ribavirin therapy in improving clinical outcome was observed. Here we have accumulated the sample size to 634, and by performing prospective observation on the clinical progress and laboratory parameters, we found a significantly higher incidence of anemia and hyperamylasemia in patients who received ribavirin therapy in comparison with those who received no therapy. Generalized estimating equation model disclosed a significant effect on hemoglobin reduction and blood amylase augmentation from ribavirin administration. The occurrence of anemia and hyperamylasemia was associated with SFTS patients receiving ribavirin therapy, which might be adverse event of this drug administration. The recommendation of ribavirin for treating SFTS should be applied with caution.



## 1. Results and discussion

Severe Fever with Thrombocytopenia Syndrome (SFTS) is an emerging infectious disease, firstly reported in central China, but with a wide distribution in 16 provinces in mainland China and other Asian countries recently (Liu et al., 2014). The causative agent is identified to be a novel bunyavirus named SFTS virus (SFTSV), which is a phlebovirus in the *Bunyaviridae* family. Although with a high case fatality rate of over 10%, no specific therapy strategy has been standardized in clinical practice. Ribavirin has been recommended in the therapy of SFTSV infection by the Chinese Ministry of Health (Chinese Ministry of Health, 2011), due to its broad antiviral activities and known effectiveness in the treatment of Lassa fever and hepatitis C (Malleo et al., 2007; Oh et al., 2014). In our previous study to evaluate the clinical effect of ribavirin administration, no evidence of its efficiency in reducing case fatality or improving clinical recovery was obtained (Liu et al., 2013). Instead, it was unexpectedly found that the patients receiving ribavirin therapy had lower platelet counts than the non-ribavirin group throughout the observation period, although the differences attained no significance (Liu et al., 2013). It's queried whether the effect was generated from the infection itself or from the adverse event of ribavirin administration, as hemolytic anemia had been reported from ribavirin administration in treating other viral infections (da Silva et al., 2009; Sulkowski et al., 2013). Here by reutilizing the established patient cohort and additionally recruiting more patients, we made an observational study on a larger cohort of SFTS patients to observe the potential adverse events that might be related with ribavirin administration.

The study was carried out in one sentinel hospital for SFTS (PLA 154 hospital) in Xinyang, Henan Province, and all laboratory-confirmed patients were recruited as defined in previous report (Liu et al., 2013). The research protocol was approved by the human ethics committee of the PLA 154 hospital, and all participants provided written informed consent. The assay to detect SFTSV RNA by real-time RT-PCR and SFTSV-specific IgG antibodies by

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enzyme-linked immunosorbent assay (ELISA) were performed as previously described (Liu et al., 2013). Patients with immunosuppressed status, including with cancer, diabetes and acute hepatitis, were excluded from the study. The medical records were reviewed to collect the patients' demographic information and to identify the development of two major outcomes, i.e., anemia and hyperamylasemia. For any event occurrence throughout the hospitalization, the dates of its emergence and disappearance were also recorded. As routinely practiced in China, the anemia was defined as hemoglobin < 120 g/L for male and hemoglobin < 110 g/L for female.

Categorical variables among different patient groups were compared with $\chi^2$ or Fisher exact tests and continuous variables were compared with two-sample Wilcoxon rank–sum test. Logistic regression model and generalized estimating equation (GEE) were used to explore the associations between the diseases and other variables. All statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, North Carolina) and $P < 0.05$ was considered statistically significant.

During 2011–2013, a total of 634 laboratory confirmed patients were recruited and patients with cancer (3) and acute hepatitis (57) were excluded. Therefore altogether 574 SFTS patients were included for final analysis, among whom 408 (71.1%) received ribavirin therapy and 166 (28.9%) received no antiviral therapy. For those patients receiving ribavirin therapy, standard regimen and dose were used, i.e., intravenous administration with 500 mg for consecutive 3–12 days. The two groups were comparable for age, gender and delay of hospital admission after disease onset. Therapeutic decisions were individualized by the attending physicians and no preference of being given ribavirin treatment in sicker patients was found. Most of the clinical and laboratory findings were comparable between two groups on admission into the hospital, except for more presence of myalgias, decreased level of consciousness and higher levels of ALT among non-ribavirin recipients. Other therapy was administered evenly between two groups (Supplemental Table 1). During the follow up observation of the hospitalization, severe clinical outcome, comprising hemorrhagic manifestations, or presence of one or more organ failure or the altered consciousness development, developed in 36.8% of the ribavirin group and 42.8% of the non-ribavirin group ($P = 0.180$, Supplemental Table 1).

The anemia was observed in 104 of the patients (18.6% of the ribavirin group and 16.9% of the non-ribavirin group, $P = 0.620$) before the ribavirin therapy was initiated. At the observation endpoint, altogether 282 (49.1%) developed anemia, which occurred at a median of 5 days (range 1–12 days) after receiving the therapy. The anemia incidence rate in ribavirin group was significantly higher than that obtained from the non-ribavirin receiving group (52.0% *vs.* 42.2%, $P = 0.033$). This difference remained significant after adjusting for age, sex, underlying condition and delay from hospitalization (adjusted OR = 1.153, 95% CI: 1.042–2.195; $P = 0.029$). If the anemia before ribavirin administration were excluded, the difference of subsequent anemia occurrence remained to be significant between two groups (40.6% in ribavirin group *vs.* 30.7% in non-ribavirin group, $P = 0.043$. Adjusted OR = 1.604, 95% CI: 1.045–2.462; $P = 0.031$).

When observed sequentially, the hemoglobin measurement reduced and the anemia developed with comparable rate between two groups at initial phase, but subsequently with an enhanced rate in the ribavirin group at 12 days post therapy (Fig. 1A). Significantly rapid decay of hemoglobin was observed in ribavirin group by GEE model if adjusted for age, sex and delay of hospitalization ($P = 0.047$). This trend persisted till the last observation time point, when a significantly lower hemoglobin level was attained in the ribavirin group ($P = 0.004$). Patients of older age, female gender and with prolonged hospital stay also displayed more rapid decay of hemoglobin (Supplemental Table 2).

Among the 574 patients, 235 patients failed to be evaluated for blood amylase measurements due to the missing information. Altogether 339 patients were observed for the occurrence of hyperamylasemia. The recruited and non-recruited patients were comparable for age, gender and delay of hospitalization, indicating no selection bias of two groups (Supplemental Table 3).

The hyperamylasemia developed was found in 39 patients at a median of 5 days (range 2–12 days) post ribavirin therapy with ribavirin (Fig. 1B). All of the hyperamylasemia in 39 patients occurred from the ribavirin receiving group (39/236, 16.5%), in contrast 7 (6.8%) of the patients receiving no ribavirin therapy developed the hyperamylasemia ($P = 0.016$). At day 6 post therapy, the median value of amylase level was 155.5 U/L in the ribavirin group, higher than 98.5 U/L in the non-ribavirin group. Female patients were more likely to develop the hyperamylasemia than male patients (OR = 6.330; 95% CI: 1.405–28.516; $P = 0.016$).

The dynamic profile of blood amylase levels was shown separately for two groups of patients (Fig. 1B). The median (range) amylase values at the early phase of hospitalization was 96 (28–2850) U/L and 87 (8–475) U/L in ribavirin and non-ribavirin group, respectively ($P = 0.336$). Thereafter at 6 days post therapy, a rapid increase was observed in the ribavirin group, resulting in yielding a significantly higher amylase level than the non-ribavirin group ($P = 0.013$). GEE model was similarly applied to evaluate the increase rates of amylase for two groups, which displayed a significantly rapid increase of amylase in ribavirin group, after adjusting age, sex and delay of hospitalization ($P = 0.002$) (Supplemental Table 2).

The current study described the overrepresentation of anemia and hyperamylasemia in SFTS patients who received ribavirin therapy. This effect was postulated to be partially attributed to the adverse effect of the therapy. Ribavirin is a broad-spectrum purine nucleoside analogue antiviral agent that has been recommended for SFTS therapy, in view of its broad-spectrum antiviral activity. High-dose intravenous ribavirin has been used in the treatment of Lassa fever and hemorrhagic fever with renal syndrome, yet with common adverse events temporally associated with the use of ribavirin (Chinese Ministry of Health, 2011; Malleo et al., 2007).

We disclosed the occurrence of anemia and hyperamylasemia with higher frequencies in ribavirin therapy group, although their demographic and clinical characteristics were comparable with those of non-ribavirin group. The hyperamylasemia predominantly developed in patients receiving ribavirin therapy, presented as one of the complication post SFTSV infection. To explain this adverse effect, there is other impacting factor that should be considered. As has been investigated, the cytokine storm also played a pivotal role in the pathogenesis of acute pancreatitis, mainly manifesting as the hyperamylasemia, in addition to abdominal pain (Malleo et al., 2007; Sah et al., 2013). Therefore combined effect from both cytokine production and use of ribavirin might cause the hyperamylasemia ensuing SFTSV infection. The unexplored factors, as well as the potential interaction warrant further investigation in the future studies. Before the ribavirin therapy, the anemia has occurred, however, proceeding to a more severe extent in ribavirin group after 12 days' therapy. The occurrence of anemia is therefore postulated as the combined effect of ribavirin therapy and SFTV infection. Due to the short hospitalization duration, the symptoms resolve after discontinuation of ribavirin therapy cannot be evaluated in this study.

As with all hemorrhagic fever syndromes, the mainstay of treatment for SFTS is supportive, including supplement of blood and blood products and providing intensive care for severe cases. Although ribavirin is recommended for clinical use (Chinese