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Review

Clinical significance of C-reactive protein in patients with severe fever with thrombocytopenia syndrome

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Abstract

Objective: To examine the clinical significance of elevated C-reactive protein (CRP) levels in cases of severe fever with thrombocytopenia syndrome (SFTS), with a particular focus on their role in predicting outcomes beyond that of previous reports.
Patients and Methods: CRP values and SFTS case data retrieved from a PubMed search were extracted for analysis. For comparison, the subjects were divided into two groups based on their CRP levels: normal (CRP ≤0.3 mg/mL) and elevated (CRP >0.3 mg/dL).
Results: Forty-four cases were identified: 25 with normal CRP levels and 19 with elevated CRP levels. In an univariate analysis, no significant differences were observed between the two groups with respect to age, sex, date of blood examination, white blood cell count, outcome, or lactate dehydrogenase, alanine transaminase, creatine, or ferritin levels. However, the normal group contained a higher proportion of women, and the incidence of other infectious diseases was relatively low.
Conclusion: In cases of SFTS, a CRP level >0.3 mg/dL in the first collection indicates the potential for a mixed infection other than an SFTS-associated infection and male prevalence. Further prospective studies are necessary to confirm whether the findings of the present study are generalizable among patients with SFTS.

Key words: C-reactive protein, severe fever with thrombocytopenia syndrome, mixed infection, male prevalence

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is thought to be transmitted to humans through the bites of Diptera, hawksbill, and llama ticks, which carry *Bandavirus dabieense* of the family *Fenuiviridae*. The possibility of animal-to-human or human-to-human transmission has also been suggested[1]. Patients are predominantly elderly (median age, 75 years), with 11% younger than 60 years. No sex-related differences have been observed[1]. Deaths occur more frequently in older than in younger patients, and the estimated fatality rate in Japan is 27%[1].

The principal clinical signs of severe SFTS include hemorrhagic fever, gastrointestinal symptoms, myalgia, arthralgia, dizziness, chills, and localized lymph node enlargement[1]. In severe cases, there is the potential for multiple organ failure, including rhabdomyolysis, hemophagocytosis, renal failure, coagulopathy, shock, and disturbance of consciousness[1]. The most common laboratory abnormalities are thrombocytopenia (95%); leukopenia (86%); elevated serum alanine aminotransferase (ALT), aspartate aminotransferase, lactate dehydrogenase (LDH), creatine kinase (CK), and ferritin levels; and prolonged activated partial thromboplastin time[1–3]. Although C-reactive protein (CRP) levels are often within normal limits[2, 3], reports from China indicate that high CRP levels are a risk factor for death[4–6]. Therefore, in the present study, we examined the clinical significance of elevated CRP levels other than predicting outcome in SFTS cases, using previous reports.

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Patients and Methods

The PubMed database was searched on December 5, 2024 using the following search terms: "SFTS" + "CRP" and "SFTS" + "case report". CRP values and case data were extracted from the retrieved papers for analysis. The dataset comprised the subject's age; sex; initial CRP level (if tested multiple times); date of initial CRP blood collection; white blood cell count on the same day as the initial CRP measurement; LDH, CK, ALT, creatinine (Cre), and ferritin levels; infection-related complications; and final outcome (alive or dead). For comparison, the subjects were divided into two groups based on their CRP level: normal (control) (CRP ≤0.3 mg/dL) and elevated (CRP >0.3 mg/dL).

All statistical analyses were performed using the JMP 18.0 software program (SAS Japan Incorporation, Tokyo, Japan). Comparisons between the two groups were analyzed using the non-paired Student's t-test or χ^2 test. *P*-values <0.05 were considered statistically significant. All data are presented as numbers or means with 95% confidence (CI) intervals. Finally, multivariate logistic regression was performed using the results of the univariate analysis to identify independent predictors of elevated CRP levels (>0.3 mg/dL).

Results

We retrieved 41 reports with 44 cases of SFTS: in these cases, 25 patients were in the normal CRP group and 19 in the elevated CRP group[7–47]. The results of the comparisons between the two groups are shown in Table 1. There were no statistically significant differences in age; date of blood examination; white blood cell count; LDH, ALT, Cre or ferritin levels; or outcome between the groups. Women were more common in the normal group, and the infection-complication rate was low.

Multivariate logistic regression analysis identified both a mixed infection [odds ratio (OR):7.6, *P*=0.01, 95% CI: 1.4–63.4] and male (OR: 4.3, *P*=0.03, 95% CI: 1.1–19.1) as independent predictors of elevated CRP levels. The diagnoses were pathogen infection (galactomannan- and 1,3-β-D glucan-positive *aspergillosis*, *Acinetobacter baumannii*, and *Orientia tsutsugamushi*), urinary tract infection due to *Escherichia coli* (two cases), oral *Streptococci*, and necrotizing lymphadenitis or pneumonia due to an undescribed pathogen.

Discussion

This study presents the initial findings of elevated CRP levels (>0.3 mg/dL) in SFTS cases, suggesting the potential for a mixed infection other than an SFTS-associated infection and a notable prevalence in male patients.

In a comparative study of patients with SFTS and Japanese spotted fever (JSF), Kawaguchi *et al.* identified leukopenia and normal CRP levels (≤1.0 mg/dL) as variables that could distinguish SFTS from JSF[3]. In their study, normal CRP levels exhibited 95% sensitivity and 97% specificity for SFTS, with a positive likelihood ratio of 37.1[3]. Additionally, CRP levels were elevated in two SFTS cases with a secondary infection (pneumonia), which is consistent with our findings.

Chen *et al.* investigated the association between classical inflammatory biomarkers, including ferritin, procalcitonin (PCT), and CRP, and viral load in 256 patients with SFTS divided into survivors and non-survivors[6]. Their findings revealed that the ferritin level had the strongest positive association with viral load. Both PCT and CRP levels were

Table 1 Results of the comparisons between the two groups

	Normal (<0.3 mg/dL) (n=25)	Over (≥0.3 mg/dL) (n=19)	*P*-value
CRP (mg/dL)	0.12 (0.07, 0.17)	2.22 (0.78, 3.66)	<0.0001
Age (years)	60.7 (51.0, 70.4)	63.1 (55.1, 71.0)	0.94
Sex (female/male)	16/9	6/13	0.03
Days from onset to measurement	5.0 (4.0, 6.0)	6.1 (4.9, 7.3)	0.11
White blood cell (/μL)	1,712 (1,191, 2,233)	3,091 (265, 5,917)	0.56
Lactate dehydrogenase (IU/L)	801 (481, 1,121)	941 (655, 1,227)	0.16
Creatine kinase (IU/L)	1,854 (97, 3,610)	5,649 (−695, 6,484)	0.40
Alanine transaminase (IU/L)	95 (44, 145)	108 (69, 147)	0.07
Creatinine (mg/dL)	1.01 (0.69, 1.33)	1.30 (0.95, 1.65)	0.14
Ferritin (ng/mL)	4,485 (842, 8,128)	25,266 (−31,668, 82,200)	0.32
Complications of other infections (yes/no)	2/23	12/7	0.01
Outcome (live/dead)	18/7	12/9	0.53

CRP: c-reactive protein.

significantly higher in non-survivors than in survivors at 13–15 days after symptom onset. Thus, there appears to be a positive correlation between PCT and CRP levels. Elevated PCT levels usually suggest a bacterial rather than a viral infection[48]. Numerous studies indicate that patients with (vs. without) SFTS are more susceptible to pulmonary bacterial or fungal coinfections, which are associated with high mortality rates[49]. Consequently, the results of these studies suggest that an elevated CRP level in the late phase may contribute to the development of a complicated bacterial or fungal infection, a finding analogous to our own.

In the retrospective investigation of 290 consecutive patients with SFTS conducted by Zhang *et al.*, systemic inflammatory response syndrome (SIRS) was an independent risk factor for the prognosis of patients with SFTS[5]. The cumulative survival rate was significantly lower in patients with SIRS than in those without SIRS. Patients who presented with SIRS had elevated levels of AST, LDH, lipase, CK, troponin I, D-dimer, and CRP and an increased activated partial thromboplastin time, thrombin time, and viral load compared with patients who did not present with SIRS. Moreover, patients with SIRS had a higher prevalence of bacterial or fungal infections than did those without SIRS. Consequently, the authors proposed that bacterial or fungal infections may contribute significantly to the higher in-hospital mortality of patients with SIRS-positive SFTS. Accordingly, their findings suggest that elevated CRP levels in patients with SIRS may indicate the severity of bacterial or fungal infections, a hypothesis that is consistent with our observations.

The present study did not demonstrate a heightened risk of mortality associated with elevated CRP levels, which is contrary to the findings of previous reports from China on elevated CRP levels linked to multiple organ failure and fatality[4–6]. However, a considerable number of the SFTS reports in the present study measured CRP levels in countries with longer life expectancies and more advanced medical care than in China. Specifically, 26 studies were conducted in Japan, 12 in Korea, and only three in China[49]. When appropriate medical care is provided for complicated mixed infections, deaths due to mixed infections might be rare. Consequently, even if elevated CRP levels were identified, they may not have resulted in increased mortality.

Women generally have higher CRP levels than do men. One potential explanation for this phenomenon is the existence of sex-specific relationships between CRP and obesity. Specifically, it has been postulated that CRP levels increase to a greater extent with increasing adiposity in women than in men[50]. However, men have higher plasma levels of innate immune cytokines, which may contribute to the upregulation of CPR production[51]. Men are more susceptible to severe symptoms and corona virus disease 2019 (COVID-19)-associated mortality than are women[51], and median CRP levels are significantly higher in male vs. female patients with COVID-19[52]. Men have greater disease severity, with significantly higher intensive care unit admission and hospital mortality[52]. These findings may reflect the affect of sex hormones and sex chromosomes on immune cells and their regulatory genes[52]. With regard to SFTS, the overall reported case fatality rate was 15.3% among 2,938 patients, with a higher incidence observed in men than in women[53]. In individuals with SFTS, the immune response has been shown to differ according to sex[53]. These differences may have potentially influenced the CRP levels in the male and female participants in this study.

The present study is limited by several factors. The number of cases was small, and previous case reports from different back grounds were analyzed. Additionally, the timing of CRP measurement from SFTS onset varied, making it unclear whether the patient's CRP level remained negative throughout the entire course of the SFTS-associated infection. Additionally, the CRP measurement method may have differed among the previous reports. Therefore, further prospective studies are necessary to address these limitations.

Conclusion

The present study demonstrates that in cases of SFTS, initial serum CRP levels exceeding 0.3 mg/dL indicate the potential for a mixed infection other than an SFTS-associated infection and male prevalence. Further prospective studies are necessary to confirm whether the findings of the present study are generalizable among patients with SFTS.

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References

1. Ujiie M, Kato Y, Kutsuna S, *et al*. Severe fever with thrombocytopenia syndrome. Guide to medical treatment. 2024. In Japanese https://dcc.ncgm.go.jp/prevention/resource/2019SFTS.pdf.
2. Sul H, Yun NR, Kim DM, *et al*. Development of a scoring system to differentiate severe fever with thrombocytopenia syndrome from scrub typhus. Viruses 2022; 14: 1093. [Medline] [CrossRef]
3. Kawaguchi T, Umekita K, Yamanaka A, *et al*. Impact of C-reactive protein levelson differentiating of severe fever with thrombocytopenia syndrome from Japanese spotted fever. Open Forum Infect Dis. 2020; 7: ofaa473.
4. Guo C, Wang H, Wang X, *et al*. High CRP/PNI levels predict an unfavorable prognosis in severe fever with thrombocytopenia syndrome: a propensity score matching study. Immun Inflamm Dis 2024; 12: e1184. [Medline] [CrossRef]
5. Zhang Z, Hu X, Jiang Q, *et al*. Systemic inflammatory response syndrome in patients with severe fever with thrombocytopenia syndrome: prevalence, characteristics, and impact on prognosis. BMC Infect Dis 2024; 24: 149. [Medline] [CrossRef]
6. Chen K, Sun H, Geng Y, *et al*. Ferritin and procalcitonin serve as discriminative inflammatory biomarkers and can predict the prognosis of severe fever with thrombocytopenia syndrome in its early stages. Front Microbiol 2023; 14: 1168381. [Medline] [CrossRef]
7. Fukumoto N, Miyamoto K, Nakashima T, *et al*. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome due to severe fever with thrombocytopenia syndrome. Cureus 2023; 15: e39138. [Medline]
8. Meng X, Liu Y, Li J, *et al*. Metagenomic next-generation sequencing for diagnosis and efficacy evaluation of a critical case of SFTS complicated by invasive pulmonary aspergillosis. IDCases 2023; 33: e01884. [Medline] [CrossRef]
9. Nishiyama M, Yokota K, Morimoto N. Recurrent rhabdomyolysis in a patient with a history of rhabdomyolysis due to severe fever with thrombocytopenia syndrome. IDCases 2023; 32: e01807. [Medline] [CrossRef]
10. Okutsu S, Futami M, Arimura T, *et al*. Acute myocarditis with severe fever and thrombocytopenia syndrome. Intern Med 2022; 61: 1779–1784. [Medline] [CrossRef]
11. Iwao K, Kawaguchi T, Kimura M, *et al*. Severe fever with thrombocytopenia syndrome accompanied by invasive pulmonary aspergillosis: an autopsy case. Viruses 2021; 13: 1086. [Medline] [CrossRef]
12. Lee H, Choi WY, Kim CMY, *et al*. A case of SFTS coinfected with E. coli bacteremia. BMC Infect Dis 2021; 21: 25. [Medline] [CrossRef]
13. Mizoe A, Sakaue J, Takahara N. Why does activated partial thromboplastin time prolongation occur in severe fever with thrombocytopenia syndrome? BMJ Case Rep 2020; 13: e235447. [Medline] [CrossRef]
14. Choi S, Kim MC, Kwon JS, *et al*. Case report: use of plasma exchange followed by convalescent plasma therapy in a critically ill patient with severe fever and thrombocytopenia syndrome-associated encephalopathy: cytokine/chemokine concentrations, viral loads, and antibody responses. Am J Trop Med Hyg 2018; 99: 1466–1468. [Medline] [CrossRef]
15. Yoo JR, Heo ST, Kang JH, *et al*. Mixed infection with severe fever with thrombocytopenia syndrome virus and two genotypes of scrub typhus in a patient, South Korea, 2017. Am J Trop Med Hyg 2018; 99: 287–290. [Medline] [CrossRef]
16. Uchida Y, Kanekura T. Two cases of severe fever with thrombocytopenia syndrome virus infection. J Dermatol 2018; 45: e106–e107. [Medline] [CrossRef]
17. Kim UJ, Kim DM, Ahn JH, *et al*. Successful treatment of rapidly progressing severe fever with thrombocytopenia syndrome with neurological complications using intravenous immunoglobulin and corticosteroid. Antivir Ther 2016; 21: 637–640. [Medline] [CrossRef]
18. Sako Y, Fujihara T, Ishida R, *et al*. Fatal severe fever with thrombocytopenia syndrome virus and Pasteurella multocida coinfection. Intern Med 2024; 63: 749–752. [Medline] [CrossRef]
19. Otsuka Y, Tanizaki R, Nomura Y. Leukocytoclastic vasculitis secondary to severe fever with thrombocytopenia syndrome. Intern Med 2024; 63: 1479–1483. [Medline] [CrossRef]
20. Yamauchi N, Hongo T, Kawakami M, *et al*. Successful recovery from severe fever with thrombocytopenia syndrome and hemophagocytic lymphohistiocytosis with standard treatment and a calcium channel blocker of nicardipine hydrochloride. Intern Med 2023; 62: 1365–1369. [Medline] [CrossRef]
21. Miyauchi A, Sada KE, Yamamoto H, *et al*. Suspected transmission of severe fever with thrombocytopenia syndrome virus from a cat to a veterinarian by a single contact: a case report. Viruses 2022; 14: 223. [Medline] [CrossRef]
22. Kim AR, Kim T, Shin DH, *et al*. Severe fever with thrombocytopenia syndrome with necrotizing lymphadenitis in a patient who underwent ^{18}F-FDG PET/CT: a case report. Int J Environ Res Public Health 2021; 18: 10488. [Medline] [CrossRef]
23. Kim UJ, Park H, Kim KH, *et al*. Veno-arterial extracorporeal membrane oxygenation for severe fever with thrombocytopenia syndrome with fulminant myocarditis: a case report. BMC Infect Dis 2021; 21: 803. [Medline] [CrossRef]
24. Kim M, Heo ST, Seong GM, *et al*. Severe fever with thrombocytopenia syndrome (SFTS) associated with invasive pulmonary Aspergillosis in a patient with a low CD4+ T-cell count: a case report. Int J Crit Illn Inj Sci 2020; 10(Suppl 1): 53–56. [Medline] [CrossRef]
25. Chung JK, Kim CM, Kim DM, *et al*. Severe fever with thrombocytopenia syndrome associated with manual de-ticking of domestic dogs. Vector Borne Zoonotic Dis 2020; 20: 285–294. [Medline] [CrossRef]
26. Imataki O, Uemura M, Masugata H. Severe rhabdomyolysis associated with severe fever with thrombocytopenia syndrome in a married couple: a case report. BMC Infect Dis 2019; 19: 885. [Medline] [CrossRef]
27. Fujikawa K, Koga T, Honda T, *et al*. Serial analysis of cytokine and chemokine profiles and viral load in severe fever with thrombocytopenia syndrome: case report and review of literature. Medicine (Baltimore) 2019; 98: e17571. [Medline] [CrossRef]
28. Sato T, Nishida H, Goto M, *et al*. Cutaneous histopathology of the tick-bite region in severe fever with thrombocytopenia syndrome. J Dermatol 2019; 46: 409–412. [Medline] [CrossRef]
29. Miyamoto S, Ito T, Terada S, *et al*. Fulminant myocarditis associated with severe fever with thrombocytopenia syndrome: a case report. BMC Infect Dis 2019; 19: 266. [Medline] [CrossRef]
30. Shimazu Y, Saito Y, Kobayashi KI, *et al*. Non-severe form of severe fever with thrombocytopenia syndrome (SFTS). Ann Hematol 2018; 97: 735–736. [Medline] [CrossRef]
31. Nakano A, Ogawa H, Nakanishi Y, *et al*. Hemophagocytic Lymphohistiocytosis in a fatal case of severe fever with thrombocytopenia syndrome. Intern Med 2017; 56: 1597–1602. [Medline] [CrossRef]
32. Zhu CH, Xu D, Liu W, *et al*. Pediatric huaiyangshan virus infection: a case report with literature review. IDCases 2017; 9: 21–24. [Medline] [CrossRef]
33. Park I, Kim HI, Kwon KT. Two treatment cases of severe fever and thrombocytopenia syndrome with oral ribavirin and plasma exchange. Infect Chemother

2017; 49: 72–77. [Medline] [CrossRef]
34. Oh HS, Kim M, Lee JO, *et al*. Hemophagocytic lymphohistiocytosis associated with SFTS virus infection: a case report with literature review. Medicine (Baltimore) 2016; 95: e4476. [Medline] [CrossRef]
35. Shin SY, Cho OH, Bae IG. Bone marrow suppression and hemophagocytic histiocytes are common findings in Korean severe fever with thrombocytopenia syndrome patients. Yonsei Med J 2016; 57: 1286–1289. [Medline] [CrossRef]
36. Kurihara S, Satoh A, Yu F, *et al*. The world first two cases of severe fever with thrombocytopenia syndrome: an epidemiological study in Nagasaki, Japan. J Infect Chemother 2016; 22: 461–465. [Medline] [CrossRef]
37. Kawaguchi T, Matsuda M, Takajo I, *et al*. Severe fever with thrombocytopenia syndrome with myocardial dysfunction and encephalopathy: a case report. J Infect Chemother 2016; 22: 633–637. [Medline] [CrossRef]
38. Zhang Y, Huang Y, Xu Y. Infection of severe fever with thrombocytopenia syndrome virus as a cause of a child's fever of unknown origin: a case report. Infect Drug Resist 2022; 15: 4871–4875. [Medline] [CrossRef]
39. Utsunomiya Nishimizu R, Shiota S, Ishii T, *et al*. Plasma exchange did not reduce viral load in a recovered case of severe fever with thrombocytopenia syndrome. Intern Med 2022; 61: 253–256. [Medline] [CrossRef]
40. Toyota Y, Uda K, Shirabe K, *et al*. Pediatric severe febrile thrombocytopenia syndrome: a case report and literature review. Acta Med Okayama 2024; 78: 401–405. [Medline]
41. Tsuru M, Suzuki T, Murakami T, *et al*. Pathological characteristics of a patient with severe fever with thrombocytopenia syndrome (SFTS) infected with SFTS virus through a sick cat's bite. Viruses 2021; 13: 204 [CrossRef]. [Medline]
42. Yamanaka A, Kirino Y, Fujimoto S, *et al*. Direct transmission of severe fever with thrombocytopenia syndrome virus from domestic cat to veterinary personnel. Emerg Infect Dis 2020; 26: 2994–2998. [Medline] [CrossRef]
43. Nakamura S, Iwanaga N, Hara S, *et al*. Viral load and inflammatory cytokine dynamics associated with the prognosis of severe fever with thrombocytopenia syndrome virus infection: an autopsy case. J Infect Chemother 2019; 25: 480–484. [Medline] [CrossRef]
44. Kaneko M, Shikata H, Matsukage S, *et al*. A patient with severe fever with thrombocytopenia syndrome and hemophagocytic lymphohistiocytosis-associated involvement of the central nervous system. J Infect Chemother 2018; 24: 292–297. [Medline] [CrossRef]
45. Lee J, Jeong G, Lim JH, *et al*. Severe fever with thrombocytopenia syndrome presenting with hemophagocytic Lymphohistiocytosis. Infect Chemother 2016; 48: 338–341. [Medline] [CrossRef]
46. Uehara N, Yano T, Ishihara A, *et al*. Fatal severe fever with thrombocytopenia syndrome: an autopsy case report. Intern Med 2016; 55: 831–838. [Medline] [CrossRef]
47. Yanagawa Y, Nagasawa H, Isogai R, *et al*. A case of severe fever with thrombocytopenia syndrome with normal CRP levels and an inverse relationship between LDH and CRP. J Emerg Trauma Shock (in press).
48. Kiya GT, Asefa ET, Abebe G, *et al*. Procalcitonin guided antibiotic stewardship. Biomark Insights 2024; 19: 11772719241298197. [Medline] [CrossRef]
49. Countries with the Best Health Care Systems 2024. CEO World Magazine. https://ceoworld.biz/2024/04/02/countries-with-the-best-health-care-systems-2024/ Accessed December 6, 2024.
50. Khera A, Vega GL, Das SR, *et al*. Sex differences in the relationship between C-reactive protein and body fat. J Clin Endocrinol Metab 2009; 94: 3251–3258. [Medline] [CrossRef]
51. Takahashi T, Ellingson MK, Wong P, *et al*. Yale IMPACT Research Team. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 2020; 588: 315–320. [Medline] [CrossRef]
52. El Aidaoui K, Ait Benhamou R, Haoudar A, *et al*. Sex differences in COVID-19 outcomes. Cureus 2022; 14: e25760. [Medline]
53. Zhao J, Lu QB, Li H, *et al*. Sex differences in case fatality rate of patients with severe fever with thrombocytopenia syndrome. Front Microbiol 2021; 12: 738808. [Medline] [CrossRef]