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MAJOR ARTICLE

Impact of C-Reactive Protein Levels on Differentiating of Severe Fever With Thrombocytopenia Syndrome From Japanese Spotted Fever

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Background. Severe fever with thrombocytopenia syndrome (SFTS) is an emerging viral hemorrhagic fever in China, Korea, and Japan. Japanese spotted fever (JSF), which belongs to spotted fever group rickettsioses, is also endemic to Western Japan. Patients with SFTS and those with JSF display many of the same clinical manifestations. Sudden fever, rash, tick bite, and neurological and gastrointestinal symptoms may be seen in both infections, but the frequency and severity of each disease have not been compared and studied. Because laboratory confirmation of pathogens takes time, it is important to predict diagnosis of SFTS vs JSF based on the features of the clinical characteristics at the initial presentation, particularly in primary care settings.

Methods. We conducted a case series review at 4 medical facilities in Miyazaki, Japan. Based on the medical records, clinical and laboratory characteristics were compared between patients with SFTS and those with JSF.

Results. Eighty-one patients were enrolled in this study, including 41 with SFTS and 40 with JSF. The absence of rash ($P < .001$), leukopenia ($P < .001$), and normal C-reactive protein (CRP) levels ($P < .001$) were the variables distinguishing SFTS from JSF. Normal CRP levels (≤1.0 mg/dL) had a 95% sensitivity (84%–99%) and 97% specificity (87%–100%) for SFTS, with a positive likelihood ratio of 37.1 (5.35–257).

Conclusions. Normal serum CRP levels were shown to differentiate SFTS from JSF with a very high probability.

Keywords. differentiation; Japanese spotted fever; severe fever with thrombocytopenia syndrome.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging viral hemorrhagic fever in East Asia [1]. The causative agent of SFTS is a novel *Banyangvirus* of the *Phenuiviridae* family, *Huaiyangshan bangyangvirus*, also called SFTS virus (SFTSV). SFTS was first reported in China in 2011 [2], and many cases of SFTS have been reported in China, South Korea, and Western Japan. Between 2013 and 2019, 50–70 cases of SFTS per year were reported in Japan [3]. Although the fatality rate of SFTS is 10%–20% in China and South Korea [4, 5], it is 31% in Japan [6] for unknown reasons. Japanese spotted fever (JSF) was first described in 1984 and is a member of the spotted fever group rickettsiosis [7]. JSF is caused by *Rickettsiae japonica* and presents a clinical manifestation similar to that of Mediterranean spotted fever. Except for 20 cases reported in China [8], 1 case reported in South Korea [9], and 1 case of a spotted fever group *Rickettsia* species closely related to *R. japonica* in Thailand [10], JSF has been confined to Western Japan. JSF cases in Japan increased from 66 in 2004 to 215 in 2015, with a fatality rate of 1.5%–2.3% [11]. Both SFTS and JSF are potentially fatal diseases; however, SFTS has a higher mortality rate.

These 2 endemic zoonoses are both tick-borne infections. Because the species of vector mites that carry both SFTS and JSF are *Haemaphysalis longicornis*, *H. flava*, and *Amblyomma testudinarium*, the seasons and regions in which both diseases occur are identical. Patients with SFTS and JSF show similar clinical manifestations. These include sudden fever, rash, tick bite, and neurological and gastrointestinal symptoms for both infections [12, 13]; however, no studies have compared the frequency and severity of each disease. Therefore, it is difficult to differentiate between SFTS and JSF during the initial presentation of acute febrile patients suspected of having a tick-borne infection. Early differential diagnosis of these 2 diseases is important because patients with each disease require different

Received 28 July 2020; editorial decision 28 September 2020; accepted 30 September 2020.

Prior presentation: This work was presented at the 2nd Annual Meeting of the Japanese Association for Severe Fever with Thrombocytopenia Syndrome on September 15, 2019, in Tokyo, Japan, under the title "Differentiation of Severe Fever With Thrombocytopenia Syndrome With Thrombocytopenia Syndrome From Japanese Spotted Fever."

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DOI: 10.1093/ofid/ofaa473

treatments and infection-control strategies. JSF can be treated with antibiotics, whereas an effective antiviral therapy for SFTS is lacking. Human-to-human transmission of SFTSV may occur through exposure to blood or body secretions [14]. Although a laboratory diagnosis of SFSTV and *R. japonica* infections can be established by the detection of pathogen genes or a serological analysis of antibodies, these tests take time and require special laboratory equipment. It would be more useful to predict a diagnosis of SFTS or JSF based on clinical characteristics at initial presentation, particularly in primary care settings. Two previous studies have analyzed the differences between SFTS and scrub typhus [15, 16], but the differences in the clinical manifestations of SFTS and JSF remain unknown. Additionally, it is important to differentially distinguish JSF from SFTS because patients with JSF frequently display more severe conditions than patients with scrub typhus [13]. Therefore, we assessed the clinical characteristics of SFTS and JSF, which is useful for differentiating these infections in Miyazaki, Japan, where both diseases are prevalent.

METHODS

Study Protocol

We conducted a retrospective case series review at 4 medical facilities (University of Miyazaki Hospital, Miyazaki Prefectural Miyazaki Hospital, Miyazaki Prefectural Nichinan Hospital, and Miyazaki Prefectural Nobeoka Hospital) in Miyazaki, Japan.

Based on the medical records, the baseline clinical and laboratory parameters were compared between patients with SFTS and those with JSF. Baseline characteristics included the season of infection, comorbidities, and the duration from the onset of illness to the first hospital visit. The laboratory parameters consisted of a complete blood count, chemistry, and coagulation system tests. Central nervous system involvement was evaluated to assess altered mental status and was defined as a Glasgow coma scale score <15, apathy, lethargy, dysarthria, tremors, or convulsions. Pulmonary involvement, such as bacterial pneumonia, pulmonary mycoses, and pulmonary hemorrhage, was evaluated. Cardiac involvement, including shock, heart failure, arrhythmia, cardiomyopathy, and ischemic heart disease, was also evaluated.

Patients

Adult patients aged ≥20 years with SFTS or JSF who presented to the medical facilities described above from January 2008 to December 2018 were enrolled in this study. These patients were suspected of having tick-borne infections because they showed several of the following symptoms: sudden fever, mountain dwelling, history of mountain activity, tick bite, rash, neurological and gastrointestinal symptoms, elevated liver enzymes, and no finding of other suspected infections. Patients with sudden fever, elevated liver enzymes, leukopenia, and thrombocytopenia were suspected of having SFTS regardless of a rash or tick bite. SFTS or JSF was diagnosed in each hospital described above. Reverse transcription polymerase chain reaction (RT-PCR) was used to detect the presence of the SFTSV gene in patient blood samples [17] or the *R. japonica* gene in blood or eschar [18]. Alternatively, in patients with JSF, a 4-fold increase in immunoglobulin G (IgG) of an indirect immunofluorescence assay to pathogens in samples obtained after a 2-week interval was also used for diagnosis [19]. These tests were performed in the Miyazaki Prefectural Institute for Public Health and Environment (Miyazaki, Japan), which is the local government-authorized laboratory for testing these infectious agents in Japan.

Statistical Analysis

We used the Fisher exact test to analyze categorical data and the Mann-Whitney *U* test to analyze continuous variables to compare patient characteristics by disease. A receiver operating characteristics (ROC) curve was constructed to compare the discrimination ability of each variable. All tests were 2-tailed, and a *P* value <.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria).

Patient Consent Statement

The study protocol was approved by the research ethics review committee of the Faculty of Medicine, University of Miyazaki (No. O-0241). Informed consent was obtained in the form of opt-out on the website from January 2008 to December 2017, and written informed consent was obtained from January to December 2018.

RESULTS

A total of 81 patients diagnosed in each hospital were enrolled in this study, including 41 with SFTS and 40 with JSF. The 40 patients with SFTS had their diagnoses confirmed by RT-PCR analysis of plasma samples, and 1 patient was diagnosed by the presence of increased antibodies to SFTSV. Twenty patients with JSF had diagnoses confirmed by PCR analysis (plasma sample in 8 patients and eschar sample in 12 patients). The remaining 20 patients were diagnosed by the increase of antibodies to *R. japonica*.

The clinical characteristics, outcomes, and treatments of these patients are shown in Tables 1–4. On average, the patients with SFTS (77 years) were older than those with JSF (70 years). Underlying diseases or durations before visiting the hospital were comparable between groups (Table 1).

Gastrointestinal and hemorrhagic symptoms and altered mental status were more frequently observed in patients with SFTS. By contrast, skin involvements were more frequently observed in patients with JSF than in those with SFTS (Table 2).

Table 1. Clinical Characteristics of the Subjects (n = 81)

Variable	SFTS (n = 41)	JSF (n = 40)	*P* Value
Season			.614
Spring–Summer (March–August)	32 (78.0)	29 (72.5)	
Autumn–Winter (September–February)	9 (22.0)	11 (27.5)	
Age, mean (SD), y	77 (12.7)	70 (13.5)	.05
Male sex	17 (41.5)	24 (60.0)	.12
Underlying disease[a]			
No obvious underlying disease	8 (20.0)	9 (25.0)	.78
Diabetes	4 (9.8)	8 (22.2)	.21
Hypertension	18 (43.9)	13 (36.1)	.48
Dyslipidemia	9 (22.0)	4 (11.1)	.23
Cardiovascular disease	3 (6.3)	3 (8.3)	1
Cerebrovascular disease	2 (4.9)	2 (5.6)	1
Chronic liver disease	3 (6.3)	0	.24
Rheumatic disease	0	3 (8.3)	.11
Solid tumor	0	1 (2.8)	.48
Immunosuppressive condition	0	2 (5.6)	.23
Independence in activities of daily living[b]	39 (95.1)	33 (97.1)	1
Duration before hospital visit, mean (SD), d	4 (2.0)	4 (2.0)	.45

All clinical characteristics were evaluated when the patients initially visited our hospital. Data are presented as the No. (%) of patients unless otherwise specified.

Abbreviations: JSF, Japanese spotted fever; SFTS, severe fever with thrombocytopenia syndrome.

[a]The available data are from 39 and 36 patients with SFTS and JSF, respectively.

[b]The available data are from 41 and 34 patients with SFTS and JSF, respectively.

Higher proportions of patients with SFTS had leukopenia, thrombocytopenia, prolonged activated partial thromboplastin time (aPTT), and elevated levels of aspartate aminotransferase, lactate dehydrogenase, and creatine kinase than the patients with JSF. C-reactive protein (CRP) levels were higher in the patients with JSF than in those with SFTS (Table 3).

The patients with SFTS had more complications than those with JSF, including central nervous system involvement, pulmonary involvement, and secondary bacterial and fungal infections. The patients with SFTS had a greater tendency to develop bacterial pneumonia, pulmonary mycoses, and bacteremia than those with JSF. All patients with JSF were treated with antibiotics, and the JSF fatality rate was 5%. None of the patients with SFTS received ribavirin or plasma exchange, and almost half of the patients with SFTS were administered corticosteroids for the treatment of virus-associated hemophagocytic syndrome. The SFTS fatality rate was 31.7%, which was higher than that of JSF (Table 4). Corticosteroid administration and secondary infections were more common in severe SFTS cases, including fatal cases, than in mild SFTS cases, but it is not clear whether corticosteroid administration affected death and secondary infections.

We tried to extract the variables that can distinguish SFTS from JSF at the first visit based on the data described above. When normal CRP levels or leukopenia was used, SFTS could be differentiated from JSF in most cases.

We compared the predictive accuracy of each variable for differentiating SFTS from JSF using the area under the ROC curve (AUC) (Table 5). The AUC was high for variables including absence of rash, leukopenia, and normal CRP levels, and it was the highest for normal CRP levels. Based on the ROC curves obtained for each variable, the optimal cutoff for differentiating SFTS from JSF was normal CRP <0.85 mg/dL (100%) and a white blood cell (WBC) count <3230/μL (99%), reflecting the presence of leukopenia (Supplementary Figure 1). Even if the cutoff for normal CRP levels was set to CRP ≤1.0 mg/dL, nearly the same AUC (96%) was reported. The same was true for a leukopenia cutoff with a WBC count <4000/μL (94%). Therefore, a normal CRP level of ≤1.0 mg/dL may be convenient for clinicians when distinguishing between SFTS and JSF. In this case, normal CRP levels (≤1.0 mg/dL) had a 95% sensitivity (84%–99%) and 97% specificity (87%–100%) for SFTS, with a positive likelihood ratio of 37.1 (5.35–257).

Table 2. Clinical Symptoms and Physical Findings (n = 81)

Variable	SFTS (n = 41)	JSF (n = 40)	*P* Value
Fever	40 (97.6)	40 (100)	1
Loss of appetite	**35 (85.4)**	**23 (57.5)**	**.007**
Vomiting	6 (14.6)	4 (10.0)	.74
Diarrhea	**22 (53.7)**	**5 (12.5)**	**<.001**
Tick bite/eschar	**13 (31.7)**	**33 (82.5)**	**<.001**
Rash	**10 (24.4)**	**39 (97.5)**	**<.001**
Lymphadenopathy	**15 (36.6)**	**4 (10.0)**	**.008**
Altered mental status	**21 (51.2)**	**11 (27.5)**	**.04**
Convulsion	1 (2.4)	0	1
Petechiae/purpura	**8 (19.5)**	**1 (2.5)**	**.02**
Oral bleeding	**8 (19.5)**	**0**	**.005**
Melena	5 (12.2)	1 (2.5)	.2

All physical findings were evaluated when the patients initially visited our hospital. Data are presented as the No. (%) of patients.

Abbreviations: JSF, Japanese spotted fever; SFTS, severe fever with thrombocytopenia syndrome.

DISCUSSION

JSF and scrub typhus are common tick-borne infections in Japan and are curative with antibiotics; however, it can take a few weeks for laboratory confirmation tests to see an increase in antibodies. Indeed, 20 (50%) of the JSF cases in the current study were diagnosed by serological tests. In addition, SFTS showed severe clinical manifestations in the patients in this study. Many complications, including bacterial and fungal infections in patients with SFTS, indicate the importance of early differentiation of SFTS from JSF.

In our study, altered mental status, thrombocytopenia, and prolonged aPTT were observed relatively frequently in patients with JSF and SFTS; however, these indicators occurred less frequently in JSF than in SFTS. Thrombocytopenia has previously been reported to occur more frequently in patients with JSF than in patients with scrub typhus [13]. Therefore, these variables are

Table 3. Laboratory Data at the Initial Presentation (n = 81)

Variable	SFTS (n = 41)	JSF (n = 40)	*P* Value
White blood cell count, /μL[a]	**1450 (910)**	**7250 (4150)**	**<.001**
Leukopenia (WBC count <4000/μL)[a]	**39 (95.1)**	**3 (7.7)**	**<.001**
Leukocytosis (WBC count >10 000/μL)[a]	**0**	**12 (30.8)**	**<.001**
Neutrophils, %[b]	**58.0 (17.4)**	**84.5 (9.6)**	**<.001**
Lymphocytes, %[b]	**32.0 (13.8)**	**10.0 (6.9)**	**<.001**
Monocytes, %[b]	5.5 (5.2)	5.0 (3.3)	.09
Hemoglobin, g/dL[a]	14.1 (2.0)	13.4 (1.8)	.16
Platelet, $\times 10^3$/μL[a]	**5.8 (4.2)**	**9.2 (4.6)**	**<.001**
Thrombocytopenia (platelet count <80 $\times 10^3$/μL), No. (%)[a]	**32 (78.0)**	**14 (35.9)**	**<.001**
Total bilirubin, mg/dL[a]	**0.48 (0.19)**	**0.80 (0.70)**	**<.001**
Aspartate aminotransferase, IU/L[a]	**164 (202)**	**66 (74)**	**<.001**
Alanine aminotransferase, IU/L[a]	**80 (95)**	**50 (43)**	**.005**
Lactate dehydrogenase, IU/L[c]	**546 (387)**	**386 (169)**	**.003**
Alkaline phosphatase, IU/L[d]	**170 (212)**	**223 (261)**	**.001**
Creatine kinase, IU/L[d]	**383 (4479)**	**185 (1330)**	**.003**
Blood urea nitrogen, mg/dL[c]	19.0 (11.8)	19.6 (11.4)	.81
Creatinine, mg/dL[c]	0.8 (0.4)	1.0 (0.8)	.1
C-reactive protein, mg/dL[a]	**0.16 (0.49)**	**14.1 (7.14)**	**<.001**
Normal CRP level (≤1.0 mg/dL), No. (%)[a]	**39 (95.1)**	**1 (2.6)**	**<.001**
Prothrombin time–INR[e]	**1.04 (0.15)**	**1.08 (0.12)**	**.03**
aPTT, sec[e]	**46.4 (14.6)**	**38.8 (11.8)**	**.007**
aPTT >40, No. (%)[e]	**31 (75.6)**	**14 (35.9)**	**0.008**

All laboratory data were evaluated when the patients initially visited our hospital. Data are presented as the median (SD) unless otherwise specified.

Abbreviations: aPTT, activated partial thromboplastin time; CRP, C-reactive protein; INR, International Normalized Ratio; JSF, Japanese spotted fever; SFTS, severe fever with thrombocytopenia syndrome; WBC, white blood cell.

[a]The available data are from 41 and 39 patients with SFTS and JSF, respectively.

[b]The available data are from 39 and 36 patients with SFTS and JSF, respectively.

[c]The available data are from 41 and 38 patients with SFTS and JSF, respectively.

[d]The available data are from 39 and 34 patients with SFTS and JSF, respectively.

[e]The available data are from 41 and 32 patients with SFTS and JSF, respectively.

valid for distinguishing between SFTS and scrub typhus, but they are not very effective for distinguishing between SFTS and JSF. Cardiomegaly in chest x-ray is more common in SFTS than in scrub typhus [20]. This simple finding may be useful in primary care settings. Unfortunately, we could not extract data on chest x-ray findings; thus, we have not examined this point in this study.

Rash was observed frequently (97.5%) in JSF and appeared a characteristic systemic macular erythematous eruption. Conversely, rash was relatively rare (24.4%) in SFTS and was limited to the area around the eschar. Typical rash in JSF has diagnostic value itself for the well-experienced clinician; however, the presence of a rash is not sufficient for distinguishing between these 2 diseases.

Normal CRP levels had a particularly high sensitivity and specificity for distinguishing SFTS from JSF. However, CRP was elevated in 2 SFTS cases with secondary infection (pneumonia). In cases with elevated CRP levels, leukopenia and the absence of rash were shown to be helpful for distinguishing SFTS from JSF. In fact, 2 cases with elevated CRP levels had leukopenia, and 1 of the 2 cases lacked a rash. These parameters could be obtained by routine physical examination and laboratory blood tests, which are available in primary care settings.

Two studies previously proposed a scoring system for differentiating SFTS from scrub typhus using variables including altered mental status, leukopenia (WBC count < 4000/μL), thrombocytopenia (platelet count < 150×10^3/μL or 80×10^3/μL), prolonged aPTT (>35 sec), and normal CRP levels (≤1.0 mg/dL) [15, 16]. Therefore, we first attempted to establish a scoring system to differentiate SFTS from JSF using these 3 variables (normal CRP levels, leukopenia, and the absence of rash); however, we found that these variables caused quasi-complete separation. Furthermore, these variables had a large variance inflation factor. Therefore, we did not perform a multivariate analysis and did not establish a scoring system.

CRP is a nonspecific acute-phase protein produced in hepatocytes under the control of cytokines such as interleukin-6 (IL-6) and IL-1 [21]. Sun et al. reported that the serum levels of several cytokines, including IL-6, IL-1, and IL-10, were elevated in patients with SFTS [22]. Therefore, it is questionable that CRP levels are normal in SFTS despite the production of

Table 4. Major Complications, Clinical Course, and Treatment

Variable	SFTS (n = 41)	JSF (n = 40)	*P* Value
Complications			
Central nerve system involvement[a]	**25 (61.0)**	**12 (32.5)**	**.01**
Pulmonary involvement[b]	**11 (26.8)**	**1 (2.5)**	**.003**
Cardiac involvement[c]	10 (24.4)	10 (24.4)	1
Infection	**13 (31.7)**	**1 (2.5)**	**.005**
Bacterial pneumonia	6 (14.6)	1 (2.5)	.12
Pulmonary mycoses	4 (9.8)	0	.13
Bacteremia	3 (7.3)	0	.24
Clinical course			
Intensive care unit admission	3 (7.3)	2 (5.0)	1
Mechanical ventilation	6 (14.6)	2 (5.0)	.26
Continuous renal replacement therapy	1 (2.4)	2 (5.0)	.62
In-hospital death	**13 (31.7)**	**2 (5.0)**	**.003**
Treatment			
Ribavirin	0	0	-
Antibiotics	**26 (63.4)**	**40 (100)**	**<.001**
Corticosteroid	**23 (56.1)**	**0**	**<.001**
Transfusion[d]	**12 (29.3)**	**3 (7.5)**	**.02**
Plasma exchange	0	0	-

Data are presented as the No. (%) of patients.

Abbreviations: JSF, Japanese spotted fever; SFTS, severe fever with thrombocytopenia syndrome.

[a]Central nervous system involvement: altered mental status defined as a Glasgow coma scale score <15, apathy, lethargy, dysarthria, tremor, and convulsion.

[b]Pulmonary involvement: bacterial pneumonia, pulmonary mycoses, and pulmonary hemorrhage.

[c]Cardiac involvement: shock, heart failure, arrhythmia, cardiomyopathy, and ischemic heart disease.

[d]Transfusion: platelet concentrates, red cell concentrates, and fresh frozen plasma.

Table 5. Predictive Accuracy of Each Variable on Differentiating SFTS From JSF

Variable	AUC	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
Loss of appetite	0.65 (0.55–0.74)	0.85 (0.71–0.94)	0.43 (0.27–0.59)	1.49 (1.10–1.99)	0.34 (0.15–0.78)
Diarrhea	0.70 (0.61–0.80)	0.54 (0.37–0.69)	0.86 (0.73–0.96)	4.29 (1.80–10.2)	0.53 (0.37–0.75)
Tick bite/eschar	0.75 (0.66–0.85)	0.32 (0.18–0.48)	0.18 (0.07–0.33)	0.38 (0.24–0.62)	3.90 (1.93–7.89)
Absence of rash	**0.87 (0.79–0.94)**	**0.76 (0.60–0.88)**	**0.98 (0.87–1.00)**	**30.2 (4.33–211)**	**0.25 (0.15–0.43)**
Lymphadenopathy	0.63 (0.54–0.72)	0.37 (0.22–0.53)	0.90 (0.76–0.97)	3.66 (1.33–10.1)	0.71 (0.55–0.91)
Altered mental status	0.63 (0.52–0.73)	0.51 (0.35–0.67)	0.73 (0.56–0.85)	1.86 (1.04–3.34)	0.67 (0.47–0.97)
Petechiae/purpura	0.59 (0.52–0.65)	0.20 (0.09–0.35)	0.96 (0.87–1.00)	7.80 (1.02–59.6)	0.83 (0.70–0.97)
Oral bleeding	0.60 (0.54–0.66)	0.12 (0.04–0.26)	0.98 (0.87–1.00)	4.88 (0.60–39.9)	0.90 (0.80–1.02)
Leukocytopenia					
WBC <4000/μL	**0.94 (0.88–0.99)**	**0.95 (0.84–0.99)**	**0.92 (0.81–0.99)**	**12.4 (4.16–36.8)**	**0.05 (0.01–0.21)**
<3230/μL	0.99 (0.98–1)	0.95 (0.84–0.99)	0.97 (0.87–1.00)	37.1 (5.35–257)	0.05 (0.01–0.19)
<3000/μL	0.94 (0.89–0.99)	0.90 (0.77–0.97)	0.97 (0.86–0.98)	35.2 (5.10–244)	0.10 (0.04–0.25)
Thrombocytopenia					
Platelet <150 $\times 10^3$/μL	0.54 (0.48–0.60)	0.95 (0.84–0.99)	0.13 (0.04–0.65)	1.09 (0.95–1.25)	0.38 (0.08–1.85)
<80 $\times 10^3$/μL	0.72 (0.62–0.84)	0.78 (0.62–0.89)	0.64 (0.47–0.79)	2.17 (1.39–3.41)	0.34 (0.18–0.64)
Normal CRP					
CRP ≤1 mg/dL	**0.96 (0.92–1.00)**	**0.95 (0.84–0.99)**	**0.97 (0.87–1.00)**	**37.1 (5.35–257)**	**0.05 (0.01–0.19)**
<0.85 mg/dL	1.00 (0.99–1.00)	0.93 (0.80–1.00)	1.00 (0.87–1.00)	Inf (NaN–Inf)	0.07 (0.03–0.22)

We analyzed 41 cases of SFTS and 39 cases of JSF. One patient with JSF for whom C-reactive protein data were unavailable was excluded. aPTT was excluded because it contained some missing values.

Abbreviations: aPTT, activated partial thromboplastin time; AUC, area under the curve; CRP, C-reactive protein; JSF, Japanese spotted fever; SFTS, severe fever with thrombocytopenia syndrome; WBC, white blood cell count.

these cytokines. The SFTSV nonstructural protein activates the tumor progression locus 2 and promotes the production of IL-10 [23], which suppresses the production of IL-6. Thus, the low levels of CRP in SFTS might be partially explained by high levels of IL-10 in patients with SFTS. Crimean-Congo hemorrhagic fever (CCHF) shows clinical manifestations similar to SFTS [12]. Erturk et al. [24] reported that CRP levels were not elevated in patients with CCHF, potentially due to leukopenia and acute liver failure. It remains unclear why serum CRP levels are not elevated in SFTS. Further investigation of its pathogenesis is necessary.

Our study has several limitations. First, we enrolled only patients from tertiary medical institutes. Sixty-one cases with SFTS and 91 cases with JSF were reported in our area according to the Infectious Diseases Weekly Report in Miyazaki Prefecture between 2008 and 2018 [25]. The coverage of patients with SFTS in this study was as high as 67% (41/61), whereas that of patients with JSF was only 44% (40/91). There was a possibility of selection bias for the patients with JSF because only severe cases were admitted to the hospitals and included in this study. Second, we could not identify the possibility of co-infection of SFTS and JSF. Co-infection with spotted fever group rickettsiosis was identified in 77 of 823 patients with SFTSV in China [26]. In South Korea, Park and colleagues [16] argued that the clinical evidence of the possibility of co-infection of both SFTS and scrub typhus is not substantial. In contrast, Sang et al. [27] reported that co-infection was observed in 3%–5% of both SFTS and JSF cases. The frequency of co-infection of SFTS and JSF in Japan is unknown. Unfortunately, we observed only a few cases with stored samples, and we could not identify any cases with co-infection of both SFTS and JSF. Because there are few reports about the co-infection of SFTS and JSF, further studies are necessary to identify cases with co-infection of SFTS and JSF. Third, our study was conducted retrospectively, and a limited number of patients were enrolled. Quasi-complete separation was observed when CRP and leukopenia were used as variables to distinguish SFTS from JSF, and we could not perform a multivariate analysis. However, we determined that 3 parameters (normal CRP, leukopenia, and the absence of rash) were good variables for differentiating SFTS from JSF with high sensitivity and specificity. If these criteria are met, each has a positive likelihood ratio of ≥10, resulting in a higher diagnostic value. A prospective study using these markers identified in the current study to distinguish SFTS from JSF with more patients is necessary to evaluate their value in real-world practice.

In conclusion, when clinicians intend to differentiate between SFTS and JSF among patients with suspected tick-borne infection, a single item, a normal CRP level, strongly differentiates SFTS from JSF. Additionally, variables such as the absence of rash and leukopenia may be helpful when patients have elevated CRP levels.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader,

the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We would like to thank ENAGO (http://www.enago.jp) for English language editing.

Author contributions. T.K., K.U., and A.O. conceptualized and designed the study. T.K. analyzed the information and wrote the manuscript. T.K., A.Y., S.H., and T.Y. collected the data. E.I. contributed to the statistical data analysis. All authors read and corrected the final draft.

Financial support. This study was funded by a Grant-in-Aid for Clinical Research from Miyazaki University Hospital.

Potential conflicts of interest. All authors declare that they have no competing interests. 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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