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MAJOR ARTICLE

Corticosteroid Therapy for Patients With Severe Fever With Thrombocytopenia Syndrome: A Nationwide Propensity Score–Matched Study in Japan

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Background. Severe fever with thrombocytopenia syndrome (SFTS) is a life-threatening infectious disease for which no effective treatment strategy has been established. Although corticosteroids (CSs) are widely administered to patients with SFTS, their efficacy remains uncertain. This study aimed to assess the impact of CS therapy on the in-hospital mortality of patients with SFTS.

Methods. In this nationwide observational study using the Japanese Diagnosis Procedure Combination database, patients hospitalized for SFTS from April 2013 to March 2021 were reviewed. We compared patients who were treated with CSs to those who were treated without them after propensity score matching to adjust for their background, disease severity, and combination therapy.

Results. We included 494 patients with SFTS, and 144 pairs of them were analyzed after propensity score matching. No significant difference in the 30-day mortality (19% vs 15%, $P = .272$) and the number of survival days (log-rank test, $P = .392$) was found between the CS treatment group and the non-CS treatment group. However, in subgroup analyses, the CS treatment group tended to have better survival among patients with impaired consciousness on admission and/or shock status within 7 days after admission.

Conclusions. CS therapy does not seem effective for all patients with SFTS; however, the impact might be altered by disease severity assessed by the consciousness level and shock status. A large-scale interventional study is required to determine its efficacy, especially for critically ill patients with SFTS.

Keywords. cohort studies; mortality; propensity score; severe fever with thrombocytopenia syndrome; steroids.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging and life-threatening infectious disease caused by the SFTS virus (SFTSV), which belongs to the genus *Banyangvirus* in the family Phenuiviridae. Tick species including *Haemaphysalis longicornis* and *Amblyomma testudinarium* are considered vectors of SFTSV [1]. The incubation time from infection to disease onset was reported to range from 6 to 14 days, and viral titers and cytokine levels peak 7–10 days after onset [2]. The first case of SFTS was confirmed in China in 2009, and it was also reported in Korea and Japan in 2013 [3–5]. The number of cases has been increasing with regional expansion worldwide [6–9]. In fact, the number of SFTS cases in China has increased by a scale factor of >20 from 2009 to 2019. In Japan, approximately 60 cases were confirmed per year until 2016; however, the number gradually increased to 110 per year in 2021 [10, 11]. Although it has a high mortality rate of 10%–33% [11–14], neither a specific vaccine nor antiviral treatment for SFTS has been established [15, 16].

SFTS is clinically characterized by high fever, hemorrhage with thrombocytopenia, leukopenia, and multiorgan dysfunction [16]. The cytokine storm plays a major role in the immunopathology of SFTSV. The roles of cytokines including interleukin (IL)-1, IL-6, IL-8, IL-10, interferon gamma (IFN-γ), and IFN-γ–induced protein 10 on pathogenesis have been studied [17]. Increased levels of several cytokines may cause life-threatening multiple organ failure, which is seen in patients with severe SFTS. Consequently, while supportive therapies including blood transfusion, renal replacement therapy, and plasma exchange are undergone as needed, corticosteroid (CS) therapy is considered, with the expectation of controlling the elevated levels of circulating cytokines and immune cell hyperactivation [18, 19]. Some studies have assessed the effects of CS on patients with SFTS; however, per their

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results, there was no significant effectiveness and it seems to increase the risk of secondary infections such as fungal infections and pneumonia [20–22]. Nonetheless, the sample sizes of these published studies were small or they were single-center studies, which means there may have been selection and measurement biases.

In Japan, the Infectious Disease Law requires all SFTS cases to be reported immediately once they are diagnosed, and the Japanese Diagnosis Procedure Combination (DPC) database covers the majority of hospitalized patients with SFTS. Acute SFTSV infection is virologically diagnosed by polymerase chain reaction or paired antibody assay in Japan. Patients with SFTS-like symptoms but negative for the tests are classified as suspected cases. Therefore, considering these advantages, we conducted this study to determine the impact of CS treatment on in-hospital mortality in patients with SFTS using nationwide data in Japan.

METHODS

Data Source

This was a retrospective cohort study conducted using the DPC inpatient database. The DPC system has been adopted by >1700 acute care hospitals in Japan, and it covers data on the majority of acute care patients in Japan [23]. This database contains information on age, sex, body mass index (BMI), Barthel index, comorbidities, smoking history (Brickman index), disturbance of consciousness (Japan Coma Scale) on admission, main diagnoses, complications, procedures, prescriptions, intensive care unit admission, and discharge status. Diagnoses were recorded with the *International Classification of Diseases, 10th Revision* (*ICD-10*) codes and Japanese disease names.

This study was approved by the Institutional Ethics Committee of the University of Tokyo Medical and Dental University (approval number M2000-788, revision number 44, 27 September 2022) and the Institutional Ethics Committee of Oita University (approved number 2478-C75, 17 February 2023). All aspects of the study complied with the Helsinki Declaration. The need for informed consent was waived because of the retrospective nature of the study, and information on the study was posted at the institute via an opt-out method.

Patients

SFTS patients admitted to hospitals using the DPC system from April 2013 to March 2021 were included in the study. We first extracted eligible patients from DPC data using the *ICD-10* code A938, which includes SFTS or vesicular stomatitis virus (VSV) disease. Next, we excluded patients with suspected SFTS, sequelae of SFTS, and VSV disease using the Japanese disease name. Patients who were <18 years and those who died within 24 hours after admission were also excluded, and if the same patient was hospitalized more than once, only the first hospitalization was included in the analysis. Patients who received CSs during hospitalization were assigned to the CS treatment group, and those who did not receive them were assigned to the non-CS treatment group. Since CSs generally tend to be administered to patients with severe disease, propensity score matching for patients' baseline characteristics was performed to reduce the selection bias.

Data Collection and Outcomes

Patient background data were collected on age, sex, BMI, smoking history, comorbidities, Barthel index, and the state of consciousness on admission. The Charlson comorbidity index was used to assess the comorbidities because other severity score scales are not documented in the DPC system. We also documented information on the presence of shock or hypoxia, mechanical ventilation, renal replacement therapy, and platelet transfusion therapy, which were performed within 7 days after admission. The presence of shock was determined using transvenous vasopressors. In addition to CS use, information on the following treatment was collected: plasma exchange therapy, polymyxin B immobilized fiber column direct hemoperfusion, γ-globulin, ribavirin, antibacterial drugs, and antifungal drugs. Favipiravir is a possible treatment option for SFTS [24]. However, it has not been officially approved to treat SFTS in Japan, and no data supporting its use for this indication are available yet. The primary endpoints were all-cause mortality within 30 days after admission and length of survival. Secondary endpoints were all-cause mortality within 90 days after admission and complications of secondary infection, including pneumonia and fungal infections. Secondary infections were defined as postadmission onset diseases, which were extracted from the DPC database.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 26 software (IBM, Armonk, New York). $P < .05$ was considered statistically significant. We performed comparisons between the 2 groups using the t test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Propensity score matching was performed to adjust for baseline patient backgrounds, clinical variables associated with disease severity, and treatment options other than CS therapy. We used logistic regression analysis to select the best factors for calculating the propensity score. The caliper width was set at 20% of the standard deviation of the propensity score. Kaplan-Meier curves were constructed for the matched patients, who were divided into the CS and non-CS treatment groups, and the log-rank test was performed to compare the duration of survival between the groups. Prespecified subgroup analyses focusing on previously reported prognostic factors in patients with SFTS, including impaired consciousness, shock status, and respiratory failure, were conducted [13, 22, 25, 26].

RESULTS

Patient Characteristics

In total, 868 patients were selected for screening with the *ICD-10* code A938, and 494 patients were included in the study after 374 patients (326 patients with no definitive diagnosis of SFTS, 2 patients with sequelae of SFTS, 21 patients with VSV disease, 9 patients <18 years, 4 patients who died within 24 hours, and 12 duplicate cases) were excluded (Supplementary Figure 1). Overall, approximately the same number of male and female patients with a median age of 73.0 years (interquartile range [IQR], 65.0–81.0 years) were admitted for SFTS, and the 30-day mortality rate was 18% (89/494), as shown in Table 1. CSs were administered to 44% (218/494) of the included patients; among them, 70% received high doses (>100 mg/day of a methylprednisolone equivalent). The median CS initiation time was 2.0 days after admission (IQR, 1.0–4.0 days), and most patients received CSs within 1 week of admission. The median duration of CS administration was 5.5 days (IQR, 3.0–13.3 days). As for treatment modalities other than CSs, antibiotics were used in 75% of cases, of which 66% received *Rickettsia*-covering agents (eg, minocycline, doxycycline, and azithromycin), whereas there are no data regarding antiviral drug use except for ribavirin.

Propensity Score Matching

Corticosteroids were more frequently administered to male patients, older patients, patients with low Barthel indexes or impaired consciousness on admission, patients with shock and hypoxia, and those who received mechanical ventilation, renal replacement therapy, or platelet transfusion within 7 days after admission. Patients who received CSs were also likely to be treated with plasma exchanges, globulins, ribavirin, antibiotics, and antifungal drugs as concomitant therapy (Table 2). A propensity score was calculated from these variables, except for the Barthel index because of the large number of cases with missing values (15%), and the area under the curve was estimated to be moderately high (0.785). After propensity score matching, patients' characteristics, including the Barthel index, did not differ significantly between patients who were treated with and without CSs (Table 2).

Corticosteroids and Outcomes

The 30-day mortality rate of the patients in the CS treatment group was 19% (28/144), whereas that of those in the non-CS treatment group was 15% (21/144), and the survival lengths did not differ significantly per the log-rank test ($P = .392$), as shown in Figure 1. In subgroup analyses, CS treatment may be associated with better survival among patients with impaired consciousness; however, no significant difference in this parameter was noted among patients without impaired consciousness (Figure 2*A* and 2*B*). Similarly, among patients with shock within 7 days after admission, the survival curve in the CS treatment group tended to be better than that in the non-CS treatment group, although the difference between the curves was not statistically significant (Figure 2*C* and 2*D*). In contrast, among patients with respiratory failure, the survival curve in the CS treatment group was not superior to that in the non-CS treatment group (Figure 2*E* and 2*F*).

As for secondary outcomes, there was no significant difference in 90-day mortality after propensity score matching. Secondary infections including pneumonia and fungal infections were observed in 16 patients in the CS treatment group and 10 patients in the non-CS treatment group (Table 2).

DISCUSSION

In this study, we found no statistically significant association between CS therapy and in-hospital mortality among patients with SFTS using Japanese national datasets with propensity score matching. However, the subgroup analyses revealed that CS therapy seems to provide better outcomes for patients with impaired consciousness and/or shock status. These results suggest that the effects of CSs could be altered by disease severity.

As the cytokine storm is believed to play a major role in the progression to severe SFTS, CSs tend to be administered to critically ill patients in clinical practice, and their potential efficacy has been reported in previous case reports [18, 19, 27]. Nevertheless, recent retrospective cohort studies demonstrated no favorable impact of CSs on the treatment of SFTS [20–22]. Kawaguchi et al [21] collected existing clinical data on patients with SFTS in Miyazaki prefecture, Japan, and demonstrated significantly higher mortality in the CS treatment group than in the non-CS treatment group using propensity score matching (66.7% vs 16.7%, $P = .04$). However, that study had only a few participants (24 cases in total after propensity score matching), and there were still some differences in background between patients in the CS treatment and non-CS treatment groups even after propensity score matching. Jung et al [20] conducted a multicenter retrospective cohort study in Korea, in which CS therapy was found to be associated with an increased risk of 30-day mortality (adjusted hazard ratio, 3.45 [95% confidence interval, 1.31–9.11]; $P = .012$). The number of participants in this study was 142, which is still an insufficient sample size. Another retrospective cohort study conducted in China, in which 467 patients from a single institution were included, revealed no statistically significant difference in in-hospital mortality between the CS treatment group and the non-CS treatment group after propensity score matching (10.5% vs 15.8%, $P = .391$). The present study revealed no favorable association between CS treatment and 30-day mortality in patients with SFTS, which seems to be consistent with the findings of these previously published studies, in terms of results from entire populations of patients with any type of severity.

Table 1. Baseline Characteristics of Patients With Severe Fever With Thrombocytopenia Syndrome Who Died Within 30 Days or Survived

Characteristic	All Patients (N = 494)	Nonsurvivors (n = 89)	Survivors (n = 405)	*P* Value
Sex, female	240 (49)	40 (45)	200 (49)	.448
Age, y	73.0 (65.0–81.0)	82.0 (74.0–86.0)	71.0 (63.0–79.0)	<.001
BMI, kg/m^2	22.1 (20.0–24.8)	21.2 (19.1–25.2)	22.2 (20.1–24.7)	.297
Missing data	56 (11)	17 (19)	39 (10)	…
Barthel index	30.0 (0.0–85.0)	0.0 (0.0–20.0)	45.0 (0.0–95.0)	<.001
0–24	199 (40)	59 (66)	140 (35)	…
25–49	44 (9)	7 (8)	37 (9)	…
50–79	58 (12)	2 (2)	56 (14)	…
80–100	120 (24)	8 (9)	112 (28)	…
Missing data	73 (15)	13 (15)	60 (15)	…
Smoker	118 (24)	23 (26)	95 (23)	.803
Missing data	40 (8)	4 (4)	36 (9)	…
CCI score[a]	0.0 (0.0–1.0)	0.0 (0.0–1.5)	0.0 (0.0–1.0)	.486
0	355 (72)	61 (69)	294 (73)	…
1–2	114 (23)	22 (25)	92 (23)	…
3–4	19 (4)	5 (6)	14 (3)	…
5–6	5 (1)	1 (1)	4 (1)	…
7–8	1 (0)	0 (0)	1 (0)	…
Impaired consciousness[a]	192 (39)	48 (54)	144 (36)	.001
JCS 1–3	144 (29)	32 (36)	112 (28)	…
JCS 10–30	38 (8)	9 (10)	29 (7)	…
JCS 100–300	10 (2)	7 (8)	3 (1)	…
Shock[a]	110 (22)	55 (62)	55 (14)	<.001
Hypoxemia[a]	267 (54)	84 (94)	183 (45)	<.001
Mechanical ventilation[a]	71 (14)	40 (45)	31 (8)	<.001
Renal replacement therapy[a]	50 (10)	31 (35)	19 (5)	<.001
Platelet transfusion[a]	153 (31)	52 (58)	101 (25)	<.001
Corticosteroids	218 (44)	66 (74)	152 (38)	<.001
Dose, mg/day[b]	500 (60–1000)	500 (219–1000)	375 (48–500)	.004
High dose[c]	152 (31)	53 (60)	99 (24)	<.001
Low dose[d]	66 (13)	13 (15)	53 (13)	.703
Start date after admission	2.0 (1.0–4.0)	3.0 (2.0–4.0)	2.0 (1.0–3.0)	.307
Duration, d	5.5 (3.0–13.3)	3.5 (2.0–5.3)	8.0 (3.0–15.8)	<.001
Type of corticosteroid[e]				…
Prednisolone	88 (18)	14 (16)	74 (18)	.570
Methylprednisolone	153 (31)	51 (57)	102 (25)	<.001
Hydrocortisone	65 (13)	27 (30)	38 (9)	<.001
Betamethasone	4 (1)	0 (0)	4 (1)	1.000
Dexamethasone	18 (4)	3 (3)	15 (4)	1.000
Combination therapy[f]				…
Plasma exchange	22 (4)	12 (13)	10 (2)	<.001
PMX-DHP	8 (2)	5 (6)	3 (1)	.006
Globulin	57 (12)	20 (22)	37 (9)	<.001
Ribavirin	11 (2)	2 (2)	9 (2)	1.000
Antibiotics	371 (75)	81 (91)	290 (72)	<.001
Antifungal drug	52 (11)	21 (24)	31 (8)	<.001

Data are presented as No. (%) or median (interquartile range). The *P* value of the χ^2 test or Fisher exact test is presented for categorical variables, and the *t* test *P* value for continuous variables.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; JCS, Japan Coma Scale; PMX-DHP, polymyxin B immobilized fiber column direct hemoperfusion.

[a]Impaired consciousness was evaluated on admission and others were evaluated within 7 days after admission.

[b]Maximum daily corticosteroid dose of methylprednisolone equivalent.

[c]Maximum daily corticosteroid dose ≥100 mg/day of methylprednisolone equivalent.

[d]The maximum daily corticosteroid dose <100 mg/day of methylprednisolone equivalent.

[e]Overlap allowed.

[f]Combination therapies were determined whether it was done within 7 days after admission.

Table 2. Clinical Characteristics of Patients With Severe Fever With Thrombocytopenia Syndrome and Outcomes Before and After Propensity Score Matching

	Unmatched			Matched		
Characteristic	CS Treatment (n = 218)	Non-CS Treatment (n = 276)	*P* Value	CS Treatment (n = 144)	Non-CS Treatment (n = 144)	*P* Value
Sex, female	95 (44)	145 (53)	.048	66 (46)	79 (55)	.125
Age, y	74.5 (67.0–82.0)	72.0 (64.0–80.0)	.016	74.0 (65.3–82.0)	75.0 (66.3–82.0)	.686
BMI, kg/m^2	22.6 (20.4–25.0)	21.9 (19.7–24.6)	.084	22.6 (20.5–24.7)	21.8 (19.6–24.2)	.102
Barthel index	5.0 (0.0–57.5)	50.0 (0.0–100.0)	<.001	30.0 (0.0–75.0)	22.5 (0.0–80.0)	.786
Smoker	50 (23)	68 (25)	.710	33 (23)	35 (24)	.806
CCI score	0.0 (0.0–2.0)	0.0 (0.0–1.0)	.333	0.0 (0.0–2.0)	0.0 (0.0–1.0)	.290
Impaired consciousness[a]	99 (45)	93 (34)	.008	60 (42)	65 (45)	.552
Shock[a]	85 (39)	25 (9)	<.001	27 (19)	25 (17)	.759
Hypoxemia[a]	159 (73)	108 (39)	<.001	90 (63)	95 (66)	.539
Mechanical ventilation[a]	56 (26)	15 (5)	<.001	14 (10)	15 (10)	.845
Renal replacement therapy[a]	40 (18)	10 (4)	<.001	8 (6)	10 (7)	.626
Platelet transfusion[a]	101 (46)	52 (19)	<.001	50 (35)	45 (31)	.531
Combination therapy[b]						
Plasma exchange	19 (9)	3 (1)	<.001	4 (3)	3 (2)	1.000
PMX-DHP	5 (2)	3 (1)	.310	1 (1)	3 (2)	.622
Globulin	46 (21)	11 (4)	<.001	12 (8)	11 (8)	.828
Ribavirin	10 (5)	1 (0)	.003	2 (1)	1 (1)	1.000
Antibiotics	191 (88)	180 (65)	<.001	118 (82)	120 (83)	.756
Antifungal drug	40 (18)	12 (4)	<.001	14 (10)	12 (8)	.681
30-d mortality	66 (30)	23 (8)	<.001	28 (19)	21 (15)	.272
90-d mortality	71 (33)	26 (9)	<.001	31 (22)	23 (16)	.227
Secondary infections						
Pneumonia	13 (6)	9 (3)	.148	8 (6)	6 (4)	.584
Aspergillus infection	3 (1)	3 (1)	1.000	3 (2)	3 (2)	1.000
Other fungal infection	3 (1)	1 (0)	.326	3 (2)	1 (1)	.622
Pneumocystis pneumonia	2 (1)	0 (0)	.194	2 (1)	0 (0)	.498

Data are presented as No. (%) or median (interquartile range). The *P* value of the χ^2 test or Fisher exact test is presented for categorical variables, and the *t* test *P* value for continuous variables.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CS, corticosteroid; PMX-DHP, polymyxin B immobilized fiber column direct hemoperfusion.

[a]Impaired consciousness was evaluated on admission and others were evaluated within 7 days after admission.

[b]Combination therapies were determined whether it was performed within 7 days after admission.

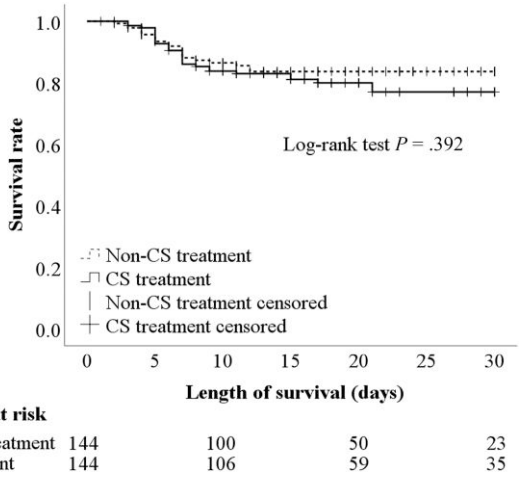

Figure 1. Kaplan-Meier curves showing lengths of survival with or without corticosteroid (CS) treatment after propensity score matching in entire cases.

Although CS treatment is likely to have a negative impact on the disease prognosis for entire SFTS cases, the efficacy of CS therapy might still be expected for patients with severe SFTS. It is known that SFTS patients with shock or encephalopathy have a high mortality rate [22, 25, 26]; thus, we performed subgroup analyses classifying cases into those with and without impaired consciousness or shock. CS use was potentially associated with better prognoses among patients with consciousness disorders, and similar trends were found in patients with shock. Since the cytokine storm is thought to contribute to the pathogenesis of shock and encephalopathy in patients with SFTS [25, 28, 29], it is reasonable to expect CSs to lead to better outcomes for these critically ill patients, suppressing overexpressed cytokines. By contrast, CS use might be harmful in patients with mild illness without impaired consciousness or shock status. CS appears to have 2 effects in the treatment for SFTS—namely, the suppression of excessive immune responses

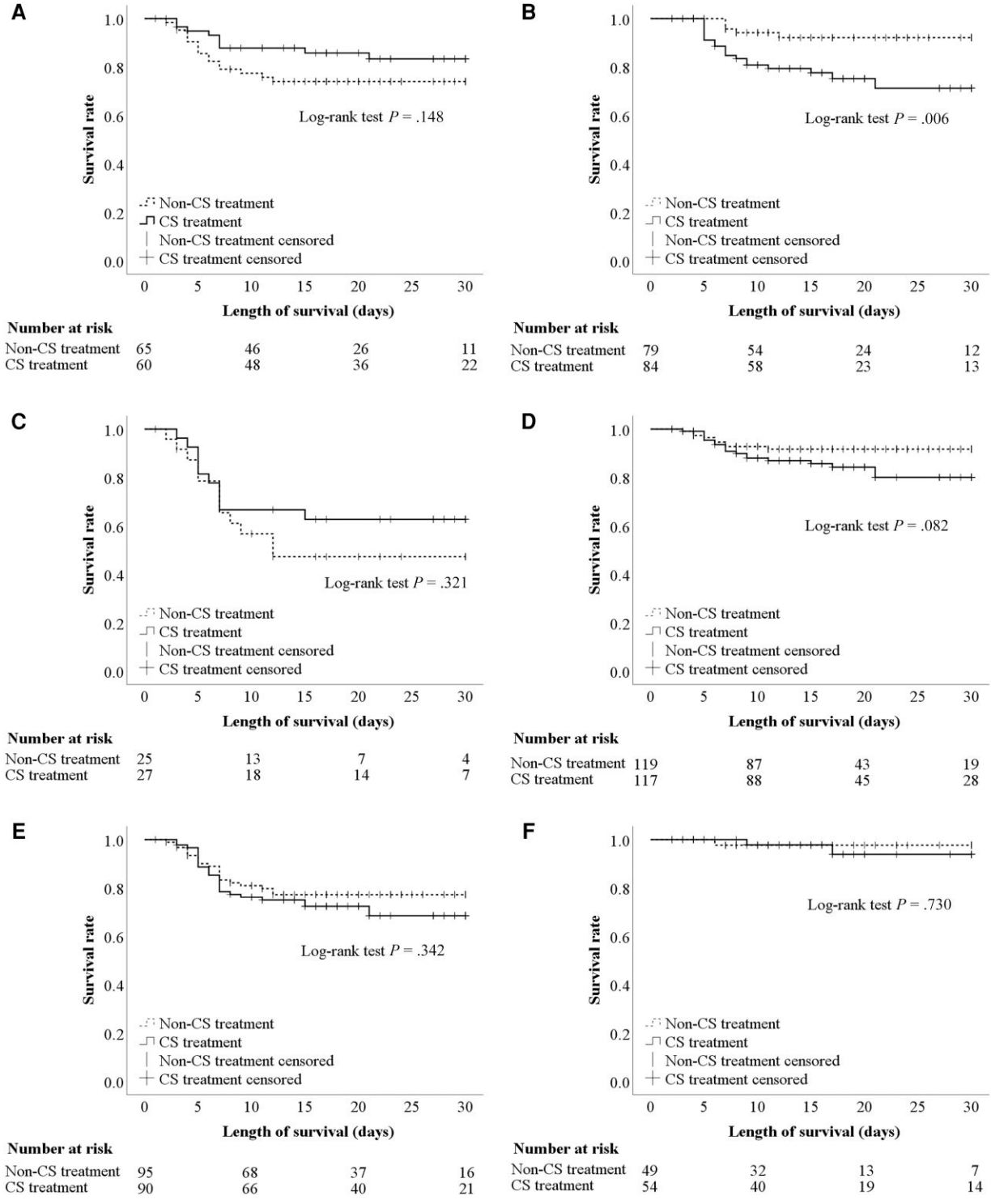

Figure 2. Kaplan-Meier curves showing survival durations with or without corticosteroid (CS) treatment after propensity score matching in each subgroup. *A*, In patients with impaired consciousness on admission, the 30-day mortality rate was 15% in the CS treatment group versus 25% in the non-CS treatment group. *B*, In patients without impaired consciousness on admission, the 30-day mortality rate was 23% in the CS treatment group versus 6% in the non-CS treatment group. *C*, In patients with shock within 7 days after admission, the 30-day mortality rate was 37% in the CS treatment group versus 48% in the non-CS treatment group. *D*, In patients without shock within 7 days after admission, the 30-day mortality rate was 15% in the CS treatment group versus 8% in the non-CS treatment group. *E*, In patients with respiratory failure within 7 days after admission, the 30-day mortality rate was 29% in the CS treatment group versus 21% in the non-CS treatment group. *F*, In patients without respiratory failure within 7 days after admission, the 30-day mortality rate was 4% in the CS treatment group versus 2% in the non-CS treatment group.

and promotion of viral proliferation. Interestingly, CS use had no advantages in patients with respiratory failure compared to its effects in patients without respiratory failure. In general, adjunctive CS treatment can be considered for central nervous system infections [30] or shock status [31], regardless of the causative pathogens; however, evidence supporting its use to treat simple respiratory failure, excluding that caused by severe pneumonia, has not been fully established to date [32]. Considering the results of the present study, critically ill patients with SFTS might be left with the possibility that CS therapy may improve their prognoses, and the indication may be suggested according to the consciousness level and/or shock status. Thus, randomized controlled trials focusing on these critically ill patients with SFTS are needed.

Methylprednisolone was the most commonly used CS in the present study, followed by prednisone and hydrocortisone. This finding was similar to that of a previous study conducted by Kawaguchi et al [21], and the used dosage was also identical. On the other hand, dexamethasone was widely used in studies conducted in Korea and China [20, 22]. Indeed, dexamethasone was used in 95% of cases in the study conducted in China. Furthermore, CS was used in lower dosages and over shorter durations in that study than in our study, whereas the timing of CS initiation (within a few days of admission) was similar. The optimal and least effective dosages and treatment durations for patients with SFTS are still unknown. Future prospective studies should be conducted with standard CS dosages and treatment durations.

The main strengths of the present study include the fact that case information was collected from a nationwide dataset on patients with SFTS in Japan, and subgroup analyses were conducted based on factors associated with poor prognostic outcomes. However, there are also several limitations worth mentioning. First, the propensity score–matching model may not have been adequate to adjust for selection bias in CS administration. CSs tend to be administered to more severely ill patients, but the DPC database does not include data on several important aspects such as laboratory data, the number of days from disease onset, or the viral load, which are potentially unadjusted confounding factors [33, 34]. Second, there is some uncertainty in the diagnosis of SFTS because the diagnosis was determined based on the DPC database rather than on medical records [35]. However, SFTS is a very specific and rare disease; thus, the diagnosis is unlikely to be registered without being a definitive one, and patients would have been selected with higher sensitivity and specificity. Third, the type, dosage, duration, and starting timing of CS were not standardized. Data on the duration of illness prior to hospitalization were not available. This limitation could lead to bias concerning the effects of CS treatment on the prognosis of patients with SFTS. We did not compare the effects of higher and lower CS doses on mortality because of several biases in addition to the dose. Fourth, no data on serum cytokine levels or viral loads at baseline or during CS treatment were available. The impact of CS treatment might be associated with these variables.

In conclusion, the current study presented the first analyzed results using a national dataset of SFTS patients in Japan. As no benefit of CS treatment was observed in the entire cohort, further randomized controlled studies are warranted in patients with impaired consciousness and/or shock.

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.

Notes

Author contributions. All authors designed this study and drafted the manuscript. H. S., K. K., Y. U., and K. F. contributed to the data collection and data analysis and drafted the manuscript. All the authors have read the manuscript and have approved this submission.

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Data availability. The datasets generated and analyzed during the current study are not publicly available due to a license agreement with Tokyo Medical and Dental University Graduate School but are available from the corresponding author on reasonable request.

Potential conflicts of interest. All authors: No reported conflicts.

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