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ORIGINAL RESEARCH

Time-Varying Effects of Glucocorticoid Treatment in Critically Ill Patients with Severe Fever with Thrombocytopenia Syndrome: An Inverse Probability of Treatment Weighting Analysis

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Purpose: To evaluate the efficacy of glucocorticoid treatment in critically ill patients with severe fever with thrombocytopenia syndrome (SFTS) and to assess whether glucocorticoid use increases the risk of fungal infections.

Patients and Methods: A retrospective cohort study was conducted involving confirmed SFTS patients from a tertiary hospital. After applying the Inverse Probability of Treatment Weights (IPTW), multivariable Cox regression and logistic regression analyses were utilized to assess the impact of glucocorticoids on the 28-day mortality rate and the risk of fungal infections. Additionally, landmark analysis and time-varying Cox regression were employed to evaluate the effects of glucocorticoids on mortality across different time intervals.

Results: The study included 112 patients with severe SFTS, comprising 67 patients in the glucocorticoid (GC) group and 45 in the non-glucocorticoid (non-GC) group. While glucocorticoid treatment did not significantly alter the overall 28-day mortality in severe SFTS (aHR 0.92, 95% CI 0.44–1.93, P = 0.828), it was associated with a notable reduction in mortality within the first 7 days of hospitalization (aHR 0.35, 95% CI 0.15–0.82, P = 0.016) and an increased mortality risk between days 7 and 28 (aHR 4.92, 95% CI 1.30–18.67, P = 0.019). Furthermore, glucocorticoid use was linked to a significantly higher risk of developing fungal infections (aOR 15.22, 95% CI 4.04–57.38, P < 0.001).

Conclusion: The effects of glucocorticoid treatment in severe SFTS patients vary depending on the disease stage, suggesting that the timing of glucocorticoid administration is crucial. Additionally, the increased risk of fungal infections warrants careful consideration when prescribing glucocorticoids in this population.

Keywords: severe fever with thrombocytopenia syndrome, critical illness, glucocorticoid, mortality, fungal infections, time-varying

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging hemorrhagic fever caused by the novel Bunyavirus, known as the SFTS virus (SFTSV), which possesses a single-stranded negative-sense RNA genome. The disease is associated with a significant mortality rate, ranging from 5% to 30%. First reported in China in 2009, SFTS has since spread to other Asian countries, including South Korea and Japan, over the past two decades.[1–4] From 2011 to 2021, the incidence of SFTS has shown an increasing trend, likely underestimated due to the limitations in diagnostic technology in China.[5] The absence of an available vaccine and specific antiviral treatments exacerbated the public health challenge posed by SFTS.

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Most SFTS patients experience mild clinical symptoms such as fever and thrombocytopenia and recover in a relatively short period. However, a subset of individuals becomes critically ill, presenting with sepsis-like symptoms including multi-organ failure and disseminated intravascular coagulation (DIC),[6] which can rapidly progress into fatal outcomes. Critically ill patients often have high serum virus load, which correlates with the production of multiple cytokines. The cytokine storm is considered a key factor in the severity of SFTS.[7,8] Glucocorticoids, widely employed to regulate host cell-mediated immune responses and mitigate inflammatory cytokines in infectious diseases, have been recommended for treating viral sepsis in severe or critical COVID-19 cases with excessive inflammation,[9] as well as caused by other RNA viruses.[10,11] However, the benefits of glucocorticoid treatment in SFTS patients remain controversial. Some reports suggest potential benefits of steroid pulse therapy in SFTS, including cases with encephalitis treated successfully without neurological sequelae.[12] In contrast, other retrospective studies have found glucocorticoid treatment does not reduce case fatal rate (CFR).[13–16] A prior study by our group developed a dynamic nomogram model to predict the likelihood of hospitalized SFTS patients progressing to severe illness within three days of admission and to estimate the 28-day mortality risk for all hospitalized patients.[17] As part of the initial exploratory analyses in that study, we observed that glucocorticoid treatment did not significantly impact 28-day mortality among all hospitalized patients. Additionally, recent studies by Gang Wang et al[13] and Sook In Jung et al[15] have suggested that the effects of glucocorticoid treatment may vary depending on the severity of the patient's condition, with potential differences in outcomes between mild and severe cases. Building on these findings, our current study focused specifically on critically ill SFTS patients, who have a more complex immune status and higher mortality compared to mild cases.

Glucocorticoid treatment is a double-edged sword. Secondary infections are a known side effect of glucocorticoid treatment.[18] Fungal infections is a common complication in SFTS patients and is associated with higher mortality,[19,20] which is especially concerning for severely immunocompromised individuals with SFTS.[21,22] Studies have found that the incidence of fungal infections in SFTS patients ranges from 10%-30%,[4,19] with aspergillus being the most frequently reported pathogen.[22,23]

Therefore, our study aims to investigate the efficacy of glucocorticoid treatment in severe SFTS patients and assess its potential to increase the risk of secondary fungal infection in this population.

Materials and Methods

Study Design and Participants

Data for confirmed SFTS patients were collected from the History Information System of Nanjing Drum Tower Hospital between April 2014 and October 2023. Both hospitalized or outpatient SFTS patients who met the following diagnostic criteria were included: (1) clinical manifestations of acute fever and thrombocytopenia; (2) positive serum nucleic acid test for SFTSV RNA using real-time polymerase chain reaction (RT-PCR) or PCR. Excluded criteria were: (1) patients with admission time ≤3 days; (2) patients who had received glucocorticoid or intravenous immunoglobulin (IVIG) before admission; (3) patients with asthma or chronic obstructive pulmonary disease (COPD); (4) patients lost to follow-up.

The severe status of SFTS patients was determined based on classic clinical manifestations and severe complications according to the consensus.[24,25] Severe SFTS patients were defined by the presence of any of the following features within 3 days of admission: (1) multiple organ failure, respiratory failure, heart failure, renal failure, DIC, or viral encephalitis; (2) pronounced neurological symptoms such as coma, delirium, or recurrent convulsions; (3) significant intracranial hemorrhage, digestive tract, lung, or uterus; (4) severe infection, including bacteremia or septic shock.

This study was approved by the Ethical Committee of Nanjing Drum Tower Hospital (NO.2023–488-02). Given the study's retrospective nature, written informed consent was waived, and all procedures adhered to the Declaration of Helsinki.

Data Collection and Definitions

Information on demographic features, clinical manifestations, laboratory parameters, and clinical outcomes of enrolled SFTS patients was extracted from electronic medical records by physicians and recorded in a standardized format. Two trained staff members reviewed the data for accuracy and consistency. Laboratory parameters included blood routine tests

and biochemical tests for liver, kidney, heart, and coagulation functions conducted at admission. Clinical manifestations included respiratory, gastrointestinal, nervous system, and hemorrhagic symptoms. All therapy protocols were administered before the diagnosis of fungal infections, and all patients received ribavirin antiviral therapy. Glucocorticoid regimens included medications such as dexamethasone, hydrocortisone, and prednisone, along with their start and end dates, daily dose, and total dosages. All glucocorticoid dosages were converted to dexamethasone-equivalent doses, using a conversion ratio of hydrocortisone 26.7:1 and methylprednisolone 5.3:1. In our study, the median total dosage was used to classify the doses: a low dose was defined as ≤10 mg of cumulative dexamethasone or its equivalent, while a high dose was defined as >10 mg. The timing of glucocorticoid initiation was categorized based on the median initiation time observed in our study. Early initiation was defined as the glucocorticoid treatment starting ≤8 days from the onset of symptoms, whereas late initiation was defined as >8 days. Given that clinicians frequently administered glucocorticoids for fever reduction in SFTS patients upon admission, single-dose administration was common. Consequently, glucocorticoid frequency was classified as either single or multiple administrations.

Respiratory symptoms included cough, expectoration, and dyspnea. Gastrointestinal symptoms included nausea, vomiting, stomachache, and diarrhea. Nervous system symptoms included headache or dizziness, disturbance of consciousness, and convulsions or tics. Hemorrhagic symptoms included purpura or petechiae, hemoptysis, gingival bleeding, melena, and hematemesis. The primary clinical outcome was defined as death or survival within 28 days from onset.

All patients were followed up for 28 days after admission via phone calls to confirm clinical outcomes. The secondary clinical outcome was the occurrence of fungal infections after onset. Fungal infections were defined according to the EORTC/MSGERC guidelines, which categorize infections as proven, probable, or possible. Microorganisms were confirmed positive through cultivation from blood, sputum or bronchoalveolar lavage fluid (BALF), metagenomic next-generation sequencing (mNGS), galactomannan (GM), and (1, 3)-b-D glucan (G) tests.[26,27]

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.2). To address the missing values in the laboratory test indicators, we first performed the missing completely at random (MCAR) test using the "macr_test" function from the "naniar" package and visualized the missing data. Subsequently, the missing data were imputed using the "mice" package through multiple imputations, generating five datasets, which were then combined into a summary estimate. Continuous variables with normal distributions were analyzed using the independent Student's *t*-test, reported as mean ± standard deviation. For non-normal distributed continuous variables, the Mann-Whitney test was used, with results presented as median and interquartile range (IQR). Categorical variables were described as frequencies and percentages, with group differences assessed using the Chi-square test or Fisher's exact test.

To reduce imbalance stemming from selection bias and potential confounders, we performed inverse probability of treatment weights (IPTW) based on the logit of the propensity score (PS) representing the probability of receiving glucocorticoid treatment. Weights were computed as stabilized inverse probability of treatment selection and used to create a pseudo-population where covariates were independent of treatment selection. Covariates included in the PS were chosen based on clinical judgment or their strong predictive value of the outcome. Baseline parameters balance between groups was assessed before and after applying IPTW weights using standardized mean differences (SMD), with SMD>20% indicating imbalance.[28,29] We analyzed 28-day mortality and fungal infections using Cox proportional-hazards (PH) models and logistic regression models, respectively. In the univariate analysis, variables demonstrating a significance level of $P < 0.1$ and a variance inflation factor (VIF) <5 were selected for inclusion in the subsequent multivariate analysis. Kaplan-Meier (KM) survival analysis, adjusted with IPTW, was used to compare 28-day survival between Non-GC and GC groups. Landmark analysis was performed to assess the conditional association between glucocorticoid treatment and survival outcomes before and after the landmark point, with hazard ratios calculated for deaths within the first 7 days of admission and from day 7 to the end of the follow-up.[30]

The PH assumption of the Cox model was examined using the cox.zph() function from the "survival" package, with the global Schoenfeld test indicating any violations. When the PH assumption was violated, the time-varying Cox regression analysis method was employed.[31,32] Specifically, we used the survSplit() function to partition the data at predefined time intervals (7 days). For instance, a patient surviving more than 28 days would be included in both the

(0, 7] and (7, 28] intervals, while a patient surviving only 4 days would only be included in the first interval. A multivariate Cox regression model stratified by the survival intervals was then fit, and the PH assumption of this model was tested using cox.zph(). All statistical tests were two-sided, with a significance level set at $P < 0.05$.

Finally, sensitivity analyses were carried out to examine the robust of associations between glucocorticoid use and 28-day mortality as well as fungal infections by using multivariable regression models, excluding participants with missing laboratory test parameters. We also evaluated the time-varying effects of glucocorticoid therapy on 28-day mortality.

Results

Patient Characteristics

From April 2014 to October 2023, 475 laboratory-confirmed SFTS cases were enrolled in our study. Following the application of the exclusion criteria, 363 patients were ineligible for the study: 72 with admission time ≤3 days, 14 who had received glucocorticoid or IVIG before admission, 8 with asthma or COPD, 53 lost to follow-up, and 216 did not meet the criteria of severe illness. Finally, 112 patients, including 45 in the non-GC group and 67 in the GC group, were eligible for further statistical analysis (Figure 1). The MCAR test ($P = 0.605$) supported missing completely at random, with the missing data pattern illustrated in sfigure 1.

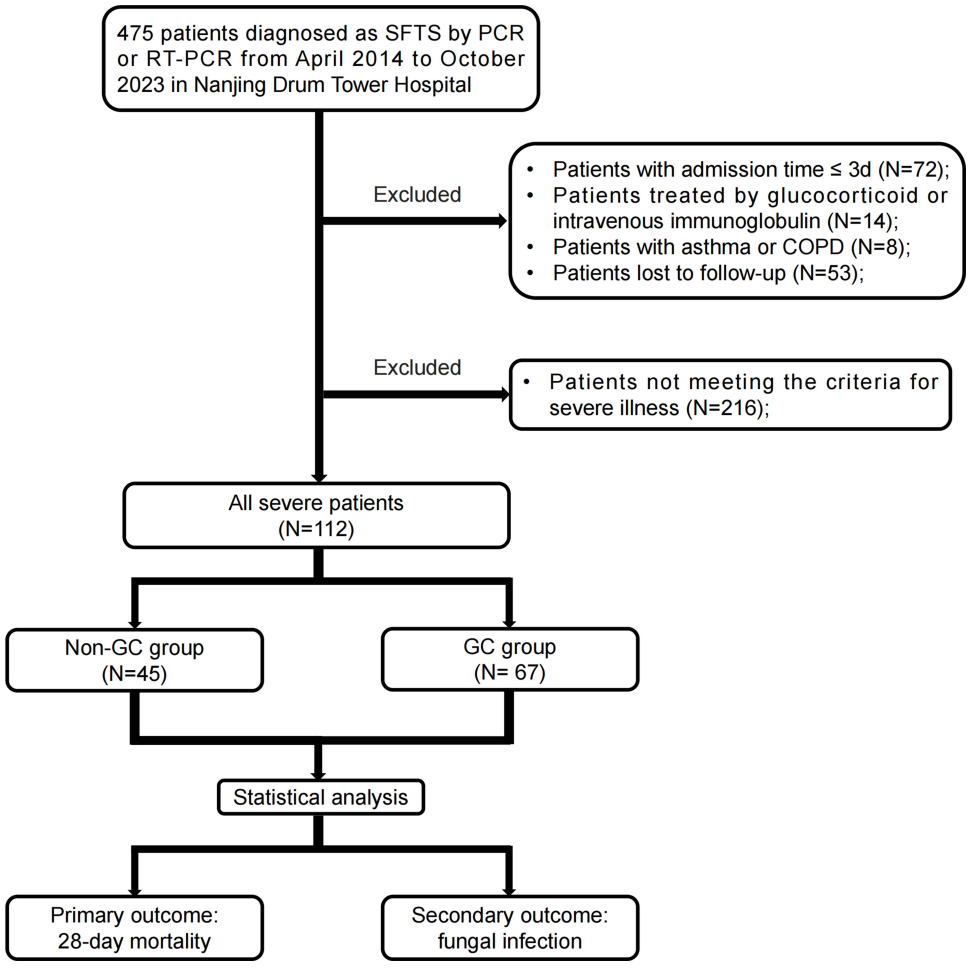

Figure 1 Flow chart of study design.
Abbreviations: SFTS, severe fever with thrombocytopenia syndrome; PCR/RT-PCR, real-time polymerase chain reaction; GC, glucocorticoid; COPD, chronic obstructive pulmonary disease.

Table 1 Corticosteroid Therapy Among Severe SFTS Patients (N=112)

Medication Variables	
Dexamethasone, n (%)	44 (65.7)
Hydrocortisone, n (%)	2 (2.9)
Prednisone, n (%)	3 (4.5)
Two or three in combination, n (%)	18 (26.9)
Duration of corticosteroids, days (IQR)	
All patients	2 (1, 4)
Survivors	2 (1, 3)
Non-survivors	3 (1, 5)
Accumulated dose, dexamethasone equivalent, mg (IQR)	
All patients	11.87 (5.00, 29.38)
Survivors	10.00 (5.00, 15.00)
Non-survivors	15.00 (5.00, 35.00)
Duration between onset of illness and glucorticosteroid initiation, days (IQR)	8.0 (6.0, 10.5)
Duration between hospital admission and glucorticosteroid initiation, days (IQR)	2 (1, 4)
Duration between onset of illness and fungal infection, days (IQR)	12 (10, 14)
Duration between fungal infection and glucorticosteroid initiation, days (IQR)	−4 (−6, −1.75)

Notes: Data presented as n (%) or median (Q1, Q3); SFTS, severe fever with thrombocytopenia syndrome.

Dexamethasone was the most frequently used glucocorticoid (44/68, 65.7%) followed by a combination of two or three glucocorticoids (18/67, 26.9%) (Table 1). The remaining patients were treated with hydrocortisone alone (2/68, 2.9%) or prednisone alone (3/68, 4.5%). Glucocorticoid treatment was initiated at a median of 2 (1, 4) days after admission and 8 (6, 10.5) days after symptom onset. The median duration of glucocorticoid treatment was 2 (1, 4) days, with the median cumulative dose of 11.87 (5.00, 29.38) mg dexamethasone equivalent.

Among 27 severe SFTS patients with fungal infections, 7 tested positive for the GM test and 1 for the G test in serum, despite negative culture results (Table 2). Additionally, 25 strains were isolated from respiratory specimens obtained from

Table 2 The Microbial Testing Results of Severe SFTS Patients with Fungal Infections

Patient ID	**Positive Microbial Testing Methods**	**G test**	**GM Test**	**Source of Strains**	**Species Distribution**	**Accessory Examination**	**Infection Sites**
1	GM test	Positive	Positive		NA	CT	Bloodstream
2	Cultivation	Positive	Positive	Sputum	A. fumigatus; A. flavus		Pulmonary
3	Cultivation	Positive	Negative	Sputum	A. flavus		Pulmonary
4	Cultivation	Negative	Positive	Sputum	A. fumigatus		Pulmonary
5	Cultivation	Positive	Positive	Sputum	A. fumigatus; A. flavus		Pulmonary
6	GM test	Positive	Positive		NA		Bloodstream
7	Cultivation	Positive	Positive	Sputum	A. flavus		Pulmonary
8	NGS; Cultivation	Positive	Positive	Sputum; BAL	A. fumigatus; A. flavus		Pulmonary
9	Cultivation	Positive	Negative	Sputum	A. fumigatus		Pulmonary; Bloodstream
10	Cultivation	Positive	Positive	Sputum	A. fumigatus		Pulmonary

(*Continued*)

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Table 2 (Continued).

Patient ID	Positive Microbial Testing Methods	G test	GM Test	Source of Strains	Species Distribution	Accessory Examination	Infection Sites
11	Cultivation	Positive	Positive	Sputum	A. fumigatus		Pulmonary; Bloodstream
12	Cultivation	Positive	Positive	Sputum	A. fumigatus		Pulmonary
13	NGS; Cultivation	Positive	Positive	Sputum	A. fumigatus		Bloodstream
14	Cultivation	Positive	Positive	Sputum	C. albicans		Bloodstream
15	Cultivation	Positive	Positive	Sputum	A. flavus; A. terreus		Pulmonary
16	GM test	Positive	Negative		NA		Pulmonary
17	Cultivation	Positive	Positive	Sputum	C. albicans		Bloodstream
18	Cultivation	Positive	Negative	Sputum	A. flavus		Pulmonary
19	GM test	Positive	Positive		NA		Pulmonary
20	G test	Positive	Positive		NA	CT	Pulmonary
21	GM test	Negative	Positive		NA	CT	Bloodstream
22	Cultivation	Positive	Positive	Sputum; BAL	A. fumigatus	Bronchoscope	Pulmonary
23	GM test	Positive	Positive		NA	Bronchoscope	Bloodstream
24	Cultivation	Positive	Positive	Sputum	A. flavus		Pulmonary
25	Cultivation	Positive	Positive	Sputum	A. flavus		Pulmonary
26	GM test	Positive	Negative		NA		Bloodstream
27	Cultivation	Positive	Positive	Sputum	A. flavus; A. terreus; C. albicans	CT	Bloodstream

Abbreviations: SFTS, severe fever with thrombocytopenia syndrome; NGS, next-generation sequencing; G, (1, 3)-β-D-glucan; GM, galactomannan; BALF, bronchoalveolar lavage fluid; A. fumigatus, Aspergillus fumigatus; C. albicans, Candida albicans; A. terreus, Aspergillus terreus; A. flavus, Aspergillus flavus; CT, computerized tomography.

19 other severe SFTS patients with fungal infections. These pathogens were isolated from sputum samples and BALF with Aspergillus fumigatus (10/25, 37.0%) and Aspergillus flavus (10/25, 37.0%) being the predominant pathogens.

Table 3 summarizes the baseline characteristics between the non-GC and GC groups. The median age of all patients was 69 (57, 74) years, and 55 (49.1%) were male. Patients in the GC group showed a higher prevalence of nervous system symptoms (P = 0.008), and higher levels of PT, CRP, and CREA at admission (all P < 0.05). Table 3 also presents the baseline characteristics after IPTW, showing balanced variations, except for CREA and D-dimer, which had SMD of

Table 3 Baseline Characteristics and Outcomes of Severe SFTS Patients on Admission in the GC and Non-GC Groups Before and After Inverse Probability of Treatment Weighting

Variables	Before IPTW			After IPTW		
	Non-GC (n=45)	GC (n=67)	P value	Non-GC (n=89)	GC (n=114)	P value
Demographic characteristics						
Sex (Male), n %	30 (44.4)	35 (52.2)	0.538	48 (53.7)	61 (53.8)	0.995
Age, years (median, IQR)	69.00 (58, 74)	67 (57, 74)	0.471	70 (56, 74)	68 (60, 75)	0.647
Interval period, days, median (IQR)						
Onset to admission	5.00 (4.00, 7.00)	5.00 (4.00, 6.50)	0.701	5.00 (4.00, 7.00)	5.00 (4.00, 6.00)	0.706

(*Continued*)

Table 3 (Continued).

Variables	Before IPTW			After IPTW		
	Non-GC (n=45)	GC (n=67)	P value	Non-GC (n=89)	GC (n=114)	P value
Comorbidities, n (%)						
Cancer	1 (2.2)	2 (3.0)	1.000	1 (1.3)	2 (1.9)	0.772
Hypertension	12 (26.7)	23 (34.3)	0.516	27 (30.3)	41 (35.6)	0.644
Diabetes mellitus	6 (13.3)	8 (11.9)	1.000	13 (14.8)	14 (12.1)	0.749
Hepatitis	4 (8.9)	5 (7.5)	1.000	6 (7.2)	7 (6.1)	0.807
Specific clinical symptoms, n (%)						
Gastrointestinal symptoms	31 (68.9)	43 (64.2)	0.755	54 (60.1)	72 (62.6)	0.835
Respiratory symptoms	15 (33.3)	32 (47.8)	0.186	41 (46.1)	53 (46.7)	0.958
Hemorrhagic symptoms	8 (17.8)	23 (34.3)	0.088	19 (21.7)	33 (28.8)	0.503
Nervous system symptoms	25 (55.6)	54 (80.6)	0.008	56 (63.1)	75 (65.6)	0.827
Laboratory results on admission, (median, IQR)						
WBC (10^9/L)	1.9 (1.5, 3.3)	2.2 (1.6, 3.15)	0.699	1.9 (1.37, 3.01)	2.0 (1.3, 2.76)	0.705
NEUT (10^9/L)	1.2 (0.8, 2.3)	1.4 (1.0, 2.2)	0.434	1.2 (0.8, 2.3)	1.3 (0.8, 2.2)	0.993
LYM (10^9/L)	0.5 (0.4, 0.7)	0.5 (0.35, 0.7)	0.644	0.5 (0.36, 0.6)	0.4 (0.3, 0.6)	0.590
PLT (10^9/L)	58 (35, 70)	56 (36.5, 75.5)	0.767	49.32 (32.73, 65.84)	54.11 (37, 69.48)	0.670
PT (s)	11.9 (11.3, 12.8)	12.6 (11.9, 13.35)	0.011	12.4 (11.50, 12.92)	12.48 (11.24, 13.1)	0.766
APTT (s)	41.1 (37.4, 47)	44.1 (36.75, 48.05)	0.587	41.84 (37.48, 47.32)	40.98 (36.30, 47.07)	0.671
TT (s)	23.7 (21.3, 36.1)	24 (20.3, 29.95)	0.504	23.17 (21.43, 31.14)	24.00 (20.33, 26.64)	0.971
D-dimer (mg/L)	3.93 (2.25, 9.99)	7.09 (3.06, 17.63)	0.107	3.87 (2.26, 12.47)	5.57 (3.05, 16.51)	0.344
CRP (mg/L)	4.61 (2.8, 16.3)	10.8 (5.35, 39.8)	0.003	4.90 (2.94, 17.74)	8.17 (5.14, 34.60)	0.149
ALT (mmol/L)	80 (46, 130)	70.2 (40.35, 108.7)	0.449	69.33 (41, 100.73)	74 (51.73, 105.68)	0.584
AST (mmol/L)	246.5 (111.3, 468)	166 (84.5, 352)	0.149	176.78 (98.55, 351.48)	198.47 (98.81, 356.00)	0.970
LDH (U/L)	1098 (500, 2150)	802 (517.5, 1497.5)	0.373	626.45 (464.47, 1709.28)	789.43 (540.11, 1491.75)	0.611
TBIL (μmol/L)	10.5 (6.9, 13.3)	9.4 (6.6, 11.7)	0.204	10.36 (6.90, 12.88)	9.40 (6.33, 11.70)	0.422
CREA (μmol/L)	73 (60.5, 89.8)	83 (69.85, 118.5)	0.010	75.48 (62.85, 89.74)	80.53 (67.47, 101.13)	0.242
BUN (mmol/L)	5.69 (4.18, 7.59)	6.34 (5.06, 8.55)	0.050	5.60 (4.31, 7.57)	6.20 (4.98, 8.00)	0.189
FBG (mmol/L)	6.80 (5.80, 8.60)	7.20 (6.02, 10.10)	0.362	6.64 (5.89, 9.10)	6.93 (5.81, 9.03)	0.988
CK (U/L)	445 (208, 853)	588 (245, 1059.5)	0.440	328.27 (203.63, 614.10)	598 (199.42, 1179.61)	0.104
Treatment variable, n (%)						
Antibiotics	33 (73.3)	58 (86.6)	0.130	65 (72.4)	90 (78.5)	0.582
IVIG infusion	34 (75.6)	60 (89.6)	0.086	72 (80.7)	95 (82.7)	0.843
G-CSF	35 (77.8)	45 (67.2)	0.315	68 (75.9)	81 (70.8)	0.640
Hepatoprotective drugs	43 (95.6)	62 (92.5)	0.803	86 (96.3)	108 (94.8)	0.695

Abbreviations: SFTS, severe fever with thrombocytopenia syndrome; GC, glucocorticoid; IQR, interquartile range; WBC, white blood cell; NEUT, neutrophil count; LYM, lymphocyte count; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TBIL, total bilirubin; CREA, creatinine; BUN, blood urea nitrogen; FBG, fasting blood glucose; CK, creatine kinase; IVIG, intravenous immunoglobulin; G-CSF, granulocyte colony-stimulating factor.

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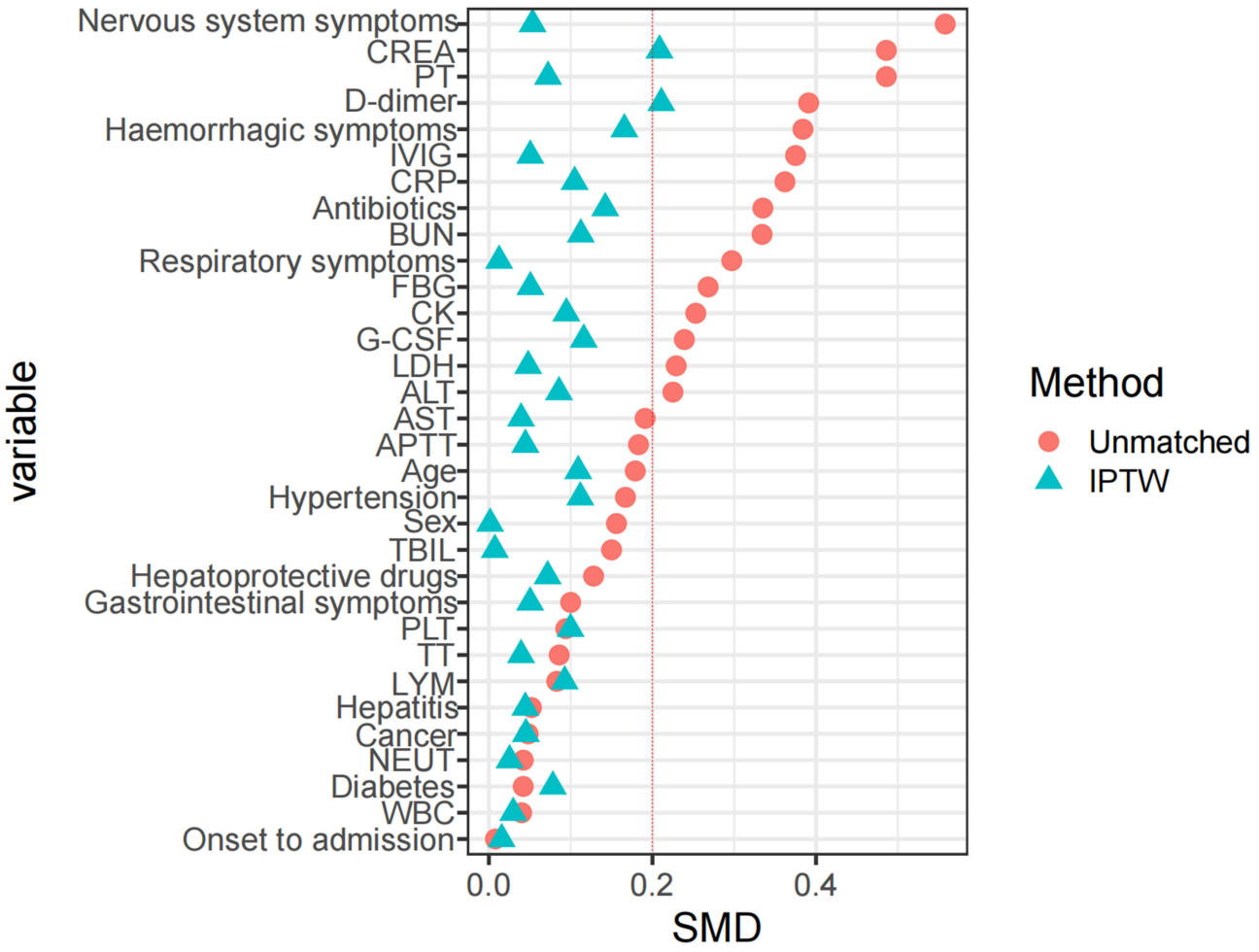

Figure 2 Standardized mean differences (SMD) before and after IPTW.
Abbreviations: IPTW, inverse probability of treatment weights; WBC, white blood cell; NEUT, neutrophil count; LYM, lymphocyte count; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TBIL, total bilirubin; CREA, creatinine; BUN, blood urea nitrogen; FBG, fasting blood glucose; CK, creatine kinase; IVIG, intravenous immunoglobulin; G-CSF, granulocyte colony-stimulating factor.

0.209 and 0.211, respectively. Changes in SMD pre- and post-IPTW SMD are visualized in Figure 2. Comparisons of outcomes including 28-day mortality and fungal infections were made between the non-GC and GC groups before and after IPTW adjustment. Following IPTW, patients in the GC group had a significantly higher incidence of fungal infections (5.0% vs 33.1%, $P < 0.001$), while there was no statistically significant difference in 28-day mortality between the two groups.

Effect of Glucocorticoid Treatment on 28-Day Mortality in Severe Patients

The overall 28-day mortality among severe SFTS patients was 48.2% (53/112). Stable 1 details the baseline characteristics of the non-fatal and fatal groups. The fatal patients were significantly older than the non-fatal patients ($P = 0.006$), with median ages of 71 (62, 78) and 65 (55, 72), respectively. The interval from onset to admission was shorter for the fatal patients ($P = 0.025$). The fatal patients also presented with a higher frequency of nervous system symptoms ($P = 0.011$) and elevated levels of TT, CREA, and BUN (all $P < 0.05$). Figure 3 shows similar mortality rates between the non-GC and GC groups, both before IPTW (37.8% vs 53.7%, $P = 0.143$) and after IPTW (40.8% vs 49.9%, $P = 0.439$). The effect of glucocorticoids on 28-day mortality was further estimated using univariate and multivariate Cox PH regression models after adjusting for covariables associated with mortality (stable 2). The analysis revealed no significant association between glucocorticoid use and 28-day mortality, either before IPTW (aHR 1.17, 95% CI 0.61–2.25, $P = 0.643$) or after IPTW (aHR 0.92, 95% CI 0.44–1.93, $P = 0.828$) (Table 4). As shown in stable 2, independent risk factors for 28-day

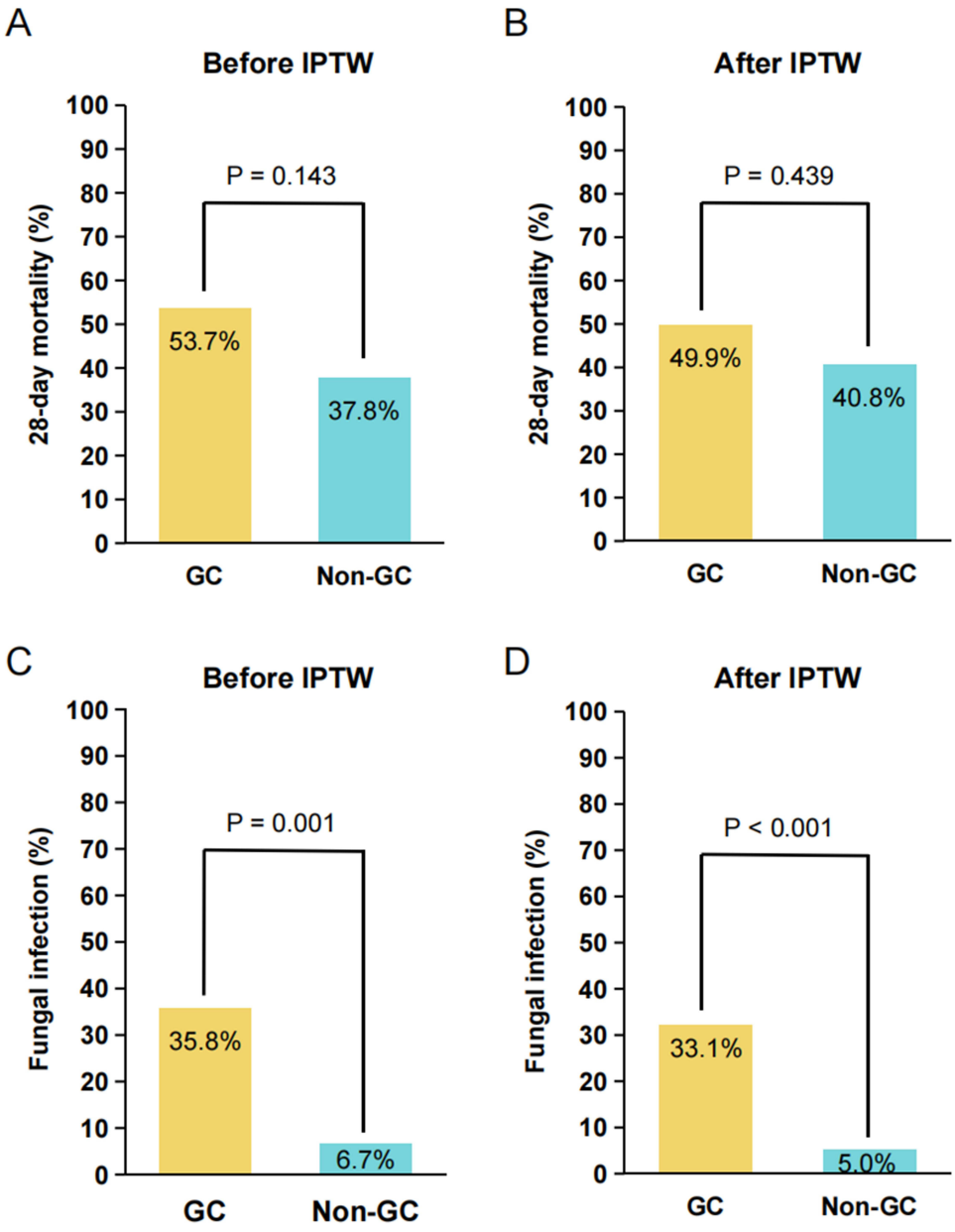

Figure 3 28-day mortality and incidence of fungal infections between the GC group and non-GC group. Comparison of 28-day mortality before (**A**) and after IPTW (**B**). Comparison of the incidence of fungal infections before (**C**) and after IPTW (**D**).
Abbreviations: GC, glucocorticoid; IPTW, inverse probability of treatment weights.

mortality included age, nervous system symptoms, D-dimer, LDH and BUN (all $P < 0.05$). Additionally, fungal infections were not significantly associated with 28-day mortality, either before IPTW (OR 1.09, 95% CI 0.60–1.99, P = 0.767) or after IPTW (OR 1.28, 95% CI 0.72–2.27, P = 0.388), indicating that it was not identified as an independent risk factor for mortality.

Figure 4 displays the Kaplan-Meier curves analysis. The survival rates between the two groups after IPTW did not differ significantly (HR 1.09, 95%Cl 0.53–2.24, P = 0.779) (Figure 4A). Notably, an intersection in the KM curves suggests that the impact of glucocorticoid treatment on mortality may change over time. To further explore this, a Global Test was conducted to assess the time-varying coefficients. As shown in stable 3, the Global test yielded a significant p-value (1.4×10^{-7}), indicating a lack of fit in the original Cox PH model. A substantial deviation from the PH assumption was identified for the glucocorticoid treatment variable ($P = 1.5\times10^{-6}$). The sfigure 2 further illustrates how the impact of

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Table 4 The Association of Glucocorticoid Treatment with 28-Day Mortality and Fungal Infections

	aHR/aOR	95% CI	P value
28-day mortality			
Original cohort	1.17	0.61–2.25	0.643
IPTW cohort	0.92	0.44–1.93	0.828
Fungal infections			
Original cohort	10.97	2.02–59.53	0.006
IPTW cohort	15.22	4.04–57.38	<0.001

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; IPTW, inverse probability treatment weighting.

glucocorticoid treatment on mortality varies over time. These findings suggest that glucocorticoid treatment acts as a time-varying coefficient, with a turning point occurring at approximately 7 days. To address the observed temporal variations, we performed a landmark analysis on the primary endpoint (Figure 4B). The survival curve for both groups showed a marked decline within the first 7 days, indicating a high early mortality rate. During this initial period (0–7 Days), the non-GC group experienced a more rapid decline in survival compared to the GC group, with the difference reaching statistical significance (HR 0.40, 95% CI 0.17–0.93, P = 0.034). After 7 days, the survival curves flattened, reflecting fewer deaths in both groups. However, in this later period, the survival curve for the GC group declined more rapidly than that of the non-GC group, again showing a statistically significant difference in survival (HR 5.95, 95% CI 1.64–21.59, P = 0.007). The stratified Cox regression model, which accounts for these time-varying effects, did not violate the PH assumption, as indicated by the global p-value (P = 0.115). Univariate time-varying Cox regression analysis (Table 5) revealed that glucocorticoid treatment significantly affected mortality within both time intervals (all P < 0.05). Multivariate time-varying Cox regression model, adjusted for age, nervous system symptoms, D-dimer LDH and BUN, confirmed a significant and protective impact of glucocorticoid treatment on 28-day mortality within the first 7 days (aHR 0.35, 95% CI 0.15–0.82, P = 0.016). However, in the period after 7 days, the effect of glucocorticoid treatment reversed, significantly increasing the risk of 28-day mortality (aHR 4.92, 95% CI 1.30–18.67, P = 0.019).

Table 6 details the glucocorticoid treatment regimens: 33 of the 67 patients received low doses (≤10 mg total) and 34 received high doses (>10 mg total) of dexamethasone equivalents. Of these, 30 patients initiated glucocorticoid treatment more than 8 days after symptom onset, while 37 initiated within 8 days. Additionally, 25 patients received

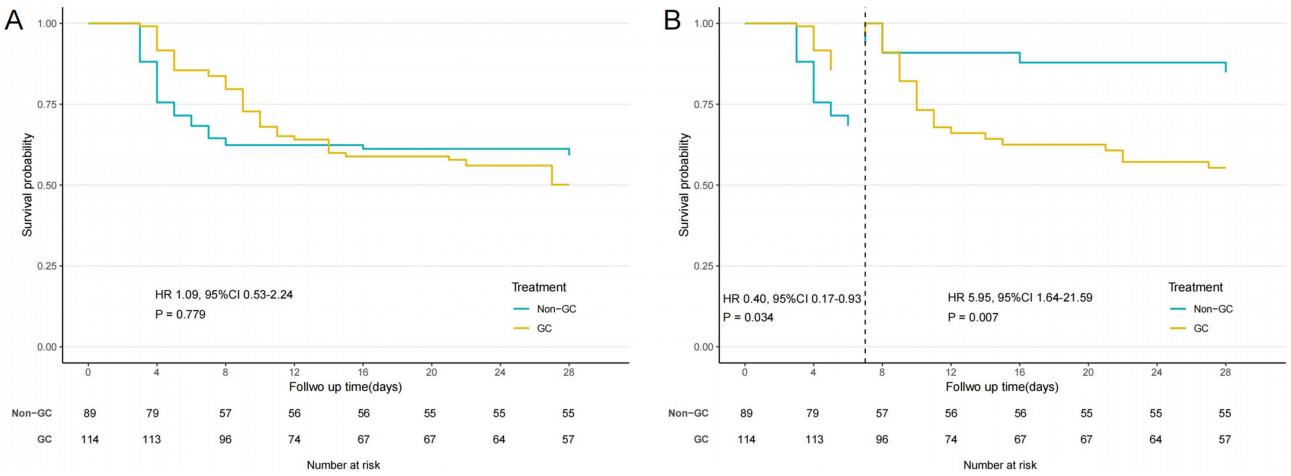

Figure 4 Comparison of survival between the GC and non-GC groups after IPTW. (**A**), Kaplan-Meier survival analysis of patients in the GC and non-GC groups. (**B**), Landmark analysis based on the 7-day landmark point.
Abbreviations: GC, glucocorticoid; IPTW, inverse probability of treatment weights.

Table 5 The Effects of Glucocorticoid Treatment on Mortality Within 7 days After Admission and from 7 days to the End of the Follow-up by Cox Regression Analysis

Time variables	Univariate Model			Multivariate Model		
	HR	95% CI	P value	aHR	95% CI	P value
< 7 days	0.40	0.17–0.93	0.034	0.35	0.15–0.82	0.016
7–28 days	5.95	1.64–21.59	0.007	4.92	1.30–18.67	0.019

Abbreviations: HR, hazard risk; aHR, adjusted hazard risk; CI, confidence interval.

Table 6 Various Adjustment Methodologies of Glucocorticoid Treatment and the Effects on 28-Day Mortality and Fungal Infections of Severe SFTS Patients (N=67)

Variables	Number	Univariate Model			Multivariate Model		
		HR/OR	95% CI	P value	aHR/aOR	95% CI	P value
28-day mortality							
Dose of glucocorticoid							
≤ 10mg	33	ref	–	–	ref	–	–
>10mg	34	1.86	0.95–3.64	0.071	1.41	0.68–2.96	0.357
Glucocorticoid initiation after onset							
> 8 days	30	ref	–	–	ref	–	–
≤ 8 days	37	1.23	0.64–2.37	0.541	1.66	0.82–3.34	0.158
Frequency of treatment							
Single	25	ref	–	–	ref	–	–
Multiple	42	1.49	0.73–3.04	0.269	0.51	0.14–1.90	0.318
Fungal infections							
Dose of glucocorticoid							
≤ 10mg	33	ref	-	-	ref	-	-
> 10mg	34	3.71	1.27–10.85	0.016	2.54	0.42–15.41	0.311
Glucocorticoid initiation after onset							
> 8 days	30	ref	-	-	ref	-	-
≤ 8 days	37	0.42	0.15–1.17	0.099	0.38	0.12–1.23	0.106
Frequency of treatment							
Single	25	ref	-	-	ref	-	-
Multiple	42	3.30	1.04–10.47	0.042	1.16	0.17–7.98	0.147

Abbreviations: SFTS, severe fever with thrombocytopenia syndrome; OR, odds ratio; aOR, adjusted odds ratio; HR, hazard ratio; aHR, adjusted hazard risk; CI, confidence interval.

glucocorticoids as a single use, and 42 received multiple use. Univariate and multivariable Cox PH model revealed that high dose, early administration, and multiple uses were not associated with a reduction in 28-day mortality adjusted for covariables.

Effect of Glucocorticoid Treatment on Fungal Infections in Severe Patients

Approximately 24.1% (27/112) of severe SFTS patients developed fungal infections during their hospitalization. Stable 1 summarizes the baseline characteristics between patients with and without fungal infections. Patients with fungal infections exhibited higher levels of fasting blood glucose (FBG) and creatine kinase (CK) and were more frequently administered antibiotics and glucocorticoids (all $P < 0.05$). As shown in Figure 3, the GC group exhibited a higher frequency of fungal infections compared to the non-GC group both before IPTW (6.7% vs 35.8%, $P = 0.001$) and after IPTW (5.0% vs 33.1%, $P < 0.001$). The median interval from illness onset to fungal infections was 12 (10, 14) days, while glucocorticoid treatment typically preceded fungal infections, with a median interval of −4 (−6, −1.75) days (Table 1).

Univariate and multivariate logistic regression analyses were conducted to evaluate the impact of glucocorticoid treatment on fungal infections (stable 4). The results indicated that glucocorticoid treatment was an independent risk factor for fungal infections before IPTW (aOR 10.97, 95% CI 2.02–59.53, $P = 0.006$) and after IPTW (aOR 15.22, 95% CI 4.04–57.38, $P < 0.001$) (Table 4). As shown in stable 4, alanine transaminase (ALT), respiratory symptoms, and nervous system symptoms were identified as independent risk factors for fungal infections among severe SFTS patients (all $P < 0.05$).

The high-dose group had a higher risk of fungal infections than the low-dose group (OR 3.71, 95% CI 1.27–10.85, $P = 0.016$) (Table 6). In addition, the multiple-use group was associated with a higher risk of fungal infection than the single-use group (OR 3.30, 95% CI 1.04–10.47, $P = 0.042$). However, the multivariable logistic regression analysis indicated high doses and multiple uses had no statistical significance adjusted for covariables.

Sensitivity Analyses

Overall, the results of sensitivity analyses were consistent with those of our primary analysis, IPTW analysis and time-varying analysis, verifying the robustness of our findings (sTable 5–6).

Discussion

SFTS is caused by infection with a novel phlebovirus in the Bunyaviridae family. During the acute phase of infection, active viral replication triggers abnormal cytokine production. The non-structural protein (NSs) of SFTSV induces transcription factors linked to cytokine upregulation, playing a crucial role in mediating cytokine storms post-infection.[33] This results in the release of numerous inflammatory cytokines (IL-1RA, IL-6, MCP-1, G-CSF, IP-10, et.al). Inappropriate cytokine responses to acute injuries in hosts can lead to multi-organ dysfunction. Sun et al demonstrated that the expression levels of cytokines in SFTS patients correlate with deterioration in multiple organ functions (including liver, heart, kidney, and hematological systems). Additionally, cytokine levels and types were higher in deceased patients than those in survivors. A return of cytokine levels to physiological norms correlated with recovery in SFTS patients.[7] The pathogenesis and pathological findings provide a theoretical basis for using anti-inflammatory agents to mitigate disease severity by blocking cytokine storms.

Among the therapies available for SFTS in clinical practice, glucocorticoids are widely used to suppress the systemic inflammatory response and mitigate disease severity. Given that SFTS predominantly affects patients in rural areas, economic constraints often dictate treatment choices, making glucocorticoids a more cost-effective option compared to immunoglobulin therapy for severe cases. While previous research has examined the impact of glucocorticoid treatment on SFTS patients' prognosis, our study introduces several novel aspects. Unlike previous studies that often lumped all SFTS patients together, our research specifically focuses on those with severe illness, who typically experience heightened inflammation and multi-organ damage. This distinction is crucial as it allows for a more targeted analysis of glucocorticoid efficacy. Secondly, using time-varying Cox regression models, we observed a nuanced temporal relationship between glucocorticoid use and 28-day mortality, which traditional static models may overlook, and systematically evaluated the occurrence of mortality associated with SFTS across different time frames. We rigorously employ IPTW to adjust for confounders in the time-varying Cox PH model, further validating our findings using Schoenfeld's Global test to assess the PH assumption, thereby enhancing the robustness of our findings. Moreover,

our study uniquely delves into various aspects of glucocorticoid administration, including dosage, duration, and frequency, to assess their impacts on 28-day mortality and secondary fungal infections. Our findings highlight the importance for cautious consideration of glucocorticoid use in severe SFTS cases, weighing potential therapeutic benefits against the risk of complications such as secondary infections.

In this study, the mortality rate among severe SFTS patients reached 48.2%, surpassing earlier reported rates.[2,5] Previous studies have indicated that glucocorticoid treatment negatively affected mortality outcomes in SFTS patients,[13,15,16] with varied results noted in those with severe illness. A recent large-scale retrospective cohort study found no significant impact of glucocorticoid treatment on the 28-day CFR in severe patients.[14] Similarly, an observational study involving 142 SFTS patients reported that glucocorticoid use did not influence the 30-day CFR in patients with Acute Physiology and Chronic Health Evaluation II scores ≥14.[16] These studies relied on fixed scoring systems and static indicators at admission to classify severe SFTS patients, which may overlook the dynamic progression of the disease in its early stages.[34,35] Given the rapid progression of severe SFTS, we focused on patients who presented severe symptoms upon admission and progressed to severe status within three days. Our study revealed that glucocorticoid treatment did not significantly increase 28-day mortality before or after IPTW adjustment using traditional Cox regression analysis. Interestingly, we observed that the survival curves for the GC and non-GC groups intersected, indicating a time-varying effect captured by KM curves.[36] This phenomenon has been reported in other studies as well,[14,37,38] where intersecting KM curves were observed but not deeply explored for their underlying causes. Furthermore, using landmark analysis and a time-varying Cox regression model, we demonstrated a differentiated impact of glucocorticoid treatment over time. Specifically, glucocorticoid treatment within the first 7 days significantly reduced mortality risk. Whereas glucocorticoid use from day 7 to day 28 increased mortality risk. The physiological responses of severe SFTS patients may vary at different stages. In the early stage, patients often exhibit sustained high viral loads, leading to elevated cytokine levels, multi-organ damage, DIC, and other severe complications associated with high mortality rates.[7,39] The initial days may represent a period where glucocorticoids temporarily improve survival rates through anti-inflammatory actions.[40] During disease progression, however, the immunosuppressive effects of glucocorticoids may increase the risk of secondary infections and other complications, and delay viral clearance.[9,41] These results underscore the complex temporal effects of glucocorticoids and highlight the need to consider both short-term and long-term impacts in clinical decision-making. These results illustrate the necessity of using time-varying models to accurately capture the dynamic effects of treatments over different periods, providing a more comprehensive understanding of therapeutic outcomes.

SFTS is often complicated by mixed infections involving viruses, bacteria, and fungi.[20,42] The risk of fungal infections in SFTS is a significant public concern. Leukopenia and thrombocytopenia induced by SFTSV are key pathological factors predisposing SFTS patients to concurrent fungal infections.[22,26,43] Previous studies have reported a higher incidence of fungal infections in patients receiving glucocorticoids than those not receiving them.[13,14,37] Consequently, fungal infections in SFTS patients likely result from a combination of disease and glucocorticoid treatment. However, few have examined whether glucocorticoids independently contribute to this risk in SFTS patients. In this study, glucocorticoid treatment was identified as an independent risk factor for fungal infections in severe SFTS patients. The predominant fungal infections observed was aspergillosis, which was accompanied by significant liver function abnormalities, severe respiratory symptoms, and neurological manifestations, aligning with previous reports.[19,44]

In our study, fungal infections did not influence the 28-day mortality rate in critically ill SFTS patients. However, previous research has reported conflicting findings regarding the impact of fungal infections on mortality. Some studies have suggested that invasive pulmonary aspergillosis (IPA) significantly increases mortality in SFTS patients.[27,42] In contrast, other studies have indicated that while co-infections may not directly elevate fatality rates, they can contribute to multi-organ dysfunction, prolong hospital stays, and increase the need for mechanical ventilation.[23] These discrepancies highlight the complexity of fungal infections in SFTS outcomes, suggesting that their impact may vary depending on the clinical context and patient characteristics. The role of prophylactic antifungal therapy in reducing the incidence of fungal infections in SFTS remains a topic of ongoing debate. While one study found no significant benefit from antifungal therapy,[23] another reported a survival advantage.[20] However, neither study explicitly differentiated between prophylactic and therapeutic antifungal use, nor did they assess the association between antifungal drugs and fungal infections in SFTS patients. Given these uncertainties, large-scale prospective studies are needed to comprehensively

evaluate the benefits and risks of prophylactic antifungal therapy in SFTS patients, particularly those receiving glucocorticoids.

Different administration methods of glucocorticoid administration can influence treatment outcomes and lead to various adverse reactions. Gang Wang et al reported that high-dose glucocorticoid (> 60 mg daily methylprednisolone or equivalent) may worsen outcomes in SFTS patients by increasing the risk of secondary infections.[14] In their study, the median cumulative dose of glucocorticoid treatment was 340 (212, 559) mg methylprednisolone equivalent, administered over a median duration of 5.0 (3.0, 6.5) days. However, after adjusting for confounding factors and stratifying patients by glucocorticoid dosage, initiation time, and administration frequency, our study did not find significant effects on the incidence of fungal infections or 28-day mortality. This discrepancy may be attributed to the fact that glucocorticoid dosage and duration in our cohort −11.87 (5.00, 29.38) mg over a median of 2 (1, 4) days – were lower and shorter, respectively, compared to those reported in other studies.[14–16] This limitation may have affected our ability to detect the impact of different administration methods on patient outcomes.

This study also encountered several limitations. Firstly, as a retrospective, single-center investigation of severe SFTS cases, our analysis is inherently constrained by potential selection bias and unmeasured confounding factors despite employing IPTW to balance baseline characteristics. We further employed sensitivity analysis to enhance the robustness of our findings. Due to the limited number of outcome events, our analysis yielded a high aOR/aHR with a wide 95% CI, emphasizing the need for validation in larger sample studies. Furthermore, the absence of cytokine and viral load data restricts our ability to elucidate the underlying mechanisms of glucocorticoid therapy. Additionally, the diagnosis of fungal infections in this study was primarily based on retrospective data. However, additional confirmatory tests, such as fungal smears, were unavailable. To enhance the robustness and generalizability of our findings, future studies should integrate multi-center data, incorporate regional epidemiological insights, and prioritize the comprehensive analysis of viral load, cytokine profiles, and fungal biomarkers. Ultimately, large-scale, randomized controlled trials are warranted to confirm our findings and validate the efficacy of prophylactic antifungal therapy to optimize treatment strategies for severe SFTS.

Conclusion

The use of glucocorticoids for treating severe SFTS should be approached with caution due to limited efficacy and the potential for significant adverse events. Although glucocorticoids do not impact the overall 28-day mortality in critically ill patients, the treatment may have time-varying effects, significantly reducing mortality within the first 7 days after admission while increasing mortality after 7 days. Vigilant monitoring for fungal infections is essential, particularly with high doses and prolonged use. Given the widespread use of glucocorticoids among severe SFTS patients and the limited research on their effects in this cohort, our study provides crucial insights that can inform clinical treatment strategies.

Abbreviations

SFTS, severe fever with thrombocytopenia syndrome; GC, glucocorticoid; IPTW, inverse probability of treatment weighting; DIC, disseminated intravascular coagulation; CFR, case fatal rate; RT-PCR, real-time polymerase chain reaction; COPD, chronic obstructive pulmonary disease; EORTC/MSGERC, The European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; BALF, bronchoalveolar lavage fluid; mNGS, metagenomic next-generation sequencing; GM, galactomannan; interval; G, (1, 3)-b-D glucan; MCAR, missing completely at random; IQR, interquartile range; PS, propensity score; SMD, standardized mean differences; VIF, variance inflation factor; PH, proportional hazards; TT, thrombin time; PT, prothrombin time; CREA, creatinine; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine transaminase; IPA, invasive pulmonary aspergillosis; HR, hazard ratio; OR, odds ratio; CI, confidence; KM, Kaplan-Meier; LDH, lactate dehydrogenase; FBG, fasting blood glucose; CK, creatine kinase; CRP, C-reactive protein. NSs, non-structural protein.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethical Committee of Nanjing Drum Tower Hospital (NO.2023-488-02). Written informed consent was waived and all procedures adhered to the Declaration of Helsinki. All patient data used in this study was handled in strict accordance with ethical standards and institutional guidelines to ensure confidentiality and privacy. No personal identifying information was disclosed in any part of the manuscript and confidentiality of patient information was maintained throughout the study.

Consent for Publication

All authors gave their consent for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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