THERAPEUTIC ADVANCES in
Infectious Disease

Review

Evolving therapeutic strategies for severe fever with thrombocytopenia syndrome: from past to future

Ther Adv Infect Dis

2025, Vol. 12: 1–21

DOI: 10.1177/20499361251340786

Yuxi Zhao, Xiaoxin Wu, Xinyu Wang and Lanjuan Li

***Abstract*:** Severe fever with thrombocytopenia syndrome (SFTS) is a hemorrhagic fever caused by *Bandavirus dabieense*. SFTS was first identified in China in 2009 and has been reported since then in neighboring countries and regions. The clinical manifestations of SFTS include fever, thrombocytopenia, and leukocytopenia and are often accompanied by gastrointestinal symptoms and bleeding. In severe cases, patients experience life-threatening immune damage and cytokine storms. Despite nearly 15 years since its discovery, no effective vaccine has been approved. However, significant progress has been achieved in elucidating the mechanisms of host immune responses, accompanied by the clinical implementation of various therapeutic agents. This article provides a comprehensive review of commonly utilized treatments supported by current clinical evidence. Favipiravir has advantages over ribavirin in terms of viral clearance and prognosis. Conventional immunomodulators like interferon, intravenous immunoglobulin, and glucocorticoids have limited effects and may even worsen conditions, whereas novel immunomodulators such as tocilizumab and ruxolitinib have shown potential for improving prognosis. Prophylactic platelet transfusions neither prevent bleeding nor improve clinical outcomes. Additionally, plasma exchange, calcium channel blockers, and arginine can improve laboratory values and expedite viral clearance. In the future, screening Food and Drug Administration-approved drugs and conducting multiomics analyses may lead to the discovery of new effective therapeutic options.

Keywords: *Bandavirus dabieense*, severe fever with thrombocytopenia syndrome, SFTS, therapy, treatment, viral hemorrhagic fever

Received: 20 November 2024; revised manuscript accepted: 23 April 2025.

Correspondence to:
Lanjuan Li
State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou City 310003, China
ljli@zju.edu.cn

Yuxi Zhao
Xiaoxin Wu
Xinyu Wang
State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou City, China

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) was first identified in the Dabie Mountains of China in 2009,[1] and cases have been reported since then in neighboring East Asian countries, including South Korea,[2] Japan,[3] Vietnam,[4] and Myanmar.[5] The pathogen *Bandavirus dabieense* (formerly known as novel bunyavirus), according to the 2024 updated taxonomy released by the International Committee on Taxonomy of Viruses (ictv.global/taxonomy), belongs to the order *Hareavirales*, family *Phenuiviridae*, and genus *Bandavirus*.[6] Ticks serve as the main vector, transmitting the virus through bites,[6] and family members and health care staff can be infected through contact with infected blood and body fluids.[7] Migratory birds carrying virus-infected ticks facilitate cross-regional transmission.[8,9] Predictive models have indicated that, beyond East Asia, regions such as the southeastern United States, New Zealand, and parts of Australia are potential high-risk areas.[10] Therefore, the prevalence and spread of SFTS present significant challenges to future efforts in disease prevention, control, diagnosis, and treatment.

SFTS, while demonstrating broad population susceptibility,[11] with an overall mortality rate of approximately 7.8%,[12] exhibits marked interindividual heterogeneity in clinical manifestations,

ranging from self-limiting febrile illness to rapidly progressive multiple organ failure. Following an incubation period of 5–14 days, the clinical course typically progresses through three overlapping stages.[11,13,14] The fever stage is characterized by abrupt high fever, thrombocytopenia, leukocytopenia, fatigue, headache, myalgia, gastrointestinal disorders, and lymphadenopathy. The multiple organ dysfunction (MOD) stage emerges around 5 days after disease onset, marked by elevated liver and muscle enzymes, proteinuria, hemorrhagic manifestations, and potential progression to multiple organ failure and disseminated intravascular coagulation (DIC). Common complications include acute renal failure, cardiac arrhythmias, and myocarditis. Survivors enter the convalescent stage, with gradual resolution of clinical symptoms and laboratory abnormalities. Patients with mild or self-limited infections may bypass the MOD stage entirely and recover directly.

Clinical severity stratifies into three distinct profiles.[15,16] Mild-moderate cases are characterized by low-grade fever (<39°C) and self-limiting symptoms, including mild fatigue and gastrointestinal disorders. Laboratory findings include a platelet (PLT) count $>50\times10^9$/L and aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and lactate dehydrogenase (LDH) levels below five times the upper limit of normal (ULN). Complications are typically absent. Severe cases present with high fever (>39°C), profound fatigue, prominent gastrointestinal symptoms, and emerging neurological signs (e.g., lethargy, confusion, tremor). Laboratory abnormalities include a platelet count $<50\times10^9$/L and AST, ALT, CK, and LDH levels $>5\times$ ULN. Complications may include pneumonia or minor hemorrhagic events. Critical cases exhibit severe features plus additional critical manifestations, such as coma, seizures, or delirium; major hemorrhage; platelet count $<30\times10^9$/L; AST, ALT, CK, and LDH levels $>10\times$ ULN; organ failure; disseminated intravascular coagulation (DIC); and refractory infections.

Currently, there is no approved vaccine for SFTS.[17] Over the past 15 years, various therapeutic strategies for SFTS have been explored, with recent retrospective analyses and clinical trials demonstrating their efficacy. Novel immunomodulators, which gained significant attention during the coronavirus disease 2019 (COVID-19) pandemic for their remarkable efficacy, have also shown substantial potential in improving SFTS prognosis.[18,19] Furthermore, the screening of Food and Drug Administration (FDA)-approved drugs and advancements in omics studies have identified promising new therapeutic options, such as nifedipine and ariginine.[20,21]

This review aims to summarize and update the reported therapeutic strategies for SFTS, assess their impact on prognosis, adverse effects, and offer insights to guide future therapeutic developments.

Methods

We conducted a comprehensive search of peer-reviewed literature on SFTS and its therapeutic strategies using PubMed, Web of Science, and EMBASE, targeting studies published between January 2010 and December 2024. Our search primarily aimed to capture evidence on antivirals, symptomatic treatment, and supportive treatments. Inclusion criteria encompassed: (1) clinical studies that reported clinical outcomes (clinical trials, observational studies); (2) mechanistic studies elucidating pharmacological actions; (3) systematic reviews/meta-analyses synthesizing treatment outcomes. Exclusion criteria included animal studies, non-English articles, and gray literature (preprints, conference abstracts). Search terms were grouped into three domains using Boolean operators (AND/OR): (1) population: "Severe Fever with Thrombocytopenia Syndrome" OR "SFTS"; (2) interventions: "Ribavirin" OR "Favipiravir" OR "Intravenous Immunoglobulin" OR "Plasma Exchange" OR "Glucocorticoid" OR "Tocilizumab" OR "Ruxolitinib" OR "Calcium Channel Blocker" OR "Arginine" OR "Transfusion" OR "Interferon"; (3) outcomes: "Mortality" OR "Prognosis" OR "Survival."

Pathogen

The shell of *Bandavirus dabieense* is composed of lipid bilayer envelopes, which are covered by capsomers composed of transmembrane glycoproteins (Gc and Gn), which act as complexes on the surface.[22] The virus contains three single-stranded, negative-sense RNA segments. The L segment encodes RNA-dependent RNA polymerase, which facilitates viral transcription and replication.[23] The M segment encodes precursors

of Gn and Gc, which are essential for viral attachment, entry, and fusion.[24] The S segment encodes the nucleocapsid protein (N) and nonstructural protein (NSs).[1] The NSs protein inhibits type I interferon (IFN) induction and induces interleukin 10 (IL-10) production, thereby suppressing the host immune response and enhancing viral pathogenicity.[25,26] Additionally, it induces a cytokine storm through excessive activation of nuclear factor kappa-B (NF-κB).[27]

Clinical features of fatal cases

In fatal cases of SFTS, both innate and adaptive immunity are severely compromised. The virus primarily targets monocytes and plasmablasts.[28] $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, NKT cells, and other immune cells are substantially depleted. Concurrently, a defective serological response of IgG antibodies against the viral nucleocapsid and glycoprotein occurs due to a failure in B-cell class switching.[28–31] In the late stages of disease, plasmablasts become the main target of the virus.[32]

Fatal cases exhibit high serum viral loads, with the coexistence of elevated levels of inflammatory and anti-inflammatory factors in early disease stages.[33,34] Compared with those in survivors, the levels of cytokines, including interleukin 6 (IL-6), IL-10, tumor necrosis factor-alpha (TNF-α), and IFN-γ, are markedly increased,[35] leading to immune paralysis and secondary infections.

Laboratory values such as AST, CK, LDH, and platelet counts, as well as coagulation profiles, are significantly abnormal,[36] and severe complications, including multiple organ dysfunction syndrome (MODS), shock, neurological symptoms, and bleeding signs, are relatively common.[13,37] Advanced age is a key risk factor for mortality.[38,39] Underlying diseases such as chronic viral hepatitis, chronic obstructive pulmonary disease, and diabetes are also associated with mortality.[40]

Autopsies of fatal cases have revealed virus nucleoprotein (NP) in various organs, including the spleen, liver, heart, lungs, and kidneys.[41,42] Aspergillosis is frequently observed in the lungs and bronchi[43–45]; hemophagocytic cells are detected in bone marrow smears; the spleen, lymph nodes, and central nervous system;[3,42,46] and bleeding occurs in organs such as the lungs and colon.[47]

Clinical treatment

The current management of SFTS primarily includes symptomatic treatment (e.g., antipyretics, immunomodulatory agents), supportive care (e.g., mechanical ventilation, plasma exchange), antiviral therapy (ribavirin, favipiravir), and complication management (e.g., hemorrhage, secondary infection). For mild-moderate cases, treatment focuses on symptomatic management and antiviral therapy, while severe and critical cases require supportive care and complication management.

Antivirals

Ribavirin. Discovered in the 1970s, ribavirin is a guanosine analog with broad-spectrum antiviral activity and is widely used for treating various viral infections. It has demonstrated efficacy in treating respiratory syncytial virus with underlying immunosuppression and chronic hepatitis C virus infections.[48,49] However, its effectiveness remains controversial for viruses such as adenovirus,[50] and hemorrhagic fever viruses, including Hantaviruses, Crimean-Congo hemorrhagic fever virus, and Lassa virus.[51–53] The efficacy of ribavirin for the treatment of SFTS is similarly debated (Table 1). Although some case reports suggest that ribavirin, in combination with glucocorticoids, intravenous immunoglobulin (IVIG), or plasma exchange (PE), may improve patient prognosis,[54–56] retrospective studies and meta-analyses do not reveal significant benefits.[57–60] Li et al.[59] reported that ribavirin was only effective in patients with a viral load less than 1×10^6 copies/mL. Furthermore, Lu et al[61] reported adverse effects such as anemia and elevated amylase levels during ribavirin treatment, which may impact safety and tolerance.

As a result, the efficacy of ribavirin in the treatment of SFTS is uncertain. With the development of newer antiviral drugs such as favipiravir, further clinical trials to confirm the effectiveness of ribavirin are increasingly unlikely. Larger retrospective studies are needed to assess the role of ribavirin in treating SFTS more comprehensively.

Favipiravir/T-705. Favipiravir, a modified pyrazine analog, inhibits RNA-dependent RNA polymerase.[62] In 2014, favipiravir was approved in Japan for treating novel or re-emerging influenza infections, it has also been used to treat several critical RNA virus infections, including Ebola

Table 1. Summary of ribavirin on severe fever with thrombocytopenia syndrome.

Author	Year	Analyzed cases	Study type	Regimen	Viral loads change	Major findings	Adverse effects
Liu[57]	2013	302	Single-center retrospective cross-sectional study	500 mg per day	No significant effect	CFRs were similar between patients with and without ribavirin, no significant effect on platelet count	ND
Lu[61]	2015	574	Single-center prospective observational study	500 mg per day, 3–12 consecutive days	ND	The occurrence of anemia and hyperamylasemia was associated with ribavirin therapy	Hyperamylasemia and anemia
Chen[60]	2017	433	Meta-analysis	NA	NA	Effectiveness to influence progression is minimal	ND
Li[59]	2018	1403	Single-center prospective observational study	Not mentioned	ND	CFR reduced only in patients with viral loads $<1\times10^6$ copies/mL	ND
Zhang[58]	2021	62	Single-center retrospective cohort study	Adults: 600 mg per day; Children: 200 mg per day	ND	No difference in mortality between the untreated group and the treated group	Delay recovery of leukocyte levels and platelet levels

Ribavirin was administered intravenously.
CFR, case fatality rate; NA, not applicable; ND, not done.

virus, Lassa virus, rabies virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), in recent years.[63,64]

Multiple studies (Table 2) have demonstrated that favipiravir effectively reduces the viral load and improves the prognosis of patients with SFTS. The adverse effects of favipiravir include gastrointestinal symptoms, rash, and elevated levels of serum transaminases and uric acid.[65-68] Although favipiravir is generally effective and has a significant effect on viral clearance, its efficacy varies across subgroups. Li et al.[66] reported that favipiravir notably improves prognosis in patients who are admitted within 6 days of symptom onset or have a low viral load (reverse-transcription polymerase chain reaction (RT–PCR) cycle threshold $\geqslant 26$), reducing the risk of death, hemorrhage, and neurological symptoms while promoting recovery of neutrophils and lymphocytes. Similarly, Suemori et al.[68] found that favipiravir has a favorable prognostic effect in patients with viral loads less than 1×10^5 copies/mL. Yuan et al[67] found that patients $\leqslant$70 years of age, with symptom-to-admission intervals of $\leqslant$5 days, treatment durations of $\geqslant$5 days, and baseline viral loads of $\leqslant1\times10^6$ copies/mL, had significantly improved prognoses following favipiravir treatment. These findings suggest that early treatment and low baseline viral loads are associated with better outcomes when favipiravir is administered. However, since these studies included few severe cases, further research is needed to assess the efficacy of favipiravir in patients with high viral loads and severe illnesses.

Immunomodulatory therapies

Intravenous immunoglobulin. Intravenous Immunoglobulin (IVIG), which is collected from the plasma of many healthy human donors, contains antibodies against multiple pathogens and was originally used for the replacement treatment of primary and secondary immune deficiencies. Owing to its anti-inflammatory and immunomodulatory effects, IVIG was subsequently approved for treating autoimmune diseases such as chronic inflammatory demyelinating

Table 2. Summary of favipiravir on severe fever with thrombocytopenia syndrome.

Author	Year	Analyzed cases	Study type	Regimen	Viral loads change	Major findings	Adverse effects
Song[65]	2020	2	Case report	Day 1: 1600 mg twice a day; Day 2–5: 600 mg twice a day	Undetectable within 5 days post-treatment	Cured	Red itchy papules and liver function abnormal in one case
Li[66]	2021	145	Single-center, single-blind, randomized controlled trial	Day 1: 1800 mg twice a day; Days 2 and onward: 1000 mg twice a day	Mean (±SD) days to viral clearance was significantly shorter than in the control group (5.6 ± 2.1 vs 6.8 ± 2.8)	No difference in the survival curves, cox regression showed a significant reduction in CFR	Skin allergy in one case, higher uric acid levels in treated group
Suemori[68]	2021	23	Multicenter, non-randomized, uncontrolled single-arm trial	Day 1: 1800 mg twice a day; Days 2–7 (up to Day 14): 800 mg twice a day	Decreased day by day in the patients' overall	28-day mortality rate was 17.3% (4/23)	Epidermal and dermal conditions, insomnia, liver function abnormal occurred in 20% or more of the patients
Yuan[67]	2021	780	A single-arm study ($n = 428$), a surveillance study ($n = 2350$), a randomized controlled trial study ($n = 145$)	Day 1: 1800 mg twice a day; Days 2 and onward: 1000 mg twice a day.	Rapid decrease than in the non-treated group, obvious decline at day 5 post-treatment	Survival curves and multivariable conditional logistic regression showed the overall CFR was decreased	Vomiting, earlier nausea and diarrhea, higher uric acid and aspartate aminotransferase level

Favipiravir was administered orally.
CFR, case fatality rate; SD, standard deviation.

polyneuropathy (CIDP) and immune thrombocytopenic purpura (ITP).[69]

In the early stages after SFTS was initially discovered, IVIG was frequently administered in combination with other therapies, especially in patients with neurological symptoms. Kim et al.[70] reported a 64-year-old male patient with altered consciousness and a Glasgow Coma Scale (GCS) score of 5 on the fifth day after admission. On the sixth day, he received IVIG (1 mg/kg over 3 days) combined with dexamethasone (10 mg/m² for 7 consecutive days). The viral load became negative by day 9, and the patient was subsequently discharged. Similarly, a 75-year-old woman presented with altered mental status on her fifth day after admission, with a GCS score of 8. When she was treated with the same regimen and dose, her GCS score improved to 15 by the eighth day, and she was discharged. Song[55] described a 10-year-old girl with SFTS treated with IVIG (0.5 mg/kg for 2 days) alongside dexamethasone and ribavirin; she also recovered and was discharged. A single-center retrospective study by Liu et al[71] observed the impact of IVIG on 28-day survival time in 62 SFTS patients with neurological symptoms. They reported higher survival rates in patients receiving a total IVIG dose of ⩾80 g and a treatment duration of 5 days or more.

However, Sin et al.[72] reported no survival benefit from IVIG among 35 SFTS patients. Similarly, Zhai et al.[73] observed no significant difference in 28-day mortality with IVIG use, both before and after case matching ($n = 389$ and $n = 48$, respectively). A large-scale retrospective cohort analysis

conducted by Zhang et al.[74] found that the prescription of IVIG did not improve the prognosis of SFTS, both before ($n = 2219$) and after matching for age, sex, admission delays, and disease severity ($n = 1578$). Instead, IVIG treatment was associated with increased viral loads and reduced counts of lymphocytes, T cells, $CD4^+$ T cells, and NK cells, suggesting potential immune disorders and inadequate virus-neutralizing antibody levels in patients receiving IVIG. Notably, Yao et al.[75] analyzed 169 SFTS patients complicated with invasive pulmonary aspergillosis (IPA) and reported no improvement in 42-day mortality.

The abovementioned research mostly originated from China, where the annual incidence from 2011 to 2021 was approximately 0.125 per 100,000, primarily in Shandong, Anhui, and Henan Provinces, with the elderly and farmers comprising the largest affected population.[76] IgG seropositivity rates vary significantly across regions, with positivity in Anhui Province at 20.16% (152/754), Henan Province at 10.46% (153/1463), Penglai County, Shandong Province at 3.85% (53/1375), Laizhou City, Shandong Province at 3.3% (35/1060), and Jiangsu Province at only 0.44% (11/2510).[77–81] In Xinyang City, Henan Province, a high-incidence area, 9.8% (50/508) of healthy individuals had neutralizing antibodies,[82] whereas in Penglai County, Shandong Province, another endemic area, only 0.58% (8/1375) had neutralizing antibodies.[81]

After SFTS infection, *Bandavirus dabieense* IgG antibody titers typically peak at approximately 6 months and then decline gradually.[83–85] Serum IgG positivity and titers of *Bandavirus dabieense* correlate positively with neutralizing antibodies.[82] Hu et al.[86] followed four SFTS survivors and reported that IgG antibodies could persist for up to 14 years at high titers. Huang et al.[87,88] reported that 4 years post infection, the neutralizing antibody positivity rate remained at 100% (25/25), with a protective titer estimated to persist for 9 years. Similarly, Li et al.[83] also reported that the positivity rate for neutralizing antibodies was 66.7% (18/27) even 10 years post infection, with asymptomatic infections showing a 62.5% (5/8) positivity rate 7 years after follow-up.[81]

Despite the extended duration of neutralizing antibodies, significant variance of IgG positivity in different regions and the limited number of SFTS patients, predominantly elderly patients, resulted in difficulty in obtaining plasma from previously infected individuals and an extremely low neutralizing antibody content in IVIG. Thus, IVIG treatment may merely increase the financial burden on patients. Plasma from convalescent patients offers a viable alternative; however, larger studies and further validation in different countries and regions are needed to assess the role of IVIG in SFTS and explore its immunomodulatory effects.

Glucocorticoids. Glucocorticoids are primarily used to alleviate fever, MODS, and neuropsychiatric symptoms associated with cytokine storms. A series of case reports suggest that some patients recover after receiving pulse therapy alone or in combination with other treatments, such as IVIG.[70,89,90] There are also cases of condition deterioration and increased viral load leading to death after pulse therapy.[91] In recent years, several retrospective cohort studies (Table 3) have investigated the impact of glucocorticoid use on prognosis. After adjustments for confounding factors through matching, most results indicate that glucocorticoids neither improve prognosis nor reduce mortality overall, and in some cases, they even contribute to adverse complications.[92–97] A meta-analysis conducted by Chen et al.,[96] incorporating data from Xiong et al.[94] and Kawaguchi et al.[93] showed that glucocorticoid use significantly increases the risk of secondary infections, whereas this difference was not significant according to the research of Shuto et al.[98] and Kutsuna et al.[97] However, glucocorticoids have shown beneficial effects in certain patient populations and subgroups. Shuto et al.[98] reported that glucocorticoid use improved the prognosis of patients presenting with impaired consciousness at admission. Wang et al.[99] reported that glucocorticoids significantly reduced the 28-day mortality rate among ICU patients. Similarly, Wang et al.[95] found that low-to-moderate doses of glucocorticoids ($\leqslant$60 mg/day of methylprednisolone or equivalent) may improve the prognosis of critical cases (L index $>$ 3.823).

Patients with severe SFTS are particularly vulnerable to immune paralysis induced by cytokine storms and impaired innate and adaptive immunity,[100] subsequently increasing the risk of secondary infections.[101] IPA typically occurs in immunosuppressed patients, but it is also prevalent in SFTS with patients.[102,103] The incidence of SFTS-associated invasive pulmonary

Table 3. Summary of glucocorticoids on severe fever with thrombocytopenia syndrome.

Author	Year	Original cases	Matched cases	Research type	Subgroup and regimen	Major findings
Tsutsumi[91]	2016	1 HLH	NA	Case report	mPSL Day 3: 250 mg per day; Day 4–6: 1000 mg per day	Died, viral loads increased
Kim[70]	2016	2 SFTSAE	NA	Case report	DXM 10 mg/m^2 per day	Cured
Nakamura[89]	2018	3 SFTSAE	NA	Case report	mPSL 500 mg per day	Cured with no neurological sequelae
Shan[90]	2024	1 SFTSAE	NA	Case report	DXM 10 mg per day	Cured with no neurological sequelae
Jung[92]	2021	142	PSM: 112	Multicenter retrospective cohort study	Severe (APACHE2⩾14) and Mild (APACHE2<14) Early treatment (⩽5 days from the start of therapy after symptom onset) and late (>5 days)	In the early GC group or with GC therapy in mild cases, 30-day survival was shorter than in the non-GC group
Kawaguchi[93]	2021	47	PSM:24	Multicenter retrospective case–control study	ND	CFR and secondary infections were higher in the GC group
Xiong[94]	2022	467	PSM: 190	Single-center retrospective cohort study	ND	GC therapy had no impact on fatality and increased secondary infections
Shuto[98]	2023	494	PSM: 288	Multicenter retrospective cohort study	Impaired consciousness on admission; Shock, respiratory failure within 7 days after admission	30-day mortality, the number of survival days, and secondary infections were no differences compared to the non-GC group
Wang[95]	2023	2478	PSM: *Mild (246) and Severe (372)	Multicenter retrospective cohort study	Low-moderate doses (mPSL or equivalent ⩽60 mg/d) and high-dose (>60 mg/d)	Reduced CFR was only observed in severe cases receiving low-moderate doses. GC therapy was significantly associated with increased CFR in mild cases.
Kutsuna[97]	2023	412	OW: 412	Multicenter retrospective cohort study	mPSL ⩾ 500 mg per day in GC group	Significantly higher in-hospital mortality rate in the GC group especially during the initial 5–7 days of admission; no statistically significant difference in fungal infection
Chen[96]	2024	566	PSM: 360 IPTW: 359	Single-center retrospective cohort study	ND	No evidence of increased mortality or secondary infection rate in the GC group
		3677	NA	Meta-analysis	NA	GC therapy might increase the mortality rate
		1291	NA	Meta-analysis	NA	Infection rate in the GC group was statistically greater
Wang[99]	2024	218	PSM: 116	Single-center retrospective observational study	GCS score, lactate levels, and use of IVIG, norepinephrine, and antiviral drugs	GC therapy lowered 28-day mortality rate, particularly combined with antivirals/IVIG and in patients with GCS < 13, hyperlactatemia (>2 mmol/L), norepinephrine used, but increased rates of secondary infections, requirement of CRRT, longer ICU and hospital stays compared to the non-GC group

The major findings were based on matched results.
*Mild: L index ⩽ 3.823, Severe: L index > 3.823.
CFR, case fatality rate; CRRT, continuous renal replacement therapy; DXM, dexamethasone; GC, glucocorticoid; GCS, Glasgow coma scale; HLH, hemophagocytic lymphohistiocytosis; IPTW, inverse probability of treatment weighting; IVIG, intravenous immunoglobulin; mPSL, methylprednisolone; NA, not applicable; ND, not done; OW, overlap weighting analysis; PSM, propensity score matching; SFTSAE, severe fever with thrombocytopenia syndrome-associated encephalopathy/encephalitis.

aspergillosis (SAPA) ranges from 10.2% to 31.9%, with mortality rates fluctuating between 26.6% and 53.3%.[75] Studies by Yao and Dai et al.[75,104] using multivariable logistic regression identified glucocorticoid use as an independent risk factor for IPA, particularly in patients receiving ⩾26.5 mg of daily methylprednisolone or equivalents for more than 5 days. In addition, Wang et al.[95] found that dyspnea, hyperglycemia, and the administration of antibiotics and antifungal drugs were more frequent in the glucocorticoids group.

In conclusion, the current evidence suggests that glucocorticoids offer limited benefits in improving the prognosis of patients with SFTS while also increasing the risk of secondary infections. Future research should focus on the use of glucocorticoid dosages, clarify the optimal timing for use, and conduct subgroup studies based on the disease severity to better weigh the risks and benefits of glucocorticoid therapy.

Interferon-alpha (IFN-α). IFN is a type of cytokine that plays a role in various immune responses, including antiviral and antiproliferative functions. It primarily regulates gene transcription via the Janus kinase signal transducer and activator of transcription (STAT) pathway.[105,106] Type I IFN, with IFN-α being the main form, is commonly used for immune modulation and has been widely applied in the treatment of malignant tumors and chronic hepatitis.[106] However, a retrospective study of 1462 cases by Li et al.[28] which matched 41 patients treated with IFN-α to 82 controls, revealed that the use of IFN-α did not reduce all-cause mortality, and there was no significant improvement in laboratory indicators such as the PLT, AST, LDH, and CK. Furthermore, the levels of IL-6 and the viral load were even increased in the IFN treatment group. These findings suggest that IFN-α fails to achieve the desired therapeutic effect in SFTS treatment. The side effects of IFN-α therapy include flu-like symptoms (fever, muscle aches, headache) related to increased proinflammatory cytokines such as IL-6 and TNF-α, thrombocytopenia and leukopenia caused by bone marrow suppression, elevated transaminases, and gastrointestinal activity.[107] These adverse effects can complicate clinical decision-making and potentially worsen the patient's condition, necessitating caution in its use.

Tocilizumab. Tocilizumab is a recombinant humanized monoclonal antibody that targets the IL-6 receptor. It competitively inhibits IL-6, a cytokine that plays a central role in inflammatory responses, and has been widely used for treating various rheumatic diseases, including polymyalgia rheumatica, giant cell arteritis,[108,109] and cytokine release syndrome following chimeric antigen receptor-T (CAR-T) cell therapy.[110] In recent years, tocilizumab has also shown promise in alleviating inflammation and improving survival outcomes in patients with COVID-19, and it has been adopted in multiple treatment guidelines for COVID-19.[111] In severe cases of SFTS, the cytokine profile, with markedly elevated levels of IL-6 and IL-10, and IL-10 was elevated earlier than IL-6, is like that observed in severe cases of COVID-19.[112] IL-6 levels are correlated with the viral load and are associated with poor prognosis and severe disease outcomes,[15,34,35,113] with the most significant increase occurring within 1 week of symptom onset.[101] Therefore, tocilizumab has been explored as a potential therapeutic option for SFTS.

Jeong et al.[114] reported a case in which a 77-year-old woman was treated with tocilizumab (8 mg/kg) on the first day of hospitalization. After the injection, her viral load decreased, and her IL-6 levels gradually declined after peaking on the third day. No obvious adverse effects were observed, and the patient ultimately survived. In a randomized clinical trial, Ge et al.[18] observed the efficacy of tocilizumab (8 mg/kg), with a 14-day outcome as the endpoint. Compared with the control group ($n = 126$) with a mortality rate of 23%, the treatment group ($n = 63$) had a significantly lower mortality rate (9.5%). The treatment group exhibited adverse reactions, including cough, sputum production, and nausea, but no significant differences were found in secondary infections or liver dysfunction. While there was no difference in the rate of decrease in viral load between the treatment and control groups, subgroup analysis revealed that patients with a lower baseline viral load ($<1 \times 10^7$ copies/mL; $n = 31$) had a significantly greater reduction in viral load than did those with a higher baseline viral load ($\geqslant 1 \times 10^7$ copies/mL) ($n = 32$). After 1:1 propensity score matching ($n = 51$), the mortality rate of patients treated with tocilizumab combined with glucocorticoids was 11.8%, which was significantly lower than that of patients treated with glucocorticoids alone (39.2%).

Given the cytokine profile of SFTS and the current evidence regarding treatment, combining

tocilizumab with glucocorticoids may help reduce adverse effects. However, larger clinical trials and further stratified evaluations of efficacy are necessary to confirm these findings and refine treatment strategies.

Ruxolitinib. Monoclonal antibodies target only specific cytokines or receptors, whereas ruxolitinib is a JAK 1/2 inhibitor that reduces the production of inflammatory cytokines such as IFN-γ and IL-6 by inhibiting the JAK-STAT signaling pathway, helping alleviate cytokine storms.[115] Ruxolitinib has demonstrated efficacy in treating primary myelofibrosis,[116] and has been investigated in clinical trials for various conditions involving excessive inflammation, yielding promising results. In patients with hemophagocytic lymphohistiocytosis (HLH),[117] and severe COVID-19 infection, ruxolitinib significantly improved patient prognosis and reduced inflammatory responses.[118,119] The severity and poor prognosis of SFTS are often associated with excessive inflammation, similar to cytokine release syndrome, with the levels of proinflammatory factors such as IL-6, TNF-α, and IFN-γ being elevated in the early stages.[101]

Wen et al.[120] reported the first case of a 73-year-old woman with SAPA who developed septic shock and multiple organ failure. Ruxolitinib treatment (5 mg twice daily for 10 days) was initiated on Day 3 of hospitalization. By Day 5, the patient's consciousness improved, her GCS score increased to 13, and her dyspnea was relieved. Eventually, the laboratory indicators improved significantly, the pulmonary inflammation resolved, and the patient was discharged. This positive response led to a subsequent single-arm trial,[19] which evaluated the 28-day overall survival time of 21 patients treated with ruxolitinib (10 mg twice daily for 10 days). The results revealed a mortality rate of 7.7%, which was significantly lower than the 46.2% reported in a historical control group ($n = 26$). Survivors showed marked improvements in neurological symptoms and laboratory parameters, including the PLT, within 14 days, while the deaths of two patients were presumed to be due to delayed treatment.

HLH, a critical complication of SFTS, has an incidence rate of 6.7%–7.1%, with a mortality rate of 24.5%–26.9%.[30,121,122] Severe SFTS patients present with overlapping clinical features of HLH, including hyperferritinemia, neuropsychiatric symptoms, and cytokine storms. Some fatal cases of SFTS may be related to multiple organ failure due to HLH. Therefore, ruxolitinib may be a treatment option in patients with suspected SFTS-associated HLH. Moreover, studies have shown that SFTS patients with encephalopathy or encephalitis exhibit short-term reversible neurological and mental symptoms such as confusion and drowsiness, with incidence rates ranging from 13.0% to 57.0%.[123–127] The virus can be detected in cerebrospinal fluid, and the levels of IL-8 and monocyte chemoattractant protein 1 (MCP-1) in the cerebrospinal fluid are significantly greater than those in the serum.[126] While the exact pathogenic mechanism of the virus in the central nervous system remains unclear, the ability of ruxolitinib to improve neurological symptoms suggests that cytokines may play a crucial role in the development of encephalopathy. For patients presenting with neurological symptoms, ruxolitinib could be a prioritized option, as it may reduce the risk of adverse effects associated with steroid pulse therapy or IVIG treatment.

In conclusion, ruxolitinib appears to be a promising therapeutic option for treating SFTS, especially in cases complicated by HLH or neurological symptoms. However, further clinical trials with larger sample sizes are necessary to validate its effectiveness. Additionally, other JAK inhibitors, such as baricitinib, could be considered in future clinical trials.

Supportive and emerging therapies

Prophylactic platelet transfusion. Thrombocytopenia is a prominent clinical feature in SFTS,[11] platelet transfusion is used to prevent or treat hemorrhage. In a retrospective study by Li et al.,[128] it was found that the effect of prophylactic platelet transfusion on platelet recovery was transient. Furthermore, after adjusting for confounding factors, there were no significant differences in mortality, bleeding events, or dynamic changes in platelet count between the treated group ($n = 250$) and the untreated group ($n = 72$). Tang et al.[129] recently demonstrated that bleeding is associated with prolonged coagulation times induced by endogenous heparinoids, rather than a low platelet count, suggesting the platelet count may not be a reliable indicator for assessing bleeding risk or guiding intervention during infection. Similarly, previous evidence from other hemorrhagic fever viruses, such as dengue, found that

prophylactic platelet transfusion was not superior to supportive care in preventing bleeding.[130] Instead, endothelial activation, dysfunction and injury, vascular leakage, platelet activation, and disturbed coagulation response induced by *Bandavirus dabieense* and proinflammatory cytokines, collectively contribute to hemorrhage.[128,131–133] Given the multifactorial mechanism, antiviral treatment and the alleviation of cytokine storms are pivotal in substantially preventing bleeding events and improving patient outcomes.

Plasma exchange. Plasma exchange (PE) is mainly used for SFTS treatment to mitigate cytokine storms, improve coagulation function, and promote viral clearance (Table 4).

Case reports by Tsutsumi et al.[91] and Utsunomiya et al.[134] showed that the viral load did not decrease significantly after PE. In a study by Won Sup Oh et al.[54] two SFTS patients recovered after receiving PE combined with ribavirin, but their further multicenter retrospective study revealed no significant difference in survival rates between the PE and non-PE groups. However, multivariate analysis suggested that receiving PE within 7 days of SFTS onset was associated with the 30-day survival time.[135]

Yoo et al.[136] observed 14 SFTS patients who underwent PE and found significant improvements in multiple laboratory indicators and viral loads. Similarly, Gao et al.[137] and Song et al.[138] retrospect critically ill patients and concluded PE effectively cleared the virus, improved coagulation function, and increased survival rates. Therefore, PE appears to benefit those with critical cases, however, its high cost and the large volume of required plasma limit its widespread use.

Convalescent plasma, which contains specific viral antibodies, has also shown promise in reducing the viral load. Both Choi et al.[139] and Park et al.[140] reported that patients with encephalopathy who underwent PE did not experience a significant reduction in viral load, nor did their condition improve. However, after receiving convalescent plasma, the viral load decreased significantly, and consciousness improved quickly.

Delayed IgG seroconversion has been observed in critical cases, and high viral loads occur in these patients compared with those with mild disease.[83–85] Furthermore, patients with fatal outcomes even experienced seroconversion failure.[29] Therefore, convalescent plasma is a significant therapeutic method for severe patients. However, its availability remains a limitation, and further research is needed to explore more feasible treatment options.

Calcium channel blockers. The Ca^{+} signaling pathway plays a crucial role in a variety of physiological processes within the cell. Many viruses, including the Zika virus and H5N1 virus, facilitate viral infection by inducing an influx of calcium ions.[141,142] Calcium channel blockers (CCBs), a class of drugs commonly prescribed to manage hypertension, work by inhibiting intracellular calcium influx, thereby affecting various cellular functions.

Li et al.[20] screened the FDA-approved drug library and identified benidipine and nifedipine as potential agents capable of reducing viral infection in a $Ca^{2}+$ uptake-dependent manner. These studies, which were conducted in Vero cells, C57BL/6 mice, and humanized mouse models, demonstrated that these CCBs could effectively reduce the viral load. In their further retrospective analysis of 2087 cases of SFTS, patients treated with nifedipine ($n=83$) presented fewer neurological symptoms, such as lethargy and coma, increased virus clearance, significantly reduced viral load, and significantly decreased mortality. Additionally, patients treated with nifedipine showed earlier recovery of LDH levels and fewer symptoms, such as hematemesis, than patients who used nifedipine before admission but did not receive nifedipine after admission ($n=48$). The PLT improved more rapidly in the nifedipine-treated group than in the group of patients who never took nifedipine ($n=249$). Notably, in the high-viral-load group ($>10^{6}$ copies/mL), nifedipine significantly improved the prognosis, which distinguishes it from other antiviral agents, such as favipiravir and ribavirin. These findings suggest that nifedipine may offer substantial clinical benefits, particularly in patients with high viral loads. Yamauchi et al[143] reported a case of a 67-year-old male patient with HLH and encephalopathy who was treated with nicardipine hydrochloride combined with PE, glucocorticoids, and IVIG. The patient improved, with decreases in soluble IL-2 receptor (sIL2R) and ferritin levels, and ultimately recovered.

While the adverse effects of CCBs are well known, there is limited research on SFTS patients,

Table 4. Summary of plasma exchange on severe fever with thrombocytopenia syndrome.

Author	Year	Cases	Research type	Regimen	Viral loads change	Other findings
Won Sup Oh[54,135]	2014	2	Case report	PE: 3 sessions (6737 mL in total) and 4 sessions (14,141 mL in total), respectively	ND	Cured
	2017	53	Multicenter retrospective cohort study	Median volume of plasma was 2491 mL/session, the median number of PE sessions was 3	ND	The overall in-hospital mortality rate was no difference
Park[56,140]	2016	1	Case report	Day 9–12: PE, Day 17: convalescent plasma 400 mL	Declined slightly during PE but decreased steeply after convalescent plasma therapy	Cured, mental status was fully recovered after convalescent plasma therapy
	2017	2	Case report	PE: 2800 mL/session for 5 days and 3400 mL/session for 4 days, respectively	ND	Cured
Tsutsumi[91]	2016	1	Case report	mPSL 500 mg per day; Day 4-6: PE	Decreased slowly	Cured, organ damage was relieved
Choi[139]	2018	1	Case report	Day 1–4: PE; Day 4 and Day 13: Convalescent plasma therapy twice; Day 1-6: ribavirin	Remained unchanged during PE but decreased after convalescent plasma therapy	Cured, no neurologic sequelae. The levels of interferon-α and inducible protein-10 significantly decreased after the start of PE
Yoo[136]	2019	14	Single-center case series	The median volume of plasma removed during PE was 7154 mL, the median number of PE sessions was three	Mean Ct value of real-time RT-PCR after PE was significantly higher than that before PE	The survival rate is 92.8% (13/14). Temperature, PAR, WBC and PLT counts, coagulation profile, sCr, and MOD score improved immediately
Utsunomiya[134]	2022	1	Case report	5 sessions	No significant difference after PE	Cured
Gao[137]	2024	96 during ICU admission	Single-center retrospective case-control cohort	2000–2500 mL/session per day for 3 consecutive days	PE effectively removes the virus in blood	PE has a significant effect on improvement of coagulation function and survival rate
Song[138]	2024	92 critically ill patients	Single-center retrospective cohort study	3–7 sessions, 40–60 mL/kg of body weight/session.	Significant reduction after PE	PE significant reduced mortality rates and improved WBC and NEU, LDH, CK-MB, PT, APTT, D-Dimer, serum sodium

APTT, activated partial thromboplastin time; CK-MB, creatine kinase isoenzyme-MB; ICU, intensive care unit; LDH, lactate dehydrogenase; MOD, multiple organ dysfunction; ND, not done; PAR, pressure-adjusted heart rate; PE, plasma exchange; PLT, platelet; PT, prothrombin time; sCr, serum creatinine; WBC, white blood cell.

particularly those who are critically ill or in shock. Therefore, further randomized clinical trials are needed to evaluate the safety and efficacy of CCBs in SFTS treatment.

Arginine. Arginine is a semi-essential amino acid with a key role in immune function, including T-cell activation and B-cell maturation. During inflammation, immune cell proliferation leads to arginine consumption.[144] Arginine is also a precursor for molecules such as ornithine and nitric oxide (NO), which are vasodilatory gases involved in various physiological functions, including PLT inhibition.[145]

Li et al.[21] analyzed the metabolomics of 242 SFTS patients and reported significant changes in the arginine metabolic pathway, with a marked reduction in the NO concentration in PLTs. The study also revealed that in 44 SFTS patients, arginine metabolism preferentially produces urea/ornithine rather than NO, contributing to impaired NO signaling. In a further randomized clinical trial, the experimental group ($n=53$) received 20 g of intravenous arginine per day while the control group ($n=60$) received a placebo. Although there was no significant difference in the mortality rate, the experimental group presented increased NO concentrations in PLTs, suppressed PLT activation, increased expression of the CD3-ζ chain and PLT counts, and accelerated virus clearance. However, adverse effects such as increased serum urea nitrogen and vomiting were observed. This study suggests that arginine could have a therapeutic role in SFTS, particularly in improving PLT function and facilitating viral clearance. While these findings are promising, further clinical data, especially from critical patients, are needed to confirm the actual therapeutic efficacy and clinical applicability of arginine supplementation in the treatment of SFTS.

Problems to be solved

Other treatments for SFTS are still inconclusive, with several fields requiring further investigation.

The supportive care of SFTS patients primarily involves maintaining fluid-electrolyte balance and monitoring organ function. In critical cases, advanced multi-organ support is essential, including total parenteral nutrition, mechanical ventilation, and renal replacement therapy. Although current evidence-based studies have not identified the association between supportive care and prognosis, a clinical prospective observational study demonstrated the significant correlation between longer delay in admission and fatal outcomes.[59] Timely supportive care may improve prognosis through maintaining internal homeostasis and potentially mitigating inflammatory cascade activation, indicating the necessity of incorporating standardized supportive protocols into SFTS clinical guidelines.

In regard to symptomatic management, a primary challenge is optimizing the treatment of early-stage leukopenia. Exogenous leukocyte-stimulating agents are often used in clinical practice, but their effectiveness remains uncertain. Song et al.[29] found that granulocyte–macrophage colony-stimulating factor (GM-CSF) levels in patients with a poor prognosis were lower than those in the surviving patients during the first week. In contrast, Hu et al.[101] observed that granulocyte colony-stimulating factor (G-CSF) levels were greater in patients with a poor prognosis during the first week than in the surviving patients. Given these findings, the impact of using G-CSF and GM-CSF to promote early leukocyte production in SFTS patients and whether these therapies can accelerate viral clearance and improve patient prognosis remains unclear and warrants further investigation. Similarly, thrombopoietin receptor agonists and recombinant human thrombopoietin are widely prescribed to enhance thrombopoiesis. However, their efficacy in platelet recovery, hemorrhage prophylaxis, and prognostic improvement among patients with SFTS remains to be validated through future research.

Current research has focused primarily on improving the overall prognosis of SFTS, but increasing attention has been given to complications associated with this disease. SAPA and HLH, as mentioned above, have high mortality rates and are associated with the severity of SFTS. The management of these complications is challenging, and improper treatment of one complication may lead to the development of other complications. For example, improper use of glucocorticoids to treat HLH or encephalopathy may promote virus production and trigger secondary complications, such as SAPA and bleeding. Therefore, there is an urgent need for more robust clinical evidence to guide the management of these complications. Yao et al.[75] reported that although antifungal therapy before and after

SAPA diagnosis showed no significant survival benefit, patients receiving combination antifungal therapy demonstrated markedly higher 14-day and 28-day survival rates compared to those without antifungal treatment. Furthermore, prolonged antifungal therapy was associated with improved survival rates compared to shorter treatment durations. These findings underscore the necessity for further research to determine whether secondary infections can be effectively prevented, whether mortality can be reduced through the prophylactic use of antibiotics or antifungal agents, and how the timing of treatment influences prognosis. These factors are key for optimizing treatment strategies and further improving survival rates for critical cases.

Directions for future research

Currently, treatment options for SFTS are still limited. However, researchers are screening FDA-approved drugs to identify agents with antiviral effects and are conducting in vitro and in vivo studies. Some selected drugs not only alleviate SFTS symptoms and complications but are also expected to promote viral clearance. For example, the calcium channel antagonist loperamide could be used to manage diarrhea,[146] whereas echinocandin antifungals, such as anidulafungin and micafungin, may help treat fungal infections.[147]

Additionally, multiple omics studies on SFTS are underway, with metabolomics and 16S rRNA analysis aiming to uncover the pathogenic mechanisms of SFTS and guide the development of targeted adjunctive therapies. Arginine, for example, has shown beneficial effects, as mentioned herein.

Several metabolic pathways are altered during and after SFTS infection. Through nontargeted metabolomics, Zhang et al.[148] identified glycerophospholipid (GPL) metabolism as a key metabolic pathway during SFTS infection that is potentially linked to viral replication. Additionally, the pentose phosphate pathway, alanine, aspartate, and glutamate metabolism were found to be critical for long-term recovery; hence, the author suggested that α-ketoglutarate supplementation may assist convalescent patients in managing long-standing oxidative stress. Additionally, Zhang et al.[149] analyzed the urine of SFTS-infected patients and revealed significant changes in tryptophan metabolism. Abnormal phenylalanine metabolism was observed in fatal cases, and patients with SFTS had lower serum glycine concentrations than healthy individuals did.

Alterations in lipid metabolism are a prominent feature of SFTS infection and may represent a potential therapeutic target. Guo et al.[150] analyzed serum samples from 11 severe SFTS cases, 37 mild cases, and 23 healthy controls via lipidomics and revealed that SFTS leads to lipid metabolism disturbances, such as increased levels of triglycerides (TGs), decreased levels of cholesterol esters (ChEs), and dual changes, including changes in the levels of phosphatidylcholine (PC) and phosphatidylethanolamine (PE). Additionally, Urata et al.[151] reported that cholesterol, fatty acids, and triglycerides regulated by site 1 protease (S1P) play roles in virus replication and that virus production is significantly reduced in vivo after treatment with lovastatin or fenofibrate.

Changes in gut microbiota are also observed during infection. Xie et al.[152] performed 16S rRNA analysis and nontargeted metabolomics on stool and serum samples and revealed that the abundance of *Akkermansia muciniphila* increased in the stool during SFTS infection but decreased in fatal cases and was inversely correlated with the proinflammatory cytokines IL-1β, IL-6, and TNF-α. By producing the β-carboline alkaloid harmaline, NF-κB-mediated inflammation is inhibited, and the liver expression of conjugated primary bile acids, such as glycochenodeoxycholic acid and taurochenodeoxycholic acid, all of which exhibit anti-inflammatory properties, is inhibited. Further study revealed that the levels of the secondary bile acid taurolithocholic acid (TLCA) are associated with reduced fatality rates and suppressed viremia. TLCA inhibits viral replication, mitigates inflammation in vitro, and indirectly suppresses ferroptosis by upregulating fatty acid desaturase 2 via the TGR5–PI3K/AKT–SREBP2 axis.[153]

In conclusion, supplementation with probiotics, along with drugs such as statins, fibrates, and bile acids, may offer benefits during acute infection by reducing inflammation and exerting antiviral effects, whereas α-ketoglutarate is beneficial for recovery. Future studies could focus on these agents, as their potential warrants further investigation for clinical application.

Conclusion

This study compiled drugs with reported clinical efficacy for SFTS and found that immunoregulatory therapy plays an equally important role as antiviral treatment. Favipiravir could be prioritized as an antiviral treatment. Based on a large-sample retrospective analysis, traditional immunomodulators such as IFN, corticosteroids, and IVIG have not substantially improved patient prognosis and may even increase the risk of complications such as secondary infections and immune disorders. Clinical trials indicate that novel immunomodulators, such as tocilizumab and ruxolitinib, are beneficial for outcomes. Given the early cytokine storms in critically ill patients, timely administration of novel immunomodulators among severe cases during the early disease stage may maximize therapeutic benefits. In patients with good tolerance, arginine and nifedipine may be considered, while therapeutic plasma exchange and advanced life support are essential for managing late-stage critical illness. Prophylactic platelet transfusions neither prevent bleeding nor improve clinical outcomes. Future research should emphasize stratified studies focused on disease severity, dosage, and complications, with the potential to significantly improve SFTS patient outcomes.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Yuxi Zhao: Conceptualization; Investigation; Writing—original draft; Writing—review & editing.

Xiaoxin Wu: Conceptualization; Writing—review & editing.

Xinyu Wang: Conceptualization; Writing—original draft.

Lanjuan Li: Conceptualization; Supervision; Writing—review & editing.

Acknowledgments

None.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by the Fundamental Research Funds for the Central Universities (2022ZFJH003) and Central Guidance Fund for Local Science and Technology Development (2024ZY01054).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

ORCID iD

Lanjuan Li https://orcid.org/0000-0001-6945-0593

References

1. Yu X-J, Liang M-F, Zhang S-Y, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med* 2011; 364: 1523–1532.
2. Yun S-M, Lee W-G, Ryou J, et al. Severe fever with thrombocytopenia syndrome virus in ticks collected from humans, South Korea, 2013. *Emerg Infect Dis* 2014; 20: 1358–1361.
3. Takahashi T, Maeda K, Suzuki T, et al. The first identification and retrospective study of severe fever with thrombocytopenia syndrome in Japan. *J Infect Dis* 2014; 209: 816–827.
4. Tran XC, Yun Y, Van An L, et al. Endemic severe fever with thrombocytopenia syndrome, Vietnam. *Emerg Infect Dis* 2019; 25: 1029–1031.
5. Win AM, Nguyen YTH, Kim Y, et al. Genotypic heterogeneity of Orientia tsutsugamushi in scrub typhus patients and thrombocytopenia syndrome co-infection, Myanmar. *Emerg Infect Dis* 2020; 26: 1878–1881.
6. Miao D, Liu M-J, Wang Y-X, et al. Epidemiology and ecology of severe fever with thrombocytopenia syndrome in China, 2010–2018. *Clin Infect Dis* 2021; 73: e3851–e3858.
7. Wen Y, Fang Y, Cao F, et al. A person-to-person transmission cluster of severe fever with thrombocytopenia syndrome characterized by mixed viral infections with familial and nosocomial clustering. *Heliyon* 2024; 10: e24502.

8. Yun Y, Heo ST, Kim G, et al. Phylogenetic analysis of severe fever with thrombocytopenia syndrome virus in South Korea and migratory bird routes between China, South Korea, and Japan. *Am J Trop Med Hyg* 2015; 93: 468–474.
9. Ji S-R, Byun H-R, Rieu M-S, et al. First detection of *Bandavirus dabieense* in ticks collected from migratory birds in the Republic of Korea. *Acta Trop* 2024; 257: 107279.
10. Miao D, Dai K, Zhao G-P, et al. Mapping the global potential transmission hotspots for severe fever with thrombocytopenia syndrome by machine learning methods. *Emerg Microbes Infect* 2020; 9: 817–826.
11. Casel MA, Park SJ and Choi YK. Severe fever with thrombocytopenia syndrome virus: emerging novel phlebovirus and their control strategy. *Exp Mol Med* 2021; 53: 713–722.
12. Cui H, Shen S, Chen L, et al. Global epidemiology of severe fever with thrombocytopenia syndrome virus in human and animals: a systematic review and meta-analysis. *Lancet Reg Health West Pac* 2024; 48: 101133.
13. Wang X, Ren X, Ge Z, et al. Clinical manifestations of death with severe fever and thrombocytopenia syndrome: a meta-analysis and systematic review. *J Med Virol* 2021; 93: 3960–3968.
14. Li DX. Severe fever with thrombocytopenia syndrome: a newly discovered emerging infectious disease. *Clin Microbiol Infect* 2015; 21: 614–620.
15. He Z, Wang B, Li Y, et al. Changes in peripheral blood cytokines in patients with severe fever with thrombocytopenia syndrome. *J Med Virol* 2021; 93: 4704–4713.
16. Yuan Y, Cui N and Yuan CJCJID. Recommendations for nomenclature, clinical staging and typing of severe fever with thrombocytopenia syndrome. *BMC Infect Dis* 2016; 34: 57–58.
17. Bopp NE, Kaiser JA, Strother AE, et al. Baseline mapping of severe fever with thrombocytopenia syndrome virology, epidemiology and vaccine research and development. *NPJ Vaccines* 2020; 5: 111.
18. Ge H-H, Cui N, Yin X-H, et al. Effect of tocilizumab plus corticosteroid on clinical outcome in patients hospitalized with severe fever with thrombocytopenia syndrome: a randomized clinical trial. *J Infect* 2024; 89: 106181.
19. Wen S, Xu N, Zhao L, et al. Ruxolitinib plus standard of care in severe hospitalized adults with severe fever with thrombocytopenia syndrome (SFTS): an exploratory, single-arm trial. *BMC Med* 2024; 22: 204.
20. Li H, Zhang L-K, Li S-F, et al. Calcium channel blockers reduce severe fever with thrombocytopenia syndrome virus (SFTSV) related fatality. *Cell Res* 2019; 29: 739–753.
21. Li X-K, Lu Q-B, Chen W-W, et al. Arginine deficiency is involved in thrombocytopenia and immunosuppression in severe fever with thrombocytopenia syndrome. *Sci Transl Med* 2018; 10.
22. Sun Z, Cheng J, Bai Y, et al. Architecture of severe fever with thrombocytopenia syndrome virus. *Protein Cell* 2023; 14: 914–918.
23. Williams HM, Thorkelsson SR, Vogel D, et al. Structural insights into viral genome replication by the severe fever with thrombocytopenia syndrome virus L protein. *Nucleic Acids Res* 2023; 51: 1424–1442.
24. Tani H, Shimojima M, Fukushi S, et al. Characterization of glycoprotein-mediated entry of severe fever with thrombocytopenia syndrome virus. *J Virol* 2016; 90: 5292–5301.
25. Ning Y-J, Feng K, Min Y-Q, et al. Disruption of type I interferon signaling by the nonstructural protein of severe fever with thrombocytopenia syndrome virus via the hijacking of STAT2 and STAT1 into inclusion bodies. *J Virol* 2015; 89: 4227–4236.
26. Choi Y, Park S-J, Sun Y, et al. Severe fever with thrombocytopenia syndrome phlebovirus non-structural protein activates TPL2 signalling pathway for viral immunopathogenesis. *Nat Microbiol* 2019; 4: 429–437.
27. Khalil J, Yamada S, Tsukamoto Y, et al. The nonstructural protein NSs of severe fever with thrombocytopenia syndrome virus causes a cytokine storm through the hyperactivation of NF-κB. *Mol Cell Biol* 2021; 41: e0054220.
28. Li H, Li X, Lv S, et al. Single-cell landscape of peripheral immune responses to fatal SFTS. *Cell Rep* 2021; 37: 110039.
29. Song P, Zheng N, Liu Y, et al. Deficient humoral responses and disrupted B-cell immunity are associated with fatal SFTSV infection. *Nat Commun* 2018; 9: 3328.
30. Huang M, Wang T, Huang Y, et al. The clinical and immunological characteristics in fatal severe fever with thrombocytopenia syndrome virus (SFTSV) infection. *Clin Immunol* 2023; 248: 109262.

31. Liu J, Wang L, Feng Z, et al. Dynamic changes of laboratory parameters and peripheral blood lymphocyte subsets in severe fever with thrombocytopenia syndrome patients. *Int J Infect Dis* 2017; 58: 45–51.

32. Suzuki T, Sato Y, Sano K, et al. Severe fever with thrombocytopenia syndrome virus targets B cells in lethal human infections. *J Clin Invest* 2020; 130: 799–812.

33. Yoshikawa T, Fukushi S, Tani H, et al. Sensitive and specific PCR systems for detection of both Chinese and Japanese severe fever with thrombocytopenia syndrome virus strains and prediction of patient survival based on viral load. *J Clin Microbiol* 2014; 52: 3325–3333.

34. Li J, Han Y, Xing Y, et al. Concurrent measurement of dynamic changes in viral load, serum enzymes, T cell subsets, and cytokines in patients with severe fever with thrombocytopenia syndrome. *PLoS One* 2014; 9: e91679.

35. Sun Y, Jin C, Zhan F, et al. Host cytokine storm is associated with disease severity of severe fever with thrombocytopenia syndrome. *J Infect Dis* 2012; 206: 1085–1094.

36. Wang Y, Song Z, Wei X, et al. Clinical laboratory parameters and fatality of Severe fever with thrombocytopenia syndrome patients: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2022; 16: e0010489.

37. Wang Y, Song Z, Xu X, et al. Clinical symptoms associated with fatality of severe fever with thrombocytopenia syndrome: a systematic review and meta-analysis. *Acta Trop* 2022; 232: 106481.

38. He Z, Wang B, Li Y, et al. Severe fever with thrombocytopenia syndrome: a systematic review and meta-analysis of epidemiology, clinical signs, routine laboratory diagnosis, risk factors, and outcomes. *BMC Infect Dis* 2020; 20: 575.

39. Yokomizo K, Tomozane M, Sano C, et al. Clinical presentation and mortality of severe fever with thrombocytopenia syndrome in Japan: a systematic review of case reports. *Int J Environ Res Public Health* 2022; 19: 2271.

40. Zhang SF, Yang ZD, Huang ML, et al. Preexisting chronic conditions for fatal outcome among SFTS patients: an observational Cohort Study. *PLoS Negl Trop Dis* 2019; 13: e0007434.

41. Li S, Li Y, Wang Q, et al. Multiple organ involvement in severe fever with thrombocytopenia syndrome: an immunohistochemical finding in a fatal case. *Virol J* 2018; 15: 97.

42. Kaneko M, Shikata H, Matsukage S, et al. A patient with severe fever with thrombocytopenia syndrome and hemophagocytic lymphohistiocytosis-associated involvement of the central nervous system. *J Infect Chemother* 2018; 24: 292–297.

43. Uehara N, Yano T, Ishihara A, et al. Fatal severe fever with thrombocytopenia syndrome: an autopsy case report. *Intern Med* 2016; 55: 831–838.

44. Hiraki T, Yoshimitsu M, Suzuki T, et al. Two autopsy cases of severe fever with thrombocytopenia syndrome (SFTS) in Japan: a pathognomonic histological feature and unique complication of SFTS. *Pathol Int* 2014; 64: 569–575.

45. Iwao K, Kawaguchi T, Kimura M, et al. Severe fever with thrombocytopenia syndrome accompanied by invasive pulmonary aspergillosis: an autopsy case. *Viruses* 2021; 13.

46. Kim K-H, Lee MJ, Ko MK, et al. Severe fever with thrombocytopenia syndrome patients with hemophagocytic lymphohistiocytosis retrospectively identified in Korea, 2008-2013. *J Korean Med Sci* 2018; 33: e319.

47. Saijo M. Pathophysiology of severe fever with thrombocytopenia syndrome and development of specific antiviral therapy. *J Infect Chemother* 2018; 24: 773–781.

48. Hézode C and Bronowicki J-P. Ideal oral combinations to eradicate HCV: the role of ribavirin. *J Hepatol* 2016; 64: 215–225.

49. Manothummetha K, Mongkolkaew T, Tovichayathamrong P, et al. Ribavirin treatment for respiratory syncytial virus infection in patients with haematologic malignancy and haematopoietic stem cell transplant recipients: a systematic review and meta-analysis. *Clin Microbiol Infect* 2023; 29: 1272–1279.

50. Ramírez-Olivencia G, Estébanez M, Membrillo FJ, et al. Use of ribavirin in viruses other than hepatitis C. A review of the evidence. *Enferm Infecc Microbiol Clin (Engl Ed)* 2019; 37: 602–608.

51. Arab-Bafrani Z, Jabbari A, Mostakhdem Hashemi M, et al. Identification of the crucial parameters regarding the efficacy of ribavirin therapy in Crimean-Congo haemorrhagic fever (CCHF) patients: a systematic review and meta-analysis. *J Antimicrob Chemother* 2019; 74: 3432–3439.

52. Cheng H-Y, French CE, Salam AP, et al. Lack of evidence for ribavirin treatment of Lassa fever in systematic review of published and unpublished studies. *Emerg Infect Dis* 2022; 28: 1559–1568.

53. Johnson S, Henschke N, Maayan N, et al. Ribavirin for treating Crimean Congo haemorrhagic fever. *Cochrane Database Syst Rev* 2018; 6: CD012713.
54. Oh WS, Heo ST, Kim SH, et al. Plasma exchange and ribavirin for rapidly progressive severe fever with thrombocytopenia syndrome. *Int J Infect Dis* 2014; 18: 84-86.
55. Song TY, Yang EM and Kim CJ. A Pediatric case of severe fever with thrombocytopenia syndrome in Korea. *J Korean Med Sci* 2017; 32: 704–707.
56. Park I, Kim HI and Kwon KT. Two treatment cases of severe fever and thrombocytopenia syndrome with oral ribavirin and plasma exchange. *Infect Chemother* 2017; 49: 72–77.
57. Liu W, Lu Q-B, Cui N, et al. Case-fatality ratio and effectiveness of ribavirin therapy among hospitalized patients in China who had severe fever with thrombocytopenia syndrome. *Clin Infect Dis* 2013; 57: 1292–1299.
58. Zhang Y, Miao W, Xu Y, et al. Severe fever with thrombocytopenia syndrome in Hefei: clinical features, risk factors, and ribavirin therapeutic efficacy. *J Med Virol* 2021; 93: 3516–3523.
59. Li H, Lu Q-B, Xing B, et al. Epidemiological and clinical features of laboratory-diagnosed severe fever with thrombocytopenia syndrome in China, 2011-17: a prospective observational study. *Lancet Infect Dis* 2018; 18: 1127–1137.
60. Chen Y, Jia B, Liu Y, et al. Risk factors associated with fatality of severe fever with thrombocytopenia syndrome: a meta-analysis. *Oncotarget* 2017; 8: 89119–89129.
61. Lu Q-B, Zhang S-Y, Cui N, et al. Common adverse events associated with ribavirin therapy for severe fever with thrombocytopenia syndrome. *Antiviral Res* 2015; 119: 19–22.
62. Furuta Y, Komeno T and Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys Biol Sci* 2017; 93: 449-463.
63. Shiraki K and Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacol Ther* 2020; 209: 107512.
64. Shiraki K, Sato N, Sakai K, et al. Antiviral therapy for COVID-19: derivation of optimal strategy based on past antiviral and favipiravir experiences. *Pharmacol Ther* 2022; 235: 108121.
65. Song R, Chen Z and Li W. Severe fever with thrombocytopenia syndrome (SFTS) treated with a novel antiviral medication, favipiravir (T-705). *Infection* 2020; 48: 295–298.
66. Li H, Jiang X-M, Cui N, et al. Clinical effect and antiviral mechanism of T-705 in treating severe fever with thrombocytopenia syndrome. *Signal Transduct Target Ther* 2021; 6: 145.
67. Yuan Y, Lu Q-B, Yao W-S, et al. Clinical efficacy and safety evaluation of favipiravir in treating patients with severe fever with thrombocytopenia syndrome. *EBioMedicine* 2021; 72: 103591.
68. Suemori K, Saijo M, Yamanaka A, et al. A multicenter non-randomized, uncontrolled single arm trial for evaluation of the efficacy and the safety of the treatment with favipiravir for patients with severe fever with thrombocytopenia syndrome. *PLoS Negl Trop Dis* 2021; 15: e0009103.
69. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. *J Allergy Clin Immunol* 2017; 139.
70. Kim UJ, Kim D-M, Ahn JH, et al. Successful treatment of rapidly progressing severe fever with thrombocytopenia syndrome with neurological complications using intravenous immunoglobulin and corticosteroid. *Antivir Ther* 2016; 21: 637–640.
71. Liu Y, Tong H, He F, et al. Effect of intravenous immunoglobulin therapy on the prognosis of patients with severe fever with thrombocytopenia syndrome and neurological complications. *Front Immunol* 2023; 14: 1118039.
72. Shin J, Kwon D, Youn S-K, et al. Characteristics and factors associated with death among patients hospitalized for severe fever with thrombocytopenia syndrome, South Korea, 2013. *Emerg Infect Dis* 2015; 21: 1704–1710.
73. Zhai Y, Li H, Xia P, et al. Intravenous immunoglobulin-based adjuvant therapy for severe fever with thrombocytopenia syndrome: a single-center retrospective cohort study. *J Med Virol* 2024; 96: e70017.
74. Zhang S-S, Du J, Cui N, et al. Clinical efficacy of immunoglobulin on the treatment of severe fever with thrombocytopenia syndrome: a retrospective cohort study. *EBioMedicine* 2023; 96: 104807.
75. Yao L, Shi Y, Fu J, et al. Risk factors for invasive pulmonary aspergillosis in patients with severe fever with thrombocytopenia syndrome: a multicenter retrospective study. *J Med Virol* 2024; 96: e29647.

76. Chen QL, Zhu MT, Chen N, et al. [Epidemiological characteristics of severe fever with thtrombocytopenia syndrome in China, 2011-2021]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2022; 43: 852–859.

77. Du Y, Cheng N, Li Y, et al. Seroprevalance of antibodies specific for severe fever with thrombocytopenia syndrome virus and the discovery of asymptomatic infections in Henan Province, China. *PLoS Negl Trop Dis* 2019; 13: e0007242.

78. You E, Wang L, Zhang L, et al. Epidemiological characteristics of severe fever with thrombocytopenia syndrome in Hefei of Anhui Province: a population-based surveillance study from 2011 to 2018. *Eur J Clin Microbiol Infect Dis* 2021; 40: 929–939.

79. Ding S, Niu G, Xu X, et al. Age is a critical risk factor for severe fever with thrombocytopenia syndrome. *PLoS One* 2014; 9: e111736.

80. Liang S, Bao C, Zhou M, et al. Seroprevalence and risk factors for severe fever with thrombocytopenia syndrome virus infection in Jiangsu Province, China, 2011. *Am J Trop Med Hyg* 2014; 90: 256–259.

81. Li D, Shao L, Bi Y, et al. Neutralizing antibodies to Severe Fever with Thrombocytopenia Syndrome Virus in general population, Shandong Province, China. *Sci Rep* 2018; 8: 15401.

82. Ye X-L, Dai K, Lu Q-B, et al. Infection with severe fever with thrombocytopenia virus in healthy population: a cohort study in a high endemic region, China. *Infect Dis Poverty* 2021; 10: 133.

83. Li J-C, Ding H, Wang G, et al. Dynamics of neutralizing antibodies against severe fever with thrombocytopenia syndrome virus. *Int J Infect Dis* 2023; 134: 95–98.

84. Hu L, Kong Q, Liu Y, et al. Time course of severe fever with thrombocytopenia syndrome virus and antibodies in patients by long-term follow-up study, China. *Front Microbiol* 2021; 12: 744037.

85. Lu Q-B, Cui N, Hu J-G, et al. Characterization of immunological responses in patients with severe fever with thrombocytopenia syndrome: a cohort study in China. *Vaccine* 2015; 33: 1250-1255. DOI: 10.1016/j.vaccine.2015.01.051.

86. Hu J, Shi C, Li Z, et al. A cluster of cases of severe fever with thrombocytopenia syndrome bunyavirus infection in China, 1996: a retrospective serological study. *PLoS Negl Trop Dis* 2018; 12: e0006603.

87. Huang Y-T, Zhao L, Wen H-L, et al. Neutralizing antibodies to severe fever with thrombocytopenia syndrome virus 4 years after hospitalization, China. *Emerg Infect Dis* 2016; 22: 1985–1987.

88. Qi R, Huang YT and Yu XJ. Persistence and gender differences in protection against severe fever with thrombocytopaenia syndrome virus with natural infection: a 4-year follow-up and mathematical prediction study. *Epidemiol Infect* 2019; 147: e78.

89. Nakamura S, Azuma M, Maruhashi T, et al. Steroid pulse therapy in patients with encephalopathy associated with severe fever with thrombocytopenia syndrome. *J Infect Chemother* 2018; 24: 389–392.

90. Shan D, Chen W, Liu G, et al. Severe fever with thrombocytopenia syndrome with central nervous system symptom onset: a case report and literature review. *BMC Neurol* 2024; 24: 158.

91. Tsutsumi K, Takafuta T, Kida M, et al. Effects of Plasma Exchange (PE) therapy in a severe fever with thrombocytopenia syndrome (SFTS) patient with high virus quantities. *Blood* 2016; 128: 4900.

92. Jung SI, Kim YE, Yun NR, et al. Effects of steroid therapy in patients with severe fever with Thrombocytopenia syndrome: a multicenter clinical cohort study. *PLoS Negl Trop Dis* 2021; 15: e0009128.

93. Kawaguchi T, Umekita K, Yamanaka A, et al. Corticosteroids may have negative effects on the management of patients with severe fever with thrombocytopenia syndrome: a case-control study. *Viruses* 2021; 13. DOI: 10.3390/v13050785.

94. Xiong L, Xu L, Lv X, et al. Effects of corticosteroid treatment in patients with severe fever with thrombocytopenia syndrome: a single-center retrospective cohort study. *Int J Infect Dis* 2022; 122: 1026–1033. DOI: 10.1016/j.ijid.2022.07.001.

95. Wang G, Xu Y-L, Zhu Y, et al. Clinical efficacy of low-dose glucocorticoid therapy for critically ill patients with severe fever with thrombocytopenia syndrome: a retrospective cohort study. *Int J Infect Dis* 2023; 130: 153–160.

96. Chen Y, Wang H, Zhou F, et al. The use of glucocorticoid in severe fever with thrombocytopenia syndrome: a retrospective cohort study. *Front Cell Infect Microbiol* 2024; 14: 1419015.

97. Kutsuna S, Ohbe H, Matsui H, et al. Steroid pulse therapy for severe fever with thrombocytopenia syndrome patients may not improve prognosis: Retrospective analysis with overlap weighting using a national inpatient database. *J Infect Chemother* 2023; 29: 490–494.

98. Shuto H, Komiya K, Usagawa Y, et al. Corticosteroid therapy for patients with severe fever with thrombocytopenia syndrome: a nationwide propensity score-matched study in Japan. *Open Forum Infect Dis* 2023; 10: ofad418.

99. Wang G, Liu P, Xie H, et al. Impact of glucocorticoid therapy on 28-Day mortality in patients having severe fever with thrombocytopenia syndrome in an intensive care unit: a retrospective analysis. *J Inflamm Res* 2024; 17: 7627–7637.

100. Wang M, Tan W, Li J, et al. The endless wars: severe fever with thrombocytopenia syndrome virus, host immune and genetic factors. *Front Cell Infect Microbiol* 2022; 12: 808098.

101. Hu L-F, Wu T, Wang B, et al. The regulation of seventeen inflammatory mediators are associated with patient outcomes in severe fever with thrombocytopenia syndrome. *Sci Rep* 2018; 8: 159.

102. Zuo Y, Wang H, Huang J, et al. Pulmonary infection in patients with severe fever with thrombocytopenia syndrome: a multicentre observational study. *J Med Virol* 2023; 95: e28712.

103. Zhang Y, Huang Y and Xu Y. Associated microbiota and treatment of severe fever with thrombocytopenia syndrome complicated with infections. *J Med Virol* 2022; 94: 5916–5921.

104. Dai Y, Pu Q, Hu N, et al. The dose-response relationship between smoking and the risk factor for invasive pulmonary aspergillosis in patients with severe fever with thrombocytopenia syndrome. *Front Microbiol* 2023; 14: 1209705.

105. Darnell JE, Kerr IM and Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science* 1994; 264: 1415–1421.

106. Pestka S, Krause CD and Walter MR. Interferons, interferon-like cytokines, and their receptors. *Immunol Rev* 2004; 202: 8-32.

107. Sleijfer S, Bannink M, Van Gool AR, et al. Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; 27: 423–431.

108. Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, et al. Effect of tocilizumab on disease activity in patients with active polymyalgia rheumatica receiving glucocorticoid therapy: a randomized clinical trial. *JAMA* 2022; 328: 1053–1062.

109. Alba MA, Kermani TA, Unizony S, et al. Relapses in giant cell arteritis: updated review for clinical practice. *Autoimmun Rev* 2024; 23: 103580.

110. Le RQ, Li L, Yuan W, et al. FDA Approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 2018; 23: 943–947.

111. Sweeney DA, Lobo SM, Póvoa P, et al. Choosing immunomodulating therapies for the treatment of COVID-19: recommendations based on placebo-controlled trial evidence. *Clin Microbiol Infect* 2024; 30: 611–618.

112. Kang SY, Yoo JR, Park Y, et al. Fatal outcome of severe fever with thrombocytopenia syndrome (SFTS) and severe and critical COVID-19 is associated with the hyperproduction of IL-10 and IL-6 and the low production of TGF-β. *J Med Virol* 2023; 95: e28894.

113. Liu M-M, Lei X-Y, Yu H, et al. Correlation of cytokine level with the severity of severe fever with thrombocytopenia syndrome. *Virol J* 2017; 14: 6.

114. Yoo JR, Lee KH, Kim M, et al. Tocilizumab therapy for IL-6 increment in a patient with non-fatal severe fever with thrombocytopenia syndrome. *Int J Infect Dis* 2022; 122: 656–658.

115. Lv Y, Mi P, Babon JJ, et al. Small molecule drug discovery targeting the JAK-STAT pathway. *Pharmacol Res* 2024; 204: 107217.

116. Verstovsek S, Mesa RA, Livingston RA, et al. Ten years of treatment with ruxolitinib for myelofibrosis: a review of safety. *J Hematol Oncol* 2023; 16: 82.

117. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. *Lancet Haematol* 2019; 6: e630–e637.

118. Hammersen J, Birndt S, Döhner K, et al. The JAK1/2 inhibitor ruxolitinib in patients with COVID-19 triggered hyperinflammation: the RuxCoFlam trial. *Leukemia* 2023; 37: 1879–1886.

119. Chen C-X, Wang J-J, Li H, et al. JAK-inhibitors for coronavirus disease-2019 (COVID-19): a meta-analysis. *Leukemia* 2021; 35: 2616–2620.

120. Wen S, Xu N and Wang G. Ruxolitinib for severe fever with thrombocytopenia syndrome (SFTS). *Heliyon* 2022; 8: e12462.

121. Wang G, Ge H-H, Hu L, et al. Severe fever with thrombocytopenia syndrome complicated by haemophagocytic lymphohistiocytosis: a retrospective cohort study. *Clin Microbiol Infect* 2024; 30: 558–560.

122. Lee M, Lee E, Kim S-W, et al. Severe fever with thrombocytopenia syndrome in South Korea, 2016-2021: clinical features of severe progression and complications. *Am J Trop Med Hyg* 2024; 111: 661–670.

123. Youdong X, Xiaofeng D, Xiyuan N, et al. Analysis of the risk factors and prognosis for severe fever with thrombocytopenia syndrome associated encephalopathy. *J Infect Chemother* 2023; 29: 464-468.

124. Fei X, Fang K, Ni X, et al. Risk factors of neurological complications in severe fever patients with thrombolytic syndrome: a single-center retrospective study in China. *Med Sci Monit* 2021; 27: e932836.

125. Cui N, Liu R, Lu Q-B, et al. Severe fever with thrombocytopenia syndrome bunyavirus-related human encephalitis. *J Infect* 2015; 70: 52–59.

126. Park SY, Kwon JS, Kim JY, et al. Severe fever with thrombocytopenia syndrome-associated encephalopathy/encephalitis. *Clin Microbiol Infect* 2018; 24: 432.e431–432.e434.

127. Xu Y, Shao M, Liu N, et al. Clinical feature of severe fever with thrombocytopenia syndrome (SFTS)-associated encephalitis/encephalopathy: a retrospective study. *BMC Infect Dis* 2021; 21: 904.

128. Li XK, Dai K, Yang ZD, et al. Correlation between thrombocytopenia and host response in severe fever with thrombocytopenia syndrome. *PLoS Negl Trop Dis* 2020; 14: e0008801.

129. Tang N, Yuan P, Luo M, et al. Prolonged coagulation times in severe fever with thrombocytopenia syndrome virus infection, the indicators of heparin-like effect and increased haemorrhagic risk. *Br J Haematol* 2024; 204: 1999–2006.

130. Lye DC, Archuleta S, Syed-Omar SF, et al. Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial. *Lancet (London, England)* 2017; 389: 1611–1618.

131. Fang L, Yu S, Tian X, et al. Severe fever with thrombocytopenia syndrome virus replicates in platelets and enhances platelet activation. *J Thromb Haemostasis* 2023; 21: 1336–1351.

132. Li X-K, Yang Z-D, Du J, et al. Endothelial activation and dysfunction in severe fever with thrombocytopenia syndrome. *PLoS Negl Trop Dis* 2017; 11: e0005746.

133. Li XK, Zhang SF, Xu W, et al. Vascular endothelial injury in severe fever with thrombocytopenia syndrome caused by the novel bunyavirus. *Virology* 2018; 520: 11–20.

134. Utsunomiya Nishimizu R, Shiota S, Ishii T, et al. Plasma exchange did not reduce viral load in a recovered case of severe fever with thrombocytopenia syndrome. *Intern Med* 2022; 61: 253–256.

135. Oh WS, Yoo JR, Kwon KT, et al. Effect of early plasma exchange on survival in patients with severe fever with thrombocytopenia syndrome: a multicenter study. *Yonsei Med J* 2017; 58: 867–871.

136. Yoo JR, Kim SH, Kim YR, et al. Application of therapeutic plasma exchange in patients having severe fever with thrombocytopenia syndrome. *Korean J Intern Med* 2019; 34: 902–909.

137. Gao H, Wang B, Yao H, et al. Application of blood purification technology in severe fever with thrombocytopenia syndrome. *Biotechnol Genet Eng Rev* 2024; 40: 4943–4952.

138. Song X, Xu X, Ren X, et al. Therapeutic plasma exchange combined with ribavirin to rescue critical SFTS patients. *J Clin Apher* 2024; 39: e22131.

139. Choi S, Kim M-C, Kwon J-S, et al. Case report: use of plasma exchange followed by convalescent plasma therapy in a critically ill patient with severe fever and thrombocytopenia syndrome-associated encephalopathy: cytokine/chemokine concentrations, viral loads, and antibody responses. *Am J Trop Med Hyg* 2018; 99: 1466–1468.

140. Park SY, Choi W, Chong YP, et al. Use of plasma therapy for severe fever with thrombocytopenia syndrome encephalopathy. *Emerg Infect Dis* 2016; 22: 1306–1308.

141. Doñate-Macián P, Jungfleisch J, Pérez-Vilaró G, et al. The TRPV4 channel links calcium influx to DDX3X activity and viral infectivity. *Nat Commun* 2018; 9: 2307.

142. Ueda M, Daidoji T, Du A, et al. Highly pathogenic H5N1 avian influenza virus induces extracellular Ca2+ influx, leading to apoptosis in avian cells. *J Virol* 2010; 84: 3068–3078.

143. Yamauchi N, Hongo T, Kawakami M, et al. Successful recovery from severe fever with thrombocytopenia syndrome and hemophagocytic lymphohistiocytosis with standard treatment and a calcium channel blocker of nicardipine hydrochloride. *Intern Med* 2023; 62: 1365–1369.

144. Canè S, Geiger R and Bronte V. The roles of arginases and arginine in immunity. *Nat Rev Immunol* 2024; 25(4): 266–284.

145. Lundberg JO and Weitzberg E. Nitric oxide signaling in health and disease. *Cell* 2022; 185: 2853–2878.

146. Urata S, Yasuda J and Iwasaki M. Loperamide inhibits replication of severe fever with thrombocytopenia syndrome virus. *Viruses* 2021; 13: 869.

147. Shen S, Zhang Y, Yin Z, et al. Antiviral activity and mechanism of the antifungal drug, anidulafungin, suggesting its potential to promote treatment of viral diseases. *BMC Med* 2022; 20: 359.

148. Zhang Z, Hu Y, Zheng X, et al. Differential short-term and long-term metabolic and cytokine responses to infection of severe fever with thrombocytopenia syndrome virus. *Metabolomics* 2024; 20: 84.

149. Zhang S-S, Yang X, Zhang W-X, et al. Metabolic alterations in urine among the patients with severe fever with thrombocytopenia syndrome. *Virol J* 2024; 21: 11.

150. Guo S, Yan Y, Zhang J, et al. Serum lipidome reveals lipid metabolic dysregulation in severe fever with thrombocytopenia syndrome. *BMC Med* 2024; 22: 458.

151. Urata S, Uno Y, Kurosaki Y, et al. The cholesterol, fatty acid and triglyceride synthesis pathways regulated by site 1 protease (S1P) are required for efficient replication of severe fever with thrombocytopenia syndrome virus. *Biochem Biophys Res Commun* 2018; 503: 631–636.

152. Xie J, Li H, Zhang X, et al. Akkermansia muciniphila protects mice against an emerging tick-borne viral pathogen. *Nat Microbiol* 2023; 8.

153. Zheng X, Zhang Y, Zhang L, et al. Taurolithocholic acid protects against viral haemorrhagic fever via inhibition of ferroptosis. *Nat Microbiol* 2024; 9: 2583–2599.