· Review ·

Recent advances in severe fever with thrombocytopenia syndrome

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Abstract

Severe fever with thrombocytopenia syndrome (SFTS) is an infectious disease caused by the severe fever with thrombocytopenia syndrome virus (SFTSV), a bunyavirus which was initially discovered in central China and has since rapidly spread to many regions in Asia. SFTS is characterized by pyrexia, leukopenia, thrombocytopenia, and multi-organ dysfunction that may lead to death. Furthermore, some patients may experience gastrointestinal symptoms such as diarrhea, nausea, and vomiting. This systematic review provides medical professionals with a comprehensive summary of SFTS pathogenesis, epidemiology, clinical manifestations, diagnosis, treatment, and preventive measures.

Keywords: severe fever with thrombocytopenia syndrome, SFTSV, pathogenesis, diagnosis, treatment

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an acute infectious disease caused by the severe fever with thrombocytopenia syndrome virus (SFTSV) [1]. SFTS is primarily found in mountainous, hilly areas, is more prevalent in the summer and fall, and is frequently associated with tick bites. SFTSV may also be transmitted through contact with contaminated blood or body fluids. The clinical manifestations of SFTS comprise pyrexia, significant leukopenia and thrombocytopenia, lymph node enlargement, fatigue, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea [2]. Although most patients have a favorable prognosis, SFTS may also cause meningitis, especially in elderly patients, those with underlying medical conditions, or patients who delay seeking medical attention [3].

Since the initial report of STFS in China in 2011, it has become an important emerging infectious disease of concern in Asia and other regions, with cases reported in surrounding countries, including South Korea and Japan [4-6]. Currently, no specific antiviral drug for SFTS is available, and therefore patients usually receive symptomatic supportive treatment. Nevertheless, multiple potential treatment strategies are being developed, such as novel antiviral drugs and immu-

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nomodulatory therapy candidates. This review offers an overview of the latest research on SFTS, including etiology, epidemiology, clinical manifestations, diagnosis, and treatment, with the aim of providing medical professionals with updated clinical diagnosis and treatment information.

Etiology of severe fever with thrombocytopenia syndrome

SFTS is caused by the SFTSV, also known as the Dabie Bandavirus or Dabie virus, which is classified under the genus Bandavirus within the family Bunyaviridae according to the International Committee on Taxonomy of Viruses. The SFTSV genome consists of three single-stranded negative-sense RNA segments: the large (L), medium (M), and small (S) segments. The L segment encodes RNA-dependent RNA polymerase, the M segment encodes viral glycoproteins and non-structural proteins, and the S segment encodes nuclear proteins and non-structural proteins [1]. The viral nucleocapsid of SFTSV replicates in cells via the RNA-dependent RNA polymerase, synthesizing new RNA molecules directly from the viral RNA template, and producing a large number of new viral particles [7]. The virion is spherical, enclosed by a lipid double-layered envelope with glycoprotein spikes [7], and between 80 and 100 nanometers in diameter.

SFTSV is susceptible to chemicals, including lipid solvents, detergents, strong acids, strong bases, glutaraldehyde, and chlorine-containing disinfectants, which have important implications for laboratory manipulation and environmental disinfection of the virus. The virus is also susceptible to ultraviolet light and heat. While SFTSV remains stable at 4°C for 1 week, and at 25°C for 6 hours, incubation at 60°C for 30 minutes is sufficient to inactivate the virus.

Epidemiology of severe fever with thrombocytopenia syndrome

SFTS has been reported in several Asian countries, including China, Japan, South Korea, Vietnam, and Myanmar. In China, the virus is predominantly prevalent in central and eastern rural areas, with cases reported in Hubei, Hunan, Anhui, Jiangsu, Guizhou, and other provinces, correlating with the transmission route and host animals. SFTS peaks in April-May and August-September and is primarily transmitted through tick bites, although it may be transmitted through close contact with blood or other body fluids from infected patients. Individuals engaging in outdoor work or residing in areas where ticks are active, including farmers and forestry workers, are at higher risk of contracting the disease [8].

The clinical manifestation of SFTS, including fever and thrombocytopenia, is essential for early identification and reporting of cases, which is required to understand epidemiological patterns and implement preventive measures. Incidence, sex ratio, case-fatality rate, and seasonality vary across different provinces due to variations in the regional environment, local agricultural activities, seasonal abundance of ticks, and prevalence of different pathogen types [9]. In 2024, the majority of SFTS cases affected middle-aged and elderly individuals; 96% of patients were 45 years or older. The gender distribution was skewed towards females, with a male-to-female ratio of 0.69:1. The majority of cases were among farmers (80.9%), followed by those engaged in housework or unemployed (12.5%). The mortality rate among individuals aged 35 years and above ranged from 0.6% to 11.1%. However, elderly patients with SFTS have a higher mortality rate of approximately 10%. In addition, the incidence of shock, respiratory failure, bleeding disorders, renal insufficiency, and arrhythmia is significantly higher in patients who die

from the disease than in those who survive [8]. Univariate binary logistic regression analysis showed that shock, arrhythmia, hemorrhage, elevated procalcitonin (PCT), serum creatinine (SCr), and blood urea nitrogen (BUN) were risk factors for death. However, multivariate logistic regression analysis showed that elevated BUN was the only independent risk factor for death [10].

Pathogenesis of severe fever with thrombocytopenia syndrome

The pathogenesis of SFTS involves multiple factors, including the direct impact of viral infection on the host immune system and subsequent dysregulation of the host immune response.

Interaction between the virus and the host immune response

Infection with SFTSV stimulates the host immune system, leading to the activation and functional modification of various immune cells, including dendritic cells, natural killer cells, macrophages, T lymphocytes, and B lymphocytes [11].

Regulation of immune cells

SFTSV can impede the activity of immune cells, including impairing the antigen-presenting capacity of dendritic cells, reducing the number of circulating natural killer and T cells, and disrupting the differentiation and antibody production of B cells. In vitro and in vivo studies have demonstrated that SFTSV can infect and replicate within macrophages. Viral infection causes significant upregulation of miR-146a and miR-146b in macrophages, downregulating STAT1 and inducing macrophage differentiation towards the M2 phenotype, thereby facilitating viral dissemination. Moreover, miR-146b specifically enhances the production of the immunosuppressive cytokine interleukin-10 (IL-10). SFTSV also triggers macrophage differentiation into M2 cells via the action of non-structural proteins (NPs), which modulate endogenous miR-146b expression. Concurrently, SFTSV infection impacts the myeloid cell population in peripheral blood, targeting human CD14+ monocytes to induce phenotypic changes. These findings suggest that monocytes/macrophages may serve as a reservoir for persistent SFTSV infection [12].

Abnormal activation of cytokines and chemokines

SFTSV infection triggers aberrant activation of proinflammatory cytokines and chemokines, including IL-6, IL-10, interferon (IFN)-γ, IL-8, and MCP-1, and the expression level of these cytokines correlates with the severity of SFTS. SFTSV NPs can also stimulate IL-10 production by modulating the TPL2 signaling pathway, consequently reducing host immune defenses and enhancing viral pathogenesis [13]. Additionally, SFTSV can activate inflammasomes, such as the NOD-like receptor protein 3 inflammasome, which results in IL-1β secretion and amplifies the inflammatory response.

SFTSV potentially impairs phagocytic function by disrupting signaling pathways or dampening key protein activity. Nuclear scaffold attachment factor A is upregulated in the cytoplasm of phagocytes following SFTSV infection and engages with the viral nucleocapsid protein. This interaction suggests that SFTSV might subvert host antiviral defenses by modulating specific intracellular signaling pathways [14].

Immune-mediated tissue damage

Excessive immune activation can result in immune-mediated tissue damage, including vascular leakage and multiple organ failure. Viruses may enhance vascular endothelial cell permeability by promoting tyrosine phosphorylation and internalization of vascular endothelial-cadherin, a critical component for maintaining endothelial integrity [11].

Mechanisms by which the severe fever with thrombocytopenia syndrome virus evades host immunity

SFTSV can suppress the host's innate immune response by targeting innate immune cells, disrupting IFN signaling transduction, and impeding the NF-κB signaling pathway. SFTSV targets host cells via specific viral proteins: the glycoprotein Gn engages with host cell receptors, while glycoprotein Gc facilitates viral entry by fusing with the cell membrane. This mechanism potentially enhances SFTSV's ability to circumvent the host's innate immune response [15]. By directly infecting host cells, SFTSV can cause cellular dysfunction and death or may facilitate viral replication and dissemination by modulating host cell apoptosis and autophagy [16, 17].

SFTSV NPs play a crucial role in evading host immunity by sequestering host proteins within inclusion bodies, thus preventing activation of both the IFN and NF-κB signaling pathways, and allowing viral replication. Furthermore, the SFTSV interacts with autophagy-related proteins to facilitate viral replication and dissemination [18].

SFTSV can also evade adaptive immunity by reducing the T cell population, particularly $CD4^+$ T cells, and disrupting the equilibrium of T cell subsets, including an increase in Th17 cells. Furthermore, SFTSV compromises the antigen-presenting capability of B cells, hindering their differentiation into plasma cells and subsequent antibody production. SFTSV may use B cells as a viral replication reservoir [19, 20].

Clinical manifestation of severe fever with thrombocytopenia syndrome

The clinical manifestations of SFTS can be divided into the initial stage, extreme stage, and recovery stage.

Initial stage

Initial symptoms of SFTS include acute fever, fatigue, loss of appetite, nausea, vomiting, chills, and enlarged lymph nodes. Some patients may experience muscle pain and diarrhea [21]. These symptoms may last from a few days to a week [22, 23].

Extreme stage

In the extreme stage of the disease, patients may experience more severe symptoms, including persistent high fever, severe dehydration, multiple organ dysfunction, and more severe thrombocytopenia and leukopenia [1]. In addition, patients may experience low blood pressure and shock, requiring emergency medical intervention. Lactate dehydrogenase (LDH) and aminotransferase levels may also increase during the extreme stage [21, 23].

Recovery stage

In the recovery stage, patients usually show improvement in their condition and physical signs. Virus-specific antibodies can be detected in the serum of convalescent patients, indicating that the immune system is responding to viral infection [1]. However, patients in the recovery stage may still need close monitoring to prevent possible complications or recurrence [22].

Complications of severe fever with thrombocytopenia syndrome

Complications of SFTS include multiple organ dysfunction, liver and kidney dysfunction, bleeding disorders, and immunosuppression (Table 1).

Multiple organ dysfunction

A case study showed that a 50-year-old female patient

Table 1. Complications of SFTS.

Complication types	Description	Citations
Multiple organ dysfunction	Common serious complications that can lead to death	[24]
Liver and kidney function impairment	Laboratory tests showed elevated aminotransferase and elevated BUN and Scr levels	[10, 21, 25]
Immunosuppressive state	Immune function is suppressed, secondary infection is easy to occur, and fungal infection can be observed in the lung	[26]
Hemorrhagic tendency	Skin and mucous membrane hemorrhage or intracranial hemorrhage, hemoptysis, digestive tract hemorrhage, etc., can also appear as coagulation dysfunction and even DIC	[21]
Neural symptom	Disturbance of consciousness or other neurological symptoms may occur and may be related to direct viral invasion or immune-mediated neurotoxic effects	[27]

died due to multiple organ dysfunction after SFTS infection [24].

Liver and kidney function impairment

Laboratory tests in SFTS patients often show elevated aminotransferases, such as LDH and alanine aminotransferase (ALT), which may indicate liver damage [21]. In addition, kidney function may be impaired, and elevated BUN and SCr levels are independent risk factors for death in SFTS patients [10, 25].

Immunosuppression

Patients with SFTS may exhibit immunosuppression and thus be more susceptible to secondary bacterial, fungal, or viral infections. Obvious fungal infections can be observed in the lungs of some SFTS patients [26].

Bleeding disorders

Thrombocytopenia, which is common in SFTS patients, can manifest as skin or mucosal hemorrhage, intracranial hemorrhage, hemoptysis, digestive tract hemorrhage, abnormal coagulation, and DIC [21].

Neurologic symptoms

Some SFTS patients may develop neurologic abnormalities, such as altered consciousness, which may be related to the virus invading the central nervous system or be indirectly caused by immune-mediated neurotoxic effects [27].

In summary, SFTS may be associated with diverse and severe complications that require timely diagnosis and comprehensive treatment to reduce the mortality rate.

Laboratory analyses and diagnosis

Laboratory analyses

Routine blood analysis

SFTS patients commonly have decreased white blood cell, lymphocyte, and platelet counts (Table 2) [28].

Blood biochemical analysis

SFTS patients may have increased blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), LDH, creatine kinase (CK), SCr, ferritin, D-dimer, C-reactive protein (CRP), PCT, amylase, lipase, and inflammatory factors such as IL-6 [29].

Serological analysis

In SFTS patients, elevated IgM levels may be observed, especially in the acute phase, reflecting the initial host immune response to viral infection [30]. A positive result for SFTSV-specific IgM in two blood samples taken from the same patient at an interval of more than 24 h is diagnostic for SFTS. IgG antibodies may rise as the disease progresses. One of the diagnostic criteria for SFTS is an SFTSV-specific IgG titer 4 times higher in the recovery phase than in the acute phase [31].

Table 2. Examination types and clinical significance of SFTS.

Examination types	Clinical significance	Citations
Blood routine examination	Viral infection and immune response	[28]
Blood biochemical examination	Tissue injury, inflammation and organ dysfunction	[29]
Serological examination	Progression of acute infection and immune response	[30, 31]
Etiological examination	Direct detection of viral RNA; Confirm the morphological characteristics of the virus; Determination of genetic characteristics; Detection of viral antigens; Fast and accurate detection of SFTSV	[1, 32]

Viral detection

Viral RNA detection: SFTSV RNA can be detected from patient blood samples by polymerase chain reaction (PCR) [1, 32].

Real-time PCR: Real-time PCR kits, such as the SFS-QS kit and PowerChek SFTSV Real-Time PCR kit, have high sensitivity and specificity, and can be used to quickly and accurately detect SFTSV [33].

Immunohistochemistry: SFTS viral antigens can be detected by immunohistochemical methods in biopsies from lymph nodes and other tissues [1].

Microscopy: Initial studies included morphologic analysis of the isolated virus to confirm that it was a member of the novel Bunyavirus family [1].

Gene sequencing: Initial studies included nucleotide sequence analysis on the isolated virus to determine its genetic characteristics and relationship with other known viruses [1, 32].

A combination of these tests can improve diagnostic accuracy, especially in early disease and during epidemiological investigations. More efficient detection tools and methods may be developed in the future.

Imaging and other tests

Imaging can aid in the diagnosis of SFTS. For example, in SFTS patients, chest Computed Tomography may show lung infiltration and Magnetic Resonance Imaging may reveal brain involvement, features that can help diagnose SFTS and rule out other diseases[34]. In addition, for those cases where laboratory test results are non-diagnostic, imaging may provide additional information to support or rule out a diagnosis of SFTS [35].

Differential diagnoses for severe fever with thrombocytopenia syndrome

Scrub typhus

According to a 2022 study, SFTS and scrub typhus are clinically similar, making differential diagnosis difficult [36]. A sensitive, specific, and objective scoring system has been developed to help distinguish between the two diseases. The scoring system includes leukopenia, increased activated partial thromboplastin time, normal CRP levels (≤3.0 mg/dL), and elevated CK levels (>1000 IU/L) [37].

Other hemorrhagic fevers

SFTS is an emerging infectious disease with pathological features, including necrotizing lymphadenitis and local lymph node infiltration with virus-infected cells. In addition, SFTS patients often have evidence of hemophagocytosis, which is less common in other hemorrhagic fevers. Therefore, these unique pathological and clinical manifestations should be considered when making a differential diagnosis [22, 38].

Other endemic diseases

A Korean study developed a predictive score for primary care providers to distinguish SFTS from other endemic animal-derived diseases. The scoring system was based on multivariate logistic regression analysis, with independent predictors, including neurologic symptoms, diarrhea, leukopenia (< 4,000/mm^3), and normal C-reactive protein (< 0.5 mg/dL) [39].

Treatments of severe fever with thrombocytopenia syndrome

Currently, no specific antiviral drugs and vaccines for the disease are available. However, if patients rapidly seek medical treatment after the onset of symptoms, antiviral drugs and/or immunoglobulin can be administered in the early stage of the disease. Patients with severe disease should be given effective antiviral and immunosuppressive treatment, and glucocorticoid and immunoglobulin should be given in a timely manner with symptomatic supportive treatment [40]. For patients with less severe disease, treatment of SFTS mainly consists of symptomatic supportive treatment, including rest, hydration and electrolyte supplementation, physical cooling, and antipyretic drugs.

The latest treatments for SFTS include several different strategies focused on antiviral therapy, immune regulation, and vaccine development:

Antiviral treatment

Currently, no specific antiviral treatment for the disease is available. Ruxolitinib has been used to treat SFTS, although specific efficacy data are not available [41]. A nonrandomized, single-arm, multicenter trial suggested that Fapiravir may be an effective treatment for SFTS, reducing mortality and morbidity [42].

Immunoregulation

SFTS patients often have a high viral load and severe clinical symptoms; therefore, traditional immunosuppressive treatments such as methylprednisolone may not be appropriate for all patients. A single-center retrospective cohort study found that glucocorticoid therapy does not significantly lower mortality rates in SFTS patients and may increase the risk of secondary infections. However, owing to limitations in the study design, these findings should be validated in a multicenter, randomized controlled trial [43]. In a single-center retrospective cohort study, one patient experienced rapid disease deterioration and eventual death despite initial methylprednisolone administration; meanwhile, another patient recovered after plasma exchange was performed instead of increasing the methylprednisolone dose [44].

Vaccine Development

No approved vaccines or specific antiviral drugs for SFTS are currently available. However, researchers are exploring various vaccine development methods, including live attenuated vaccines, DNA vaccines, inactivated virus vaccines, viral vector vaccines, protein subunit vaccines, and mRNA vaccines, to develop a safe and effective SFTS vaccine [45-47].

Other treatments

The Mirasol pathogen reduction technology system is being used to reduce the risk of transfusion-transmitted SFTSV infection by significantly reducing SFTSV activity [48].

In conclusion, the treatment strategy for SFTS needs to be personalized on the basis of the clinical condition, viral load, and complications of each patient. The con-

tinuous development of new drugs, immunomodulatory strategies, and vaccines will provide more treatment options in the future. Future studies may provide more data on the effectiveness of current and novel treatments.

Prevention and control

SFTS is a viral disease transmitted by ticks, and thus avoiding tick bites is key to prevention. Precautions should include wearing tight-fitting, long-sleeved clothing and long pants, regularly applying insect repellent containing DEET or IR3535 to exposed skin, and thoroughly checking the body after outdoor activities to remove any attached ticks [49].

The main habitat of ticks is grassland, woods, and other environments. Ticks can be removed from indoor and outdoor environments using repellents containing DEET, picaridin, and antihistamines [50].

While there are currently no approved vaccines or prophylactic drugs for SFTS, multiple vaccine and antiviral candidates are undergoing preclinical and early-stage clinical trials, and new preventive measures are expected to become available in the next few years [45]. At the same time, considering the high mortality rate of SFTS and global public health concerns, it is particularly important to accelerate research in this area.

Conclusion and future directions

The pathophysiological mechanisms of SFTS, such as the pathogenesis of multi-organ dysfunction, remain unclear. Therefore, future studies are needed to explore these mechanisms in-depth and provide a basis for the development of targeted treatment strategies. No specific therapeutic drugs or preventive vaccines for SFTS are currently available, and future studies should explore new antiviral drugs, immunomodulators, and vaccine candidates to improve treatment efficacy and prevent disease transmission. Existing diagnostic techniques have limitations in terms of sensitivity, specificity, and convenience, and future research should focus on developing diagnostic tools that are faster, more accurate, and easier to use in the clinic. Given the potential threat that SFTS poses to public health, future research needs to address not only the immediate challenges but also the long-term implications, including disease prevention, early diagnosis, effective treatment, and global health security.

In summary, comprehensive understanding and effective management of SFTS require interdisciplinary collaboration and innovative research approaches to address the challenges posed by this emerging infectious disease.

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Author Contributions

Jiaxi Ma, Jiandan Qian, Wanwan Shi, Long Xu and Guiqiang Wang wrote the manuscript.

Conflicts of Interests

The author declares no conflict of interest.

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