

Research Advances on Epidemiology of Severe Fever with Thrombocytopenia Syndrome: A Systematic Review of the Literature

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Abstract

Severe Fever with Thrombocytopenia Syndrome (SFTS) is an emerging infection disease caused by SFTSV, a newly discovered bunyavirus. Suspected SFTS cases were first reported in 2006 in Anhui province, China and SFTSV was first isolated in 2009 in Henan province, China. The disease has been reported in more than 23 provinces in central and eastern China and it was also reported in South Korea and Japan. SFTS is a hemorrhagic fever with major clinical manifestations of fever, thrombocytopenia, gastrointestinal symptoms and leucopenia. In severe SFTS patients, the clinical conditions may proceed quickly and result in multi-organ failure. The average case fatality rate was approximately 10% in humans. The incidence rate of SFTS was significantly higher in old age people and fatal cases mainly occurred in elderly people. SFTS is most likely to be transmitted by tick-bite and it also can be transmitted from person to person. The potential reservoir hosts of SFTSV including goats, dogs, cattle, chicken and even birds. This article reviews the latest advances on SFTS epidemiology characteristics including risk factors, sources of infection, distribution of SFTS cases, transmission route and aetiological characteristics, laboratory testing, clinical symptoms, susceptible population, relationship between the meteorological factors and SFTS.

Keywords: Fever; Thrombocytopenia syndrome; Epidemiology; Host animal; Vector; Meteorological factor

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Introduction

A newly emerging infectious disease is caused by a tick-borne strain of bunyavirus, which was identified as the severe fever with thrombocytopenia syndrome (SFTS), and reported in rural areas in central and eastern China since 2009. The SFTS is characterized by fever, thrombocytopenia, leucopenia, dermorrhagia and multi-organ dysfunction and has approximately 10% mortality rate on average in China [1]. The major clinical symptoms of SFTS are similar to human granulocytic anaplasmosis (HGA), but neither anaplasma phagocytophilum (AP) DNA nor antibodies against this bacterium could be detected in blood samples from a majority of the SFTS patients. Dr. Yu and his research group had isolated the virus from a patient's blood sample and identified it is a novel bunyavirus which is classified in the family Bunyaviridae, genus Phlebovirus through viral RNA detection, and molecular and serologic analyses in 2009 [2]. The transmission vectors and

animal hosts of SFTSV need further study, at present, researchers think that ticks, especially *Haemaphysalis longicornis* are the most likely transmission vectors and domestic animals including goats, dogs, cattle, and even birds are potential reservoir hosts of SFTSV according to the basis of the following evidence: (i) SFTSV has been detected from the ixodid ticks, including *H. longicornis* and *Rhipicephalus microplus* in some endemic areas [3]; (ii) the nucleic acid sequence of SFTSV that isolated from ticks has 95-100% homology with the SFTSV isolated from reservoir hosts and patients which was reported that about 52% of patients had a tick-bite history [4]. It was also reported that about 30-80% of reservoir hosts including goats, dogs, cattle, chicken and even birds have exposure to ticks, because of antibody to SFTSV had been detected [5]. This may be also proven that there would be more potential vectors linked with SFTSV life cycles, because the papers reported that 48% of patients had no tick exposure history [6].

The infection spectrum, relevant epidemiological characteristics, distribution characteristics, ecological studies of vertebrate hosts of SFTSV and the effect of meteorological factors to the disease incidence are still unclear currently in China. The clinical and epidemiological description of the newly emerging infectious disease in English literature is limited. In order to prevent and treat SFTS better, a systematic review of the literature related to the research progress of SFTS in recent years is summarized in this article.

Identification of the Pathogen

Between March and July 2009, an emerging infectious disease, which was identified as the severe fever with thrombocytopenia syndrome (SFTS), was reported in rural areas in Central China [2]. Researchers of Chinese Center for Disease Control and Prevention (China CDC) had isolated a novel phlebovirus in the Bunyaviridae family from a patient's blood sample and confirmed SFTS bunyavirus (SFTSV) is associated with SFTS by genetic analysis [2]. Researchers in China and other countries paid great attention to SFTS after the findings published openly. Subsequently, the disease had expanded to more than 23 provinces of China after the establishment of detective methods [7] and the annual incidence of the disease is approximately five per 100,000 of the rural population in China [6]. Since October 2010, Chinese ministry of health added SFTS to the list of national modifiable diseases and sentinel hospitals have been established in endemic areas to diagnose and report SFTS cases to China CDC through the China Information System for Diseases Control and Prevention (CISDCP).

Aetiological Characteristic

Family Bunyaviridae comprises of more than 300 distinct members and about 60 viruses associated with human illnesses, which are organized into five genera: Orthobunyavirus, Phlebovirus, Nairovirus, Hantavirus [8], and Tospovirus which only infect plants [9]. Most viruses of the family Bunyaviridae are arthropod-borne small mammal's act as amplifying vertebrate host whereas mosquito, tick, sand fly and rodents act as vectors of transmission and it can occasionally infect humans [10]. Orthobunyavirus is the biggest one in the family Bunyaviridae and consist of 160 viruses appropriately [11]. SFTSV is classified in the family Bunyaviridae, genus Phlebovirus [6] and consist of a single-stranded negative-sense RNA genome, which including three segments known as large (L), medium (M), and small (S) [12]. The L segment encodes the RNA-dependent RNA polymerase (RdRp), which is involved in viral transcription and replication. The segment M encodes the two viral envelope glycoproteins known as Gn and Gc, which are involved in immunogenicity and behave as neutralizing or protective epitopes. The S segment encodes two proteins, nucleocapsid protein (Np) and Non-structure protein (NSs). Np facilitates viral RNA encapsulation and is responsible for the formation of RNA and protein complex [13]. At present, there are several hundreds of the genome sequences obtained from SFTSV isolates in GenBank [14]. The gene sequence analysis of SFTSV revealed 38.83% but less than 40% nucleotide homology with other known bunyaviruses indicate

that it is a novel virus. Combine the clinical manifestations, the epidemiologic investigations, and laboratory testing results of SFTS, the etiology relationship between SFTSV and SFTS was confirmed. The inactivated conditions of SFTSV still need further study currently, but similar Bunyaviridae viruses are sensitive to acid, ultraviolet radiation, heat, and chemicals such as ether and sodium deoxycholate, etc. [6].

Laboratory Testing

At present, it mainly contains three kinds of laboratory testing methods of SFTSV: virus isolation, nucleic acids detection and serum antibody detection. Nucleic acid detection is appropriate for early diagnosis, although its cost is relatively high, but it spends less time. Generally speaking, viral nucleic acid can be detected in the acute phase serum of patients, within 2 weeks post-onset of disease [15]. Several methods have been developed to amplify the viral RNA, including reverse transcription-PCR (RT-PCR), which is useful for rapid presumptive diagnosis, real-time PCR is of high sensitivity and specificity, and reverse transcription loop-mediated isothermal amplification (RT-LAMP) is relatively simple and cheap [16,17]. In terms of virus isolation, which is often the most confident evidence for virus infection: collecting blood sample of patients in acute stage and inoculating in newborn mice or the mouse brain is the most sensitive method? African green monkey kidney cell (Vero cell), Vero E6 cell, human lung cancer cell (A549) and mosquito cell are also sensitive to SFTSV [18]. Available cells can be classified and identified by the virus neutralization (VN) test [19]. In terms of serum antibody detection: the main methods to detect the virus specific IgM, IgG, and total antibodies are the in-house Mac-EIA assay, indirect EIA assay, and double-antigen sandwich EIA assay, respectively [20]. Additionally, indirect immunofluorescence (IFA) and the serum neutralization assays are still the conventional and key methods; however these methods are costly and need more time and well-trained personnel. It was reported that IgM antibody of SFTS patients have a long duration more than one year [21]. At present, IgM antibody positive, IgG antibody positive conversion or had a 4-fold increase in antibody titer for SFTSV and SFTSV isolation have been the diagnosis criteria of SFTS in China [22].

Epidemiological Characteristics

Geographical distribution of the SFTS cases seemed highly sporadic, with a peak of incidence through May to July, and most cases distributed over the mountainous or hilly areas [22]. Patients have been reported in many provinces in China, including Jiangsu, Henan, Hubei, Anhui, Shandong and Zhejiang Province [7,23,24] after the establishment of the aetiological detection methods. Most cases live in the rural areas which were characterized by mountainous or hilly according to the epidemiological investigation [7] and it was also reported in South Korea [25,26] Japan [27,28]. SFTS is prevalent between May and July among elderly persons who live in hilly areas mostly and always occurs in spring and summer [29]. People all susceptible to SFTSV and age maybe a critical risk factor for SFTS, the elder people might have low immunity to SFTSV and become more susceptible to SFTSV infection [29]. According

to the epidemiological investigations, the residents live in the wooded and hilly region, farmers in rural areas and tourists are high risk population [5]. Meanwhile, population such as medical personnel, caregiver of patient who contact directly with the blood or other body fluids of severe patients may be also infected without suitable preventive strategies. Surveillance results show that contacting with domestic animals and other pets, working in the forest, touching the grass without protection are the risk factors for the disease [30]. At present, person-to-person transmission of infections by SFTSV had been also reported in many provinces [24,31-33].

Meteorological Factors and SFTS

Over this century, climate change will worsen virtually every health problem we know of, from heart disease and heatstroke to salmonella and insect-borne infectious diseases. SFTS, as a kind of insect-borne infectious disease, meteorological factors that determine the distribution of vectors (tick) and animal hosts have an important influence on its incidence. Du et al. [34] used ecological niche model for predicting the potential risk areas of SFTS in China reported that meteorological factors such as temperature, precipitation and sunshine duration have important effect on the incidence of SFTS, the possible reasons may be that these meteorological factors influence the growth and development of the vectors (tick) and the work habits of the susceptible people, etc. At present, there are few researchers focusing on the effect of meteorological factors on the incidence of SFTS, so it may be a research hotspot in the future. Meteorological factors play an important role in the transmission of vector-borne diseases, and maybe function in the follow ways. First, it directly influences the reproduction and dissemination of the pathogen. Second, it is also a main factor impacting the activity of the virus vectors such as ticks and the work habits of people live in epidemic areas. Third, temperature and rainfall affect the behaviors and ecological characteristics of both wild and domestic host animals, for example, a warmer winter and a colder summer enhances animal activities and migration ways.

Clinical Symptoms

SFTS is characterized by fever with gastrointestinal symptoms, thrombocytopenia, leucopenia and severe patients would die because of multi-organ failure [35]. But so far, the true incubation period of SFTS has not been confirmed definitively. It was reported that the incubation period for transmission through tick-bite in most SFTS patients ranges from 2-3 days to 1-2 weeks even 1 month [36], but the incubation period of SFTSV infection through person-to-person transmission is still unclear due to the infection route and dose of virus were different [37]. SFTS cases are characterized by acute onset, the clinical symptoms are fever (body temperature $\geq 38^{\circ}\text{C}$), severe patients' body temperature even higher than 40°C and always accompanied with some constitutional symptoms, including chill, fatigue, lack of appetite and muscle soreness [38]. The gastrointestinal symptoms are obviously in the early period which are characterized by abdominal pain, diarrhea. Patients maybe also have bleeding tendency, especially the skin petechiae and ecchymoses,

conjunctival hemorrhage, bleeding gums, etc. There aren't patients with massive hemorrhage have been reported, but a few of patients will appear disseminated intravascular coagulation (DIC). Respiratory system symptoms are relatively rare compare with the gastrointestinal symptoms. The prognosis of severe patients with nerve and mental symptoms is always poor. A few of patients in critical conditions may appear consciousness obstacle, skin ecchymosis, gastrointestinal bleeding, pulmonary hemorrhage, respiratory failure and could die because of multi-organ failure finally. The mortality is still controversially as the report: it is appropriately 10% without diagnosis and treatment in time because of having not given enough attention to the disease in the early period of SFTS [39]. It was also reported that the mortality is 30% in some provinces [22,40]. According to the current report, the mortality of SFTS is about 10% [41], but also higher than human granulocytic anaplasmosis (HGA, mortality: 0.5%-1%) [42] which has similar clinical symptoms to SFTS. One of characteristic laboratory finding in the early stage was WBC and PLT drop, WBC drop before PLT generally [35]. The abnormal liver function characteristic by liver transaminase and myocardial enzymes rise, urine protein positive, urine occult blood are also common in laboratory detection. The clinical symptoms including obviously liver function damage, coagulation disorders, glomerular filtration function damage.

Diagnosis and Differential Diagnosis

The diagnosis of SFTS mostly depended on the epidemiological investigation, clinical manifestations and laboratory detections. At the same time, SFTS should differ from other similar diseases including tick-borne diseases such as rickettsia disease or human anaplasmosis (HA), infectious diseases with fever and level of enzymatic indexes rising, gastrointestinal disease with fever, leukocytes and blood platelet reducing, internal diseases with fever, leukocytes and blood platelet reducing or bleeding tendency, internal diseases with fever and some enzymatic indexes rising. At present, medical institutions can diagnose and report patients with suspected symptoms according to "Guidelines for the prevention and control of severe fever with thrombocytopenia syndrome (2010 edition)" published by Chinese ministry of health. Confirmed cases should be reported to China CDC through the China Information System for Diseases Control and Prevention (CISDCP) within 24 hours. The study found that SFTS patients' symptoms were similar to Human granulocytic anaplasmosis (HGA) which was caused by *Anaplasma phagocytophilum* (AP). The HGA is characterized by fever, thrombocytopenia, leucopenia and multi-organ dysfunction [43] and has been reported in most areas of the world with appropriately less than 1% mortality. Tick-bite is the most likely transmission routine and wild animals, domestic animals including goats; dogs are potential amplifying hosts of AP. Although the clinical symptoms of SFTS and HGA are similar to each other, but the treatment methods of the two diseases are totally different. Doctors notice that the biggest difference between the clinical symptom of SFTS and HGA is that SFTS patients generally without skin rash, the dermorrhagia is also not seriously, and few massive hemorrhage cases were reported

[23]. It is also reported that SFTS patients had gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, which are rarely observed in HGA patients [2]. So these differences can be used as the auxiliary basis of differential diagnosis.

Treatment and Prognosis

At present, there is still no specific vaccine or antiviral therapy for SFTSV infection. Supportive treatment, including plasma, platelet, granulocyte colony stimulating factor (G-CSF), recombinant human interleukin 11, and gamma globulin is the most essential part of case treatment [44]. Meanwhile, some measures were taken to maintain water, electrolyte balance and treat complications are also very important. Ribavirin is reported to be effective for treating Crimean-Congo Hemorrhagic Fever (CCHF) infections and hemorrhagic fever with renal syndrome, but it is still inadequate to judge the effect of ribavirin on SFTS patients because of the study limitation without adequate parameters were investigated [45]. Host immune responses play an important role in determining the severity and clinical outcome in patients with infection by SFTSV [36]. The use of corticosteroids for the treatment is also controversial in SFTS patients with ALI/ARDS, but corticosteroids can suppress the cytokine storm and multiple cytokines triggered during the acute phase of SFTSV infection which are associated with the disease severity. The prognosis of SFTS has a close relationship with timely treatment and elder patient or patient with certain underlying medical conditions may severe the difficulty of the treatment [46].

Prevention and Control

SFTS, as a newly emerging infectious disease, there is still no specific vaccine for SFTSV infection currently. The main prevention works should focus on various comprehensive prevention and control measures: control the sources of infection, cut off the route of transmission, and protect the vulnerable population. Related institutions should strengthen the works of health education, propaganda and popularize health prevention knowledge to general population. People also need to keep good personal hygiene and protect themselves from tick-bite. In the

epidemic areas, people should strengthen the management of the domestic animals or pets and keep house and surroundings clean. Urban residents should pay attention to the hygiene of pets which would take ticks inside. Medical workers should study the relevant professional knowledge about SFTS to improve the level of diagnosis and treatment of the disease. For patients, the disinfection measures should be carried out as soon as possible and medical personnel's and caregivers should strengthen the personal protection during the process of treatment or nursing of severe patients. CDC of epidemic area should also strengthen the epidemic monitoring and report timely.

Problem and Prospect

In conclusion, further study about the route of transmission, transmission vectors of SFTSV are still needed. The prevention and control measures are mainly focus on tick, patients' blood and secretion according to the clinical and external environment detecting information. In-depth research and analysis should be taken on the vectors and host animals with the purpose of making more effective preventive measures for the disease. In terms of treatment, effective drugs against pathogen should be researched and developed as soon as possible to improve the cure rate and reduce the fatality of SFTS. At the same time, it's still a controversial issue about the application of ribavirin, glucocorticoid and immunoglobulin in the current literatures, but these drugs play a key role in the treatment process and the drug application needs further clinical data supporting urgently. Based on the symptom surveillance results of several cities, long-term symptom surveillance system should be established in more cities to predict and control the occurrence and development of this kind of new disease quickly. Meanwhile, the surveillance and detection works should be strengthened in the high incidence rural areas, so as to provide powerful epidemiology foundation for the next prevention and control works.

Conflict of Interests

None of the authors have any financial interests to disclose.

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