



# A new emerging pandemic of severe fever with thrombocytopenia syndrome (SFTS)

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**Abstract** The aim of this study is to make aware every one of the deadliest diseases named severe fever with thrombocytopenia syndrome (SFTS). It has become the worldwide pandemic in recent few years. It is a kind of haemorrhagic fever, caused by SFTS virus (SFTSV), a novel phlebovirus of family Bunyaviridae. This syndrome is also a tick-borne zoonosis that means the virus transmitted from tick bite (having virus) into human body, i.e. infection spread from animals to humans and also transmitted from human to human. Epidemiological data of SFTS was collected to know the nature/symptoms of SFTSV. First case of this disease has been reported in China, followed by Japan, South Korea, Taiwan, USA and many other countries. Vertebrates are the host of this disease and tick functions as a vector, where the virus can undergo brisk changes using gene mutation, homologous recombination and reassortments. The major symptoms of hemorrhagic fever are fever, thrombocytopenia, leucopenia and gastrointestinal abnormalities. Sometimes in very severe cases, full body organ failure may also take place and average death rate in humans is nearly 10 %. Old aged peoples are more prone to SFTSV infection. Apart from the fact of increasing SFTSV related health problems to humans, the pathogenesis of SFTS virus in human is not entirely understood and no treatment to this virus is still available. The simplest way to protect our self from this infection is to refrain from tick bite. Therefore, this disease has evolved to produce serious health issues to humans in various countries of world including China. This review

discussing about causative agent, epidemiology, pathogenesis, diagnosis and treatment of SFTS. In order to control the spread of SFTSV, we have to stop the viral transmission or to protect the easily vulnerable population from tick bites, avoiding direct contact of infectious and also to use personal protective devices for SFTS patients. So, the weather conditions, mode of transmission and creation of new therapeutics like vaccines and drugs are the main areas of forthcoming research.

**Keywords** SFTS (SFTSV) · Tick bite · Phlebovirus · Hemorrhagic fever · Epidemiology · Pathogenesis

## Introduction

During 2006–2007, various patients have been reported with the symptoms of having fever, stomach ache, gastrointestinal disorders, nausea, bloating, vomiting and thrombocytopenia in various regions of China [1, 2]. The first human case of severe fever with thrombocytopenia syndrome (SFTS), was also found in Shaanxi province of western China and the patient was 66 years old man with high fever, chills, pharyngeal pain, nausea and vomiting [3]. The causative agent of this disease is SFTS virus, which was identified as a phlebovirus of family Bunyaviridae. In the initial days, it was suspected that this disease caused by *Anaplasma phagocytophilum* bacterium, but the pathogen was not isolated from the patients, till the isolation of SFTSV from the blood of human granulocytic anaplasmosis patient in 2009 from Henan province. Like other phleboviruses, genome of SFTSV also consist of large, medium and small segments. Two non-overlapping open reading frames (ORFs) of small segment are encoding the nucleocapsid and non-structural proteins. The medium and

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large segments encode the RNA-dependent RNA polymerase and Gn-Gc envelope glycoproteins, respectively [4]. After complete sequencing of SFTSV, it shows close resemblance with Uukuniemi virus and sequences can also be found in GenBank. The infection is transmitted from infected tick and viral sequences obtained from these ticks on animal are closely related to those collected from human (zoonotic transmission) [5], but various reports are also available showing human to human transmission of infection [6–8]. In China, during 2013 to 2016, total 7419 cases of human have been confirmed with 355 deaths [9], SFTS has been also found in Henan, Hubei, Anhui, Shandong, Jiangsu, Zhejiang, Liaoning, Yunnan, Guangxi, Jiangxi and Shanxi [10]. After an epidemiological survey, SFTS have been also reported in Japan [11, 12], South Korea [13–15], USA [16] and Taiwan [9, 17]. So, due to the worldwide spread of SFTSV, high mortality rate and human communicable nature of virus, it poses a great menace globally.

Besides from the fact of increasing SFTSV related health problems to humans, the pathogenesis of SFTS virus in human is not entirely understood and no treatment to this virus is still available. The simple way to protect our self from this infection is to refrain from tick bite. Therefore, this disease has evolved to produce serious health issues to humans in various countries of world including China. All review articles available in literature are deficient in clinical, epidemiological and research related description of SFTS [18–20, 9]. So, this review is the systematic presentation of SFTS cases, SFTSV and detailed summary of research. This review discussing about causative agent, epidemiology, pathogenesis, diagnosis and treatment of SFTS.

## Causative agent and genome Organization

The causative agent of SFTS is a virus known as SFTSV, which is a single-stranded negative sense RNA and comprises of three segments i.e., small, medium and large (S, M, L) with nucleotides sequences of 1744, 3378 and 6368 respectively [9]. In Table 1 we have presented that the L segment is encoded by RNA-dependent RNA polymerase (RdRp) with 2084 amino acids, M segment encoded by 1073 amino acids glycoprotein (Gn and Gc) and S segment encoding the non-structural protein (29–910 nucleotides) in the sense orientation and the nucleoprotein (1702 – 965 nucleotides) in the antisense orientation with intergenic region of 54-base pairs respectively. These segments are covered with untranslated regions (UTRs) just like other bunyaviruses, which are short and highly conserved. For example, SFTSV strain HB29 with GenBank accession number: NC-018136, NC-018138 and NC-018137)

contains L, M and S segments with 16, 18 and 42 nucleotides at 5' terminus and 100, 141 and 28 nucleotides at 3' terminus respectively. Untranslated regions (UTRs) of these segments present at 5' and 3' terminus is highly complementary, which separates the viral RNAs from nonviral RNAs, and play crucial role in transcription, viral RNA replication, viral RNA encapsidation, and viral genome packaging respectively [19]. The genomic study of SFTSV revealed that there is only 38.3 % homologous sequences present in SFTSV, which are similar to other bunyaviruses. Bunyaviruses are RNA viruses with five generic groups such as orthobunyaviruses (three sequences AMLq13, AMLq14 and AMLq16 with Gene Bank accession HM107840, HM107841 and HM107842 respectively showed similarities with OROV TRVL9760 (AF64531) and to the strain BeAn19991 (AF164532),airoviruses, tospoviruses (GenBank accession numbers KC261947 to KC261976), phleboviruses (GenBank accession numbers HM119401 to HM119436 and HM466934 to HM466936) and hantaviruses [18]. Bunyviridae are only transferred by arthropod vectors [21] and can infect the animals, plants [22] and humans. Phleboviruses are classified into two groups with 70 antigenically different serotypes, phlebotomus fever transmitted by phlebotominae sandflies or mosquitoes and Uukuniemi fever by ticks [23]. Genetically, SFTSV are placed under phlebovirus, but they represent a third unique group due to some different characters [4]. SFTSV and heartland virus shows some sequence similarity with Uukuniemi group, so they are placed under that group. This group does not have middle segment (non-structural proteins), have some serological features and ticks as common arthropod vector [24, 25]. Various symptoms of this disease, worldwide study of epidemiology and SFTS testing in laboratory, all these shows an etiological relationship among SFTS and SFTSV. So, these viruses are appearing as the potent pathogen of human health, due to the increased cases in new hosts worldwide.

## Epidemiology

First case of SFTS was described in Henan and Hubei provinces of China in the middle of March–July, 2009 mentioned by National Health and Family Planning Commission [26], but the first case occurred in Dingyuan County, Chuzhou, Anhui province in September, 2006 [7]. Total 171 patients of SFTS are observed from June, 2009 to September, 2010 in Henan, Hubei, Shandong, Liaoning, Anhui, and Jiangsu provinces [2]. Towards the end of 2012, SFTSV infection has been spread into another 11 provinces such as Henan, Hubei, Anhui, Shandong, Jiangsu, Zhejiang, Jiangxi, Guangxi, Yunnan, Shaanxi, and

**Table 1** Genomic properties of SFTSV

Segments	Size (bp)	ORF (open reading frames)	Position	Direction	Proteins	Functions
Large	6368	1	17–6271	5'–3'	RNA dependent RNA polymerase (RdRp)	Replication and transcription
Medium	3378	2	19–1704	5'–3'	Glycoprotein Gn	Helps in assembly and formation of virus
			1705–3240	5'–3'	Glycoprotein Gs	Have immunogenic, neutralizing epitopes and important for virus infection
			29–910	5'–3'	Non-structural proteins (NSs)	Regulates host immune response, viral replication
Small	1744	2	1702 – 965	3'–5'	Nucleocapsid protein (NP)	Viral replication, transcription, forms intracellular inclusion bodies, packages genomic RNA into ribonucleoproteins

Liaoning. In between 2011 and 12, around 2047 cases has been reported in China including 129 deaths from 206 counties of eastern and central China. Most of the cases are from rural areas like mountainous or hilly areas [27]. The serological surveillance has reported that 1.0–3.8 % population of hilly regions have SFTSV antibodies, which suggested the widely spread nature of SFTSV in china [18]. First case of SFTS in North Korea was reported in 2009 [28] and fatal case was also observed in South Korea in 2012 [13], along with six more cases with four deaths in 2013 [29]. Eleven cases with seven deaths have been also reported from Japan, in April, 2013 [30]. In USA the disease was firstly noticed in 2009, when two farmers with high fever, fatigue, diarrhoea, thrombocytopenia and leucopenia are admitted in hospitals of northwestern Missouri due to the bite of ticks [16]. Till now, there is no case of SFTSV infection in animals, but the blood from infected animals can be a potent source of infection [31]. So, animal doctors and slaughter house workers are at higher risk risk [32]. Total number of SFTS patients reported during 2013–2018, in South Korea, Japan and China (National Centre for Infectious Diseases) has been presented in Table 2 [33–36].

### Virus structure, mechanism and pathogenesis

Virions of SFTSV are spherical and enclosed with a membrane of polypeptide spikes 5–10 nm long. SFTSV lacks protein layer, which makes the bunyaviruses flexible. Ribonucleoprotein complexes (RNPs) provides packaging to viral RNAs, each complex contains viral RNA, which is enveloped by viral protein N and the RNPs of bunyaviruses often forms closed, circular-shaped loosely coiled

structures. RNA-dependent RNA polymerase (RdRp) of virus is also connected with RNP and forms threadlike structures. SFTSV N protein forms crystal ring-shaped hexameric structures to complete the process of RNA encapsidation and RNA binding. After infection of host cells by SFTSV, virus propagates inside the cytoplasm of host cell and the secretion of RNPs from SFTSV initiates the transcription catalysed by viral RdRp. Viral RNA replication assisted by protein synthesis leads to the production of complementary RNAs (cRNAs) and viral RNAs (vRNAs). All three segments (S, M and L) vary in replication i.e.,  $M > L > S$ . Then, the synthesized cRNAs and vRNAs gets packaged in RNP due to the interaction of viral protein N and RdRp. This newly formed RNPs are used for the synthesis of viral mRNA and protein [19]. The aetiology of SFTSV is not thoroughly understood, but according to the pathogenicity of bunyaviruses, SFTSV prevent the immune response of the host, which can be seen by intense virus replication along with failure of multiple organs. After examining the SFTSV patients, it was observed that CD3-positive and CD4-positive T lymphocytes, which contributes in the immune functioning are low in number than their normal concentration and amount of natural killer cells are increased mainly in acute phase and grievous SFTSV infection [37]. The inhibition of immune function favours the increase of secondary infection by provoking patient's health status. Immunoregulatory functions have been performed by natural killer cells by producing various cytokines, such as interferon  $\gamma$ , tumour necrosis factor (TNF)  $\alpha$ , interleukin 10 and granulocyte colony-stimulating factors (G-CSF). The amount of these cytokines is proportional to the severity of disease. Inflammatory cytokines also help in pathogenesis of viral diseases and some proinflammatory cytokines expresses at abnormal rate in cytokine pool, which shows the severe

**Table 2** Total number of SFTS patients reported during 2013–2018, in South Korea, Japan and China (National Centre for Infectious Diseases)

Year	South Korea		Japan		China		Common symptoms
	Total cases	Death	Total cases	Death	Total cases	Death	
2013	36	17	40	14	676	48	Severe fever
2014	55	18	61	16	1034	81	Gastrointestinal
2015	81	21	60	11	1304	68	Thrombocytopenia
2016	166	19	60	8	1306	57	leukopenia
2017	271	54	89	7	NA	NA	Increased liver enzymes
2018	259	0	0	0	NA	NA	Myalgia
References	Kim et al. (2019), Maslow et al. (2019)		Kobayashi et al. (2020)		National Centre for Infectious Diseases (Updated on June 2020)		Anorexia
Vector	Tick borne		Body fluids of ill animals		Ticks and Person to person transmission		Fatigue
Age groups	5 to 87 years (Median 61 years)						Chill

form of SFTS [38]. Innate immune system provide protection against virus by producing interferon  $\beta$ , but patients with SFTS lacks interferon  $\beta$ . All the transcription factors related to interferon  $\beta$  are upregulated moderately in SFTSV-infected monocytes, whereas upstreaming molecules like TNF-receptor-associated factors 3, 6 and antiviral signalling protein of mitochondria are either remains unaltered or decreased, which further inhibits the induction of interferon  $\beta$  [39]. Three different patterns have been shown by the unbalanced cytokines such as expression of interleukins 6 and 10, interleukin-1 receptor antagonist, G-CSF, interferon- $\gamma$ -inducible protein and monocyte chemotactic protein 1 is increased in more fatal cases of SFTS, than in nonfatal cases. Whereas PDGF (platelet-derived growth factor) and RANTES (regulated on activation and normally T-cell expressed) expression is low. During the convalescent phase all these cytokines returns to their normal values. The expression of interleukins 1 $\beta$  and 8 and inflammatory proteins 1 $\alpha$  and 1 $\beta$  of macrophage is also increased only in fatal cases as well as in convalescent phase of survivors [40]. These cytokines have play important role in virus load in serum and other associated clinical characteristics like monocyte chemotactic protein 1 and interleukin 8 are crucial in progressive kidney injury [41], interleukin-1 receptor antagonist and interleukin 6 are associated with severe form of nephropathia epidemica [42], monocyte chemotactic protein 1 and interferon- $\gamma$ -inducible protein produces inflammation of liver along with fibrosis [43], interleukin 8 have the capability to raise the permeability of capillaries [44]. Reduced level expression of RANTES associated with viral disease severity [45] and together with platelet-derived growth factor in SFTS patients is due to low number of platelets circulating in the blood [46]. Symptoms of fever

in SFTS patients are associated with increased TNF $\alpha$ , which further work on endothelium, promotes vasodilating substances, nitric oxide synthase and increasing vascular permeability [47]. Virus of SFTS attached to platelets, these are identified and eliminated by macrophages circulating in the spleen, which causes thrombocytopenia [48]. The major cells, where SFTSV can replicate is reticular cells, but can also multiply in other cells [18]. As SFTSV targets the multiple organs resulted in multiple organ failure. So, starting from acute phase having febrile illness, turns into multiple organ failure (severe form) and further leads to the death of patient (fatal form). SFTSV infects the B-cells lymphocytes, multiple lymphoid or nonlymphoid organs, such as blood, spleen, the liver, adrenal glands, intestine, heart, lungs, and kidneys in fatal human SFTS cases [49].

## Diagnosis

In the beginning the critical investigation of SFTSV is depends on various symptoms shown by patient and their clinical testing like fever, thrombocytopenia and elevated levels of liver enzymes. The interpretation of these disease symptoms is important for the patient's survival and to stop the further spreading of the disease. Epidemiological features also help in diagnosis and these includes geographical location, history of tick bite, living or working environments and epidemic seasons [50, 18], but as the symptoms of SFTS are not specific in every case, so to make them authentic their consent from laboratory is necessary. Sometimes multiple tests have to be conducted to diagnose SFTS haemorrhagic fever along with renal syndrome, dengue fever, thrombocytopenia purpura, typhoid,

leptospirosis, and human anaplasmosis [48]. Detailed confirmation of SFTSV disease needs anyone of mentioned prerequisite such as isolation of SFTSV from various sample of the patient and RNA or antibodies detection of SFTSV from the blood or serum of patient [51]. Isolation of virus can become the full proof of SFTSV infection and this virus affect only CPE on DH82 cells not on the Vero cells or Vero E6 cells in primary isolation, this may be the cause that's why isolation of SFTSV was failed in China [4, 50]. For the isolation of virus only biosafety level-3 labs should be used as suggested by National Health and Family Planning Commission [26]. The procedure of virus isolation although simple and requires 2–5 days, but there is either low or no cytopathic effect in virus, so electron microscope and molecular or serological protocols are required [2, 4, 52].

Isolation of virus is the commonly employed method in research institutions, but this takes lots of time, however remaining two methods are frequently used for clinical confirmation. Acute phase serum from patients after the two weeks of the disease can be used for the detection of viral RNA [51]. Amplification of viral nucleic acid (RNA) have been done using reverse transcription-PCR (RT-PCR), real-time PCR, reverse transcription loop-mediated isothermal amplification (RT-LAMP) and RT cross-priming amplification [53, 54]. All these amplification techniques work on the same principle i.e., extraction of viral RNA, reverse transcription and DNA amplification. Reverse transcription (RT) PCR method is very conspicuous, sentient and intense for presumptive laboratory diagnosis of SFTSV infection. Improvement in Reverse transcription (RT) PCR generated Automated RT-PCR, which is contamination free and have high specificity or sensitivity than conventional RT-PCR [53, 55]. On the other hand, real-time PCR is also specific and sensitive in nature, but RT-LAMP is very ingenious and inexpensive. In reality, the efficiency of amplification targets the distinct portions of SFTSV varies, but amplification target the S segment is very sensitive RT-PCR assay [56]. Multiplex real-time (RT) PCR can easily explore the SFTSV, hantaan virus, seoul virus and dengue virus [57]. Reverse transcription loop-mediated isothermal amplification (RT-LAMP) and RT cross-priming amplification are the types of isothermal amplification methods and have been designed to diagnose SFTSV RNA. Currently, for the rapid detection of SFTSV, RT-cross-priming amplification (RT-CPA) combined with vertical-flow visualization strip has been developed, which is very easy, instrument free and practicable in point-of-care testing [58]. Even though SFTSV infection produces high viral titre, which assist the isolation of virus and ascertain it at molecular level, but time period is very less usually 1–6 days after the onset of infection. Special antibodies related to SFTSV are IgG and

IgM, which can be detected even after 7 days of disease onset. IgG and IgM can be detected up to 5 years and 4 months respectively, after infection as described by National Health and Family Planning Commission [26]. Various serological assays like serum neutralisation test, indirect immunofluorescence assay, double antigen sandwich ELISA, in-house mac-ELISA and indirect ELISA are used to detect SFTSV related antibodies from serum samples. To detect the virus specific antibodies indirect immune-fluorescence assay is also used, which confirm the onset and examination of viral infection [3, 59]. Neutralisation test is just like the standard gold, but this test is costly, laborious, need biosafety labs and most prominently requires modifications in live virus. ELISA assays are cheap, less time requiring and recombinant nucleoprotein-based double-antigen sandwich ELISA has been used for the detection of SFTSV antibodies in people and animals. This is more sensitive than neutralisation test (no cross-reaction between SFTSV and dengue virus or hantavirus was found) [60].

## Treatment

Currently, no treatment or vaccines are available for SFSTSV disease. Other backup treatments such as plasma, platelet, granulocyte colony stimulating factor (GCSF), recombinant human interleukin 11 and gamma globulin are the important segment of case treatment [61]. At the same time, some precautions need to be taken in order to protect water, balance of electrolytes and treatment of complications is necessary. For the treatment of Crimean-Congo Haemorrhagic Fever (CCHF) infections and haemorrhagic fever with renal syndrome, Ribavirin has been found to be effective, but due to insufficient data it is not appreciable to apply this medication for the treatment of SFTS patients [62]. For the treatment of SFTS patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS) use of corticosteroids is under dispute, due to the suppression of cytokine storm and multiple cytokines produced in acute phase of SFTSV infection are also associated with severe form of infection. Antibodies also play important role in the treatment of several viral infections including Hantaan virus [63], cytomegalovirus [64] and rabies virus [65] by using various mechanisms like neutralisation, complement activation, antibody-dependent cellular cytotoxicity and opsonisation [66]. Neutralising antibodies has tendency to lowers viral load, transmission, which further decrease the chances of getting severe form of disease. Similarly, human monoclonal antibody 4–5, isolated from phage antibody library have neutralising action for SFTSV in laboratory and can be used to prevent the spreading of disease to other peoples,



who are at high risk like staff of hospital and patient's relatives [67].

## Conclusions

SFTS is a severe form of disease emerging as worldwide pandemic including China, Japan, South Korea, USA and Taiwan along with the main epidemic region i.e., Central China. Due to the very fast changes in SFTSV using gene mutation, reassortment and recombination in tick vectors and animal hosts, it poses a great threat to the health of world's population. The current research about the vaccination and epidemiology should need to be refined to understand the pandemic globally, as only the identification and diagnosis of SFTS related virus has been done in the last few years. At present, the major approaches to control the SFTSV are either to stop the viral transmission or to protect the easily vulnerable population from tick bites, avoiding direct contact of infection and also to use personal protective devices for SFTS patients. So, the weather conditions, mode of transmission and creation of new therapeutics like vaccines and drugs are the main areas of forthcoming research.

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