



REVIEW

Current status of severe fever with thrombocytopenia syndrome in China

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Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by SFTS virus (SFTSV). SFTSV is associated with a high mortality rate and has been reported in China, South Korea and Japan. SFTSV undergoes rapid changes owing to evolution, gene mutations, and reassortment between different strains of SFTSV. In this review, we summarize the recent cases and general properties of SFTS, focusing on the epidemiology, genetic diversity, clinical features, and diagnostics of SFTSV in China. From 2010 to October 2016, SFTS cases were reported in 23 provinces of China, with increased numbers yearly. Infection and death cases are mainly found in central China, where the *Haemaphysalis longicornis* ticks are spread. The national average mortality rate of SFTS infection was 5.3%, with higher risk to elder people. The main epidemic period was from May to July, with a peak in May. Thus, SFTS reminds a significant public health problem, and development of prophylactic vaccines and effective antiviral drugs will be highly needed.

KEYWORDS severe fever with thrombocytopenia syndrome (SFTS); severe fever with thrombocytopenia syndrome virus (SFTSV); *Bunyaviridae*

INTRODUCTION

Since 2009, a newly emerging infectious disease has been brought into focus of public health in China (Yu et al., 2011). The clinical manifestations of this disease included fever, thrombocytopenia, and leukocytopenia, and mortality rates ranging from 6% to 30% were reported (Yu et al., 2011; Li et al., 2014; Park et al., 2014; Chang

et al., 2013). Accordingly, this disease was designated as severe fever with thrombocytopenia syndrome (SFTS). Although its clinical manifestations resembled the human anaplasmosis (Zhang et al., 2008), neither DNA nor antibodies against human anaplasmosis could be detected in blood samples from the majority of the patients with SFTS. The pathogen responsible for this infectious disease was identified as a novel phlebovirus of *Bunyaviridae* family, which was initially given different names, including SFTS virus (SFTSV), Dabie Mountain virus (DBM virus), Henan fever virus, or Huaiyangshan virus (HYSV) (Yu et al., 2011; Stone, 2010; Zhang et al., 2012; Xu et al., 2011); the virus was finally named as SFTSV (Yu et al., 2011). Thereafter, similar viruses have also been reported in Japan, Korea, and the United States of America (USA) (Takahashi et al., 2014; Kim et al., 2013; McMullan et al., 2012). In addition, other newly emerged phleboviruses were isolated from patients in USA in 2012, including the Heartland virus and a new

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phlebovirus, which was genetically similar to SFTSV (McMullan et al., 2012).

Electron microscopy has shown that SFTSV particles are spherical and measured 80–100 nm in diameter (Yu et al., 2011). The virions possess a unit of the membrane envelope from which polypeptide spikes (5–10 nm long) protrude (Yu et al., 2011). Although the transmission hosts and vectors of SFTSV remain unclear, *Haemaphysalis longicornis* is considered the most likely transmission vector (Luo et al., 2015). Several studies have shown that SFTSV can undergo tachytely evolution via genetic mutation and recombination (Ding et al., 2013; He et al., 2012). Moreover, microbial evolution and social and environmental factors seriously affect these emerging and re-emerging infectious diseases. Thus, SFTS is still recognized as a major threat to public health.

GENOME, TRANSMISSION VECTORS AND HOSTS OF SFTSV

The genome of SFTSV is a single-stranded negative-sense RNA and comprises three segments (S, M, L). The S segment, which contains 1744 nucleotides of ambisense RNA, harbors two nonoverlapping open reading frames (ORFs) encoding nucleocapsid protein (NP) and nonstructural proteins (NSs), in opposite directions, separated by a 62-bp intergenic region. NP is involved in viral replication and transcription and can form intracellular inclusion bodies in infected THP-1 cells (Jin et al., 2016). The nucleoprotein encapsidates and packages genomic RNA into ribonucleoprotein complexes to protect the RNA from degradation by exogenous nucleases or immune system components in the host cell (Sun et al., 2012). NSs regulate host innate immune responses and

suppress interferon (IFN)- β responses (Wu et al., 2014). Moreover, NSs interact with one another and with NP and are associated with viral RNA in infected cells, suggesting that NSs may be directly involved in viral replication (Wu et al., 2014). Additionally, some studies have shown that synaptogyrin-2 can promote the replication of SFTSV through interacting with viral NS protein (Sun et al., 2016). Both the nucleoprotein and the NS protein of SFTSV prevent the antiviral immune response in host cells by blocking the activation of IFN- β and nuclear factor κ B signaling (Qu et al., 2012) (Table 1).

The M segment contains 3378 nucleotides, encoding a 1073-amino acid glycoprotein (Gn and Gs) precursor, which contains immunogenic, protective, or neutralizing epitopes (Wang et al., 2012). Plegge and colleagues provided evidence showing that processing of the SFTSV Gn/Gc polyprotein is critical for viral infectivity and requires an internal Gc signal peptide (Plegge et al., 2016). A neutralizing monoclonal antibody (anti-SFTSV) was found to bind a linear epitope in the ectodomain of glycoprotein Gn of SFTSV. Its role is known to block the interaction between the Gn protein and the cellular receptor (Guo et al., 2013) (Table 1).

The L segment, which contains 6368 nucleotides, has one ORF encoding an RNA-dependent RNA polymerase (RdRp) with 2084 amino acids. RdRp facilitates the replication and transcription of the viral RNA. Phylogenetic analysis of SFTSV sequences indicated that this virus represents a new independent branch within Phlebovirus, roughly equidistant from the already established sandfly fever and Uukuniemi viruses (Richard et al., 2014) (Table 1).

Zhang and Xu (2016) reported that the status of SFTSV infection from domestic and wild animals was related to transmission from different tick species. They proposed a

Table 1. Genomic characteristics of SFTSV*

Segment	bp	ORF	Position	Direction	Encoded protein	Function
L	6368	1	17–6271	5'–3'	RdRp	Replication, transcription, and viral cap-dependent transcription.
M	3378	2	19–1704	5'–3'	Gn	Virus assembly, formation of virus particles, immunogenicity, neutralizing or protective epitopes, viral infectivity, precursor of glycoprotein.
			1705–3240	5'–3'	Gc	
			29–910	5'–3'	NSs	
S	1744	2	1702–965	3'–5'	NP	Host innate immune responses, formation of viral inclusion bodies, formation of viroplasm-like structures, virus replication, transcription, replication, virion assembly, formation of RNP, viral RNA encapsidation.

Note: *With references to: Liu et al., 2014; Lei et al., 2015; Li et al., 2011

tick and migratory bird model for SFTSV transmission and a hypothesis for the local transmission and wide dissemination of SFTSV by combining infection data with host and vector ecology data. They also showed that the risk of infection is reduced if the animals and vector populations are monitored (Zhang and Xu, 2016).

The distribution of *H. longicornis* ticks and the migratory routes of four wild fowl across China, South Korea, and Japan are coincident. Therefore, a tick and migratory bird model for the transmission of the SFTSV was advocated (Guan *et al.*, 2016; Zhang and Xu, 2016). Zhang *et al.* (2012) sampled 613 adult ticks, including 88.09% *H. longicornis* and 11.91% *Boophilus microplus*, which were collected from domestic animals around the villages in four counties (Dawu, Zengdu, Xinzhou, and Xinxian) of Hubei and Henan Provinces in central China, where confirmed patients lived in the nearby districts. Among these samples, the positive ratios of SFTSV were 4.93% in *H. longicornis* and 0.613% in *R. microplus* tick pools (Zhang *et al.*, 2012). However, *H. longicornis* ticks with SFTSV-positive were only discovered in SFTSV endemic places, whereas SFTSV-positive *R. microplus* ticks were detected in both endemic and non-endemic regions from some counties in Henan and Hubei Provinces. In South Korea, *H. longicornis* (90.8%) ticks were dominant, followed by *H. flava* (8.8%), *Ixodes nipponensis* (0.3%), and *I. persulcatus* (0.05%) (Park *et al.*, 2014). The positive ticks were distributed in the country, and an SFTSV-infection case was confirmed in Gangwon Province, South Korea, where positive ticks had been previously discovered (Kim *et al.*, 2013; Park *et al.*, 2014; Zhang *et al.*, 2016). Based on these surveys, *H. longicornis* was speculated to be the major vector of SFTSV. However, SFTSV-positive arthropods may be additional vectors of SFTSV or may obtain the virus from the blood of SFTSV-infected animals (Niu *et al.*, 2013). Therefore, further studies of arthropods are needed to determine whether they act as vectors of SFTSV.

Animal hosts of SFTSV are still unclear. SFTSV has a wide host range and infects several domesticated animals in endemic areas. In a seroepidemiological survey of domestic animals in Jiangsu Province, researchers collected samples from goats (57%), cattle (32%), dogs (6%), pigs (5%), and chickens (1%) (Liu *et al.*, 2014) and found that the seroprevalence of SFTSV was 69.5% for sheep, 60.5% for cattle, 37.9% for dogs, 3.1% for pigs, and 47.4% for chickens in Shandong Province (Niu *et al.*, 2013). Moreover, rodents have seropositive for SFTSV in Jiangsu Province, with 6.9% seroprevalence in wild rodents and 7.87% in house rodents (Ge *et al.*, 2012), including house shrews (Liu *et al.*, 2013), mouse (*Mus musculus*), rat (*Rattus norvegicus*) (Yun *et al.*, 2015; Ge *et al.*, 2012), and field mouse (*Apodemus agrarius*) (Ni *et al.*, 2015). In the USA, a seroepidemiological survey

showed that the positive rates of anti-Heartland virus antibodies in samples from cattle, sheep, goats, deer, and elk were 16%, 13%, 11%, 12%, and 18%, respectively (Li *et al.*, 2014). SFTSV viral RNAs were also tested in animal species, but typically at very low levels, and ranged from 1.7% to 5.3% (Niu *et al.*, 2011). Therefore, both domestic and captive farmed animals in some areas may be exposed to SFTSV, or Heartland virus (McMullan *et al.*, 2012). Many wild animals, such as deer, weasels, hedgehogs, brushtail possums, and some bird species, are regular hosts of ticks (Yun *et al.*, 2015).

Although there is no evidence that the virus can cause disease in animals, blood from subclinically infected animals could be a source of infection (Mishra *et al.*, 2011). Bao and colleagues reported a family in which SFTSV underwent person-to-person transmission through the blood (Bao *et al.*, 2011). Subsequently, a cluster of human-to-human transmission cases of SFTSV was reported in Shandong, Jiangsu, and Anhui Provinces in China; this transmission may have been related to direct contact with the blood of patients or aerosol through the mucosa (Jiang *et al.*, 2015; Gong *et al.*, 2015). However, the mechanisms of this person-to-person transmission event are still unclear. Therefore, veterinarians and slaughterhouse workers may be at high risk of SFTSV infection.

EPIDEMIOLOGY AND GENETIC DIVERSITY OF SFTSV

SFTS infectious disease was first reported in rural regions in Hubei and Henan Province of central China in March and July of 2009 (Zhang *et al.*, 2013). However, the first case of SFTS in Dingyuan County, Anhui Province was reported in September of 2006 (Liu *et al.*, 2012). From 2010 to October 2016, SFTS cases were reported in 23 provinces and experimentally confirmed in 18 provinces by the Chinese Disease Prevention and Control Information System (Figure 1). The highest numbers of reported cases occurred in Henan (37%), Shandong (26.6%), Anhui (14%), and Hubei (12.6%), and 97.7% of SFTS cases were distributed mainly in individuals of age 25–80 years. Outbreaks of SFTS occurred mostly from March to November, and the main epidemic period was from May to July, with a peak in May (Figure 2).

From 2013 to October 2016, SFTS cases in China significantly increased gradually; 7419 cases occurred in China, with 355 deaths, mainly distributed in eastern and central China. An annual report of SFTS cases from Anhui, Henan, Hubei, and Shandong Provinces showed that there were over 1000 cases since 2014. The national average mortality rate of SFTS infection in China was 5.3% from 2010 to October 2016 (Figure 3).

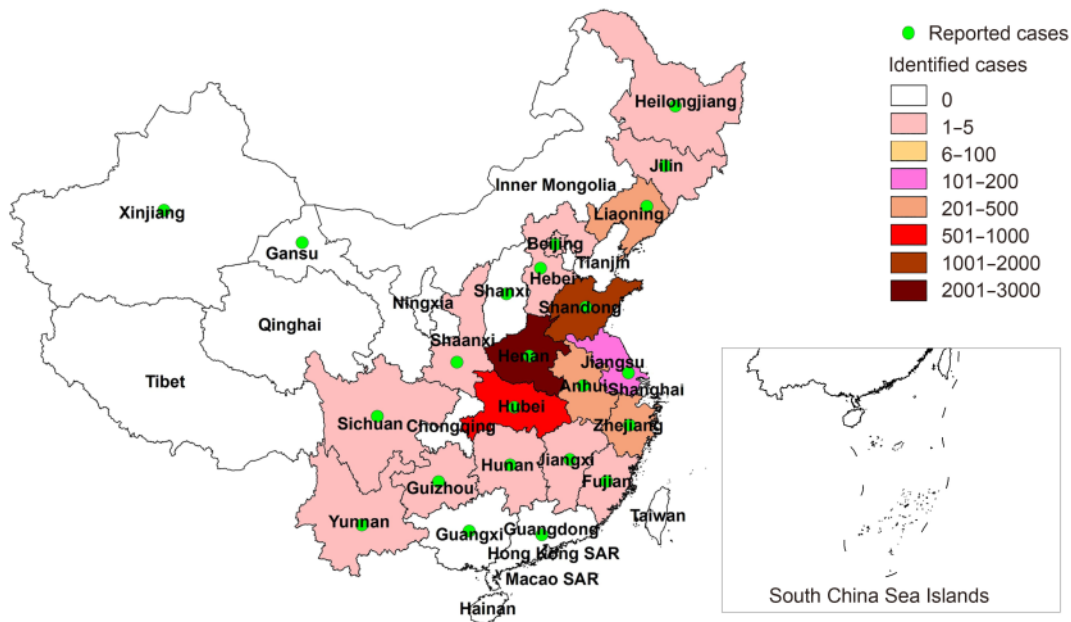


Figure 1. SFTS reported and confirmed cases in China (Data from the Chinese Disease Prevention and Control Information System, 2010 to October 2016)

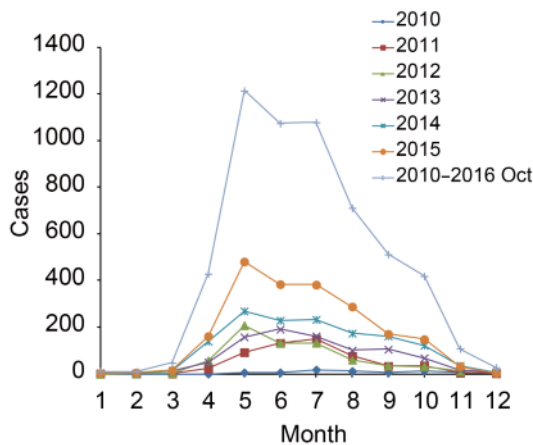


Figure 2. Monthly distributions of SFTS cases from 2010 to October 2016 in China.

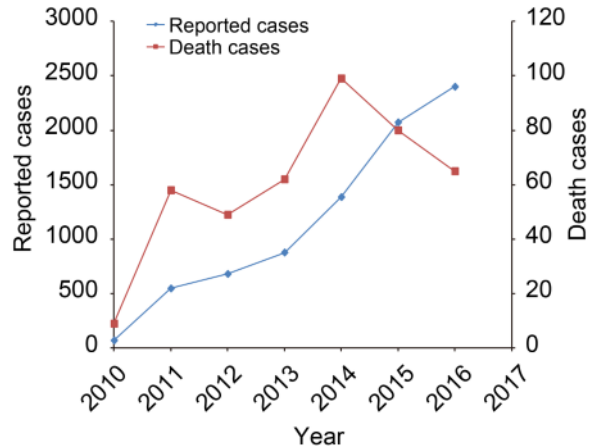


Figure 3. SFTS reported cases and death cases in China from 2010 to October 2016.

The female-to-male ratio of SFTSV infection is 1.16:1. The ages of patients with SFTS range from 5 to 87 years (median 61 years) (Liu et al., 2014; Ma et al., 2015), and the annual incidence increased with age (Ma et al., 2015). Notably, farmers in endemic areas are at a higher risk (87.6%), and almost 97% of patients with SFTS are farmers residing in wooded and hilly areas (Liu et al., 2014; Ma et al., 2015). Among patients, it was reported that 21.85% recalled for a tick bite within two weeks; the other patients did not memorize (Xu et al., 2011). The latent period is generally 7–14 days (average of 9 days) (Gai et al., 2012). An epidemiological survey showed

that about 1–3% of the population is infected with SFTSV in popular areas. SFTSV mainly infects older individuals, and death is most frequent in patients older than 50 years (79%), suggesting that SFTSV infects people with low immunity. Indeed, age may be a key risk factor for death and hospitalization in patients with SFTS (Lei et al., 2015).

SFTSV has broad genetic diversity. Because of the absence of a proofreading function in the viral RNA replication and transcription processes, SFTSV shows high mutation rates during replication (Lam et al., 2013), which may provide a basis for its genetic diversity (Zhang et al.,

2011). Interestingly, the evolutionary rates are different from three segments of SFTSV. The highest and lowest evolutionary rates are found in the S and L segments, respectively (Liu *et al.*, 2016). Using the average evolutionary rate, researchers showed that SFTSV was present 20–87 years ago in the Dabie Mountains, China and spread to some other places of China, Japan, and South Korea (Liu *et al.*, 2016). Moreover, the virus underwent frequent selection through constant reassortment (Liu *et al.*, 2016). Phylogenetic analysis of SFTSV strains isolated from 2009 to 2016 suggested that SFTSV strains could be divided into six sublineages (A–F; [Figure 4A–C](#)). The strains from South Korea were divided into four sublineages (A, B, D, and F), and the Japanese strains were divided in three sublineages (C, D, and F). The strains belonging to lineage A came from China, including Hubei, Henan, Jiangsu, Shandong and Liaoning Provinces except for three strains (KASJH/South Korea/2014, Ganwon/South Korea/2012, and KR 1020150042419-A/2). We also identified segment reassortment as the same strains belonged to different lineages. The AHL strain ascribed to lineage C in segments M and L, but to lineage B in segment S. Similarly, the S and L segments of the LN2012-14 strain ascribed to the B lineage, whereas the M segment of LN2012-14 ascribed to the A lineage. Phylogenetic trees manifested that the Zhejiang/01/2011 strain was closely related to strains from South Korea and Japan. These researches showed that human behavior pattern and various activities may provide an important role for SFTSV cyclic transmission among China, Japan, and South Korea.

A sublineage of lineage I has been shown to contain a unique M segment recombined from two of three SFTSV lineages (He *et al.*, 2012). Ding *et al.* discovered that the S segment with two SFTSV strains had a different recombined origin from L and M (Ding *et al.*, 2013). Many studies also found that the viruses could experience rapid evolution via gene mutations and recombination (He *et al.*, 2012). Moreover, although homologous recombination is known to be rare in negative-strand RNA viruses, intragenic recombination may have an important role in the rapid evolution. In segmented-genome viruses, reassortment may be an efficient process, resulting in critical adaptations, recombinations, and mutations in a single step. This could also allow major changes in adaptive space, leading to alterations in host tropism.

Reassortment of genome segments has been observed within vertebrate animal, plant, and arthropod hosts in the *Bunyaviridae* family (Webster *et al.*, 2011). However, it is unclear whether reassortment can affect the rapid evolution of SFTSV. These studies may improve our knowledge and understanding of the molecular mechanisms of viral genetic diversity and interspecies transmission.

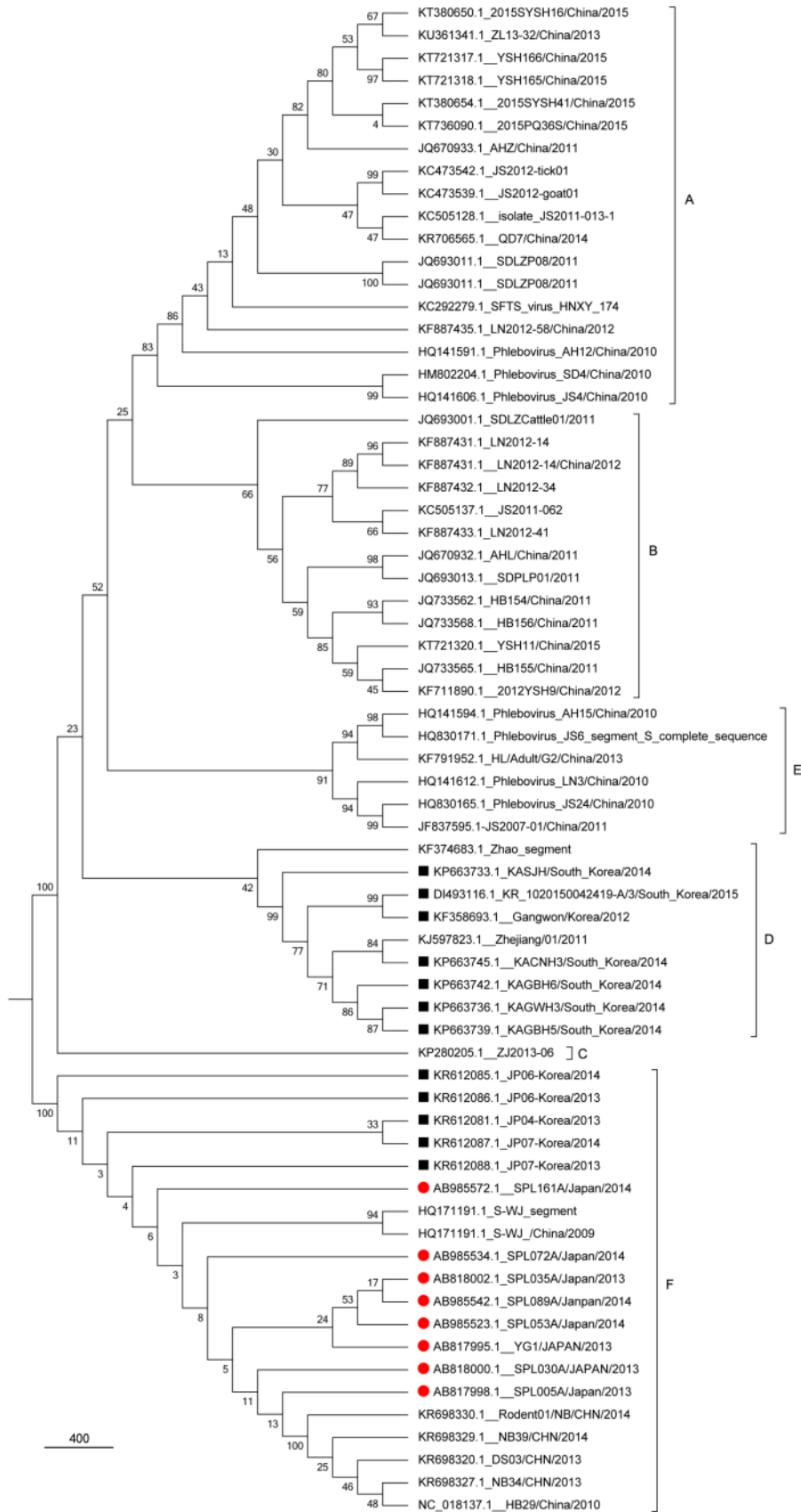
CLINICAL FEATURES AND DIAGNOSTIC METHODS

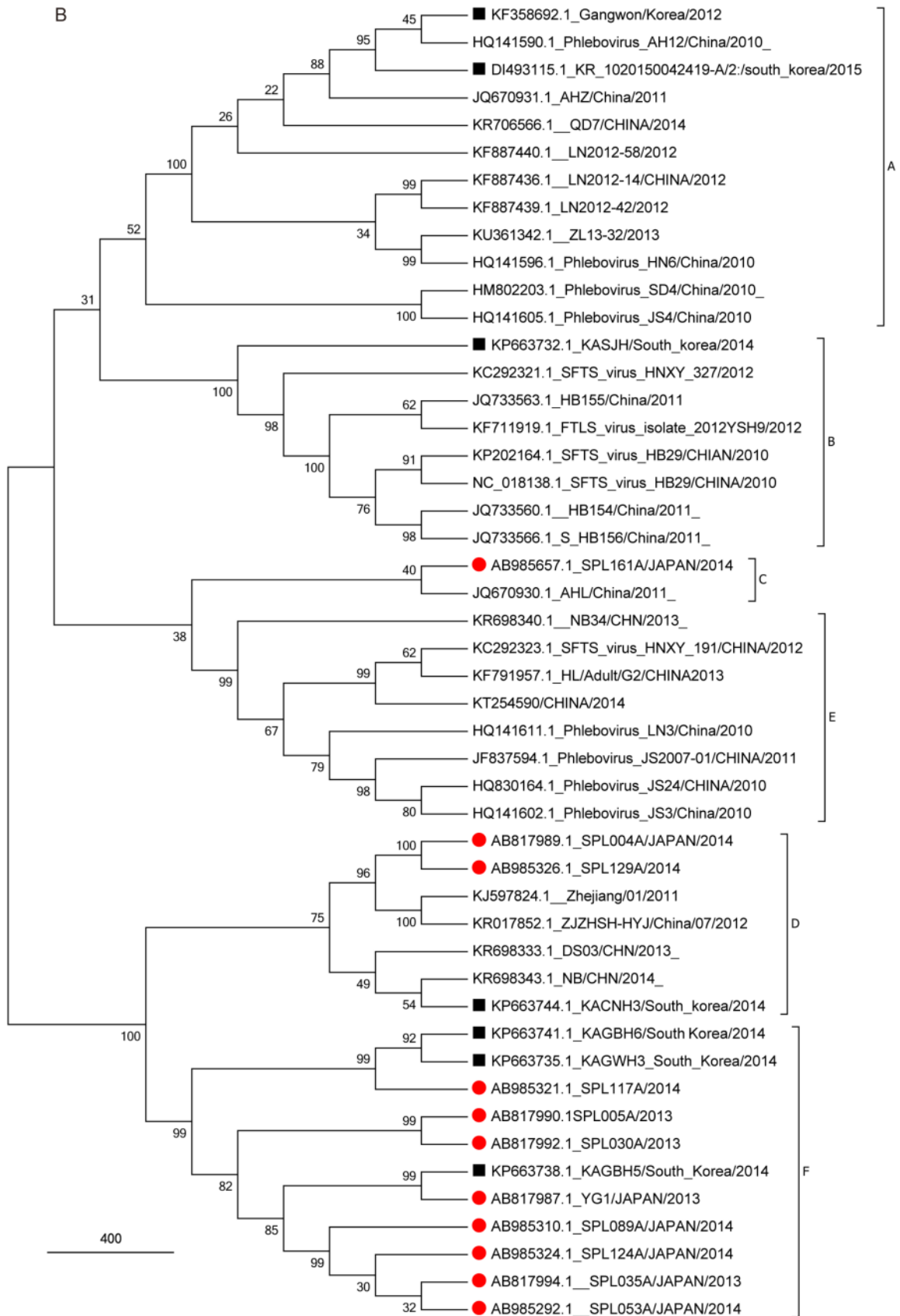
The clinical manifestation of SFTS is nonspecific and difficult to distinguish from those of human granulocytic anaplasmosis (HGA), leptospirosis, and hemorrhagic fever with renal syndrome (HFRS) (Zhang and Xu, 2016). The major clinical symptoms of SFTS include fever, gastrointestinal symptoms, myalgia, hemorrhage in the mouth, and regional lymphadenopathy. In addition, proteinuria (84%), hematuria (59%), dizziness (23.52%), headache (19.2%), and chills (10.29%) are also common symptoms in SFTSV-infected patients (Yu *et al.*, 2011). Moreover, transient myocardial dysfunction and encephalopathy can occur beyond the major clinical symptoms of SFTS (Takeshi *et al.*, 2016; Cui *et al.*, 2015). The main clinical manifestations on laboratory detection include thrombocytopenia (95%) and leukocytopenia (86%). We also listed our data for laboratory-confirmed clinical symptoms in SFTSV-infected patients ([Table 2](#)). In general, the decreased population and dysfunction of monocytes in patients with acute-phase SFTS patients may lead to more severe disease (Cheng *et al.*, 2016). Liu and colleagues found clinical indicators that were associated with seriously outcomes; however, they found no proof to indicate the use of ribavirin in the treatment for SFTSV infection (Liu *et al.*, 2013).

SFTSV strains have been isolated using DH82, Vero, or Vero E6 cells. After infection with SFTSV, the DH82 cells attached to the culture flask. However, early detection of SFTSV infection is crucial for improving the survival rates and prevention of viral transmission. Early detection is based on the epidemiological characteristics of the disease, such as epidemic season, geographical location, clinical symptoms, history of tick bite, and laboratory examination. If the clinical manifestations of SFTSV infection are nonspecific, laboratory confirmation is essential.

A lot of methods were used to amplify viral RNA, including reverse transcription polymerase chain reaction (RT-PCR) and RT-loop-mediated isothermal amplification (RT-LAMP) (Zhang *et al.*, 2011; Webster *et al.*, 2011; Yun *et al.*, 2014). Amplification of the segment S is the most sensitive RT-PCR assay (Chi *et al.*, 2012; Cui *et al.*, 2012; Sun *et al.*, 2012; Yang *et al.*, 2012). The RT-PCR primers for the viral S segment are more sensitive than those for the L segment, which may be related to the lengths of the primers (Wen *et al.*, 2014). Quantitative real-time PCR (qRT-PCR) for SFTSV infection has a lower contamination rate and higher sensitivity and specificity. Moreover, this method is also quicker than conventional one-step RT-PCR, and the identification of the SFTSV genome in the blood using qRT-PCR during the acute phase of SFTSV infection may be used as an indica-

A





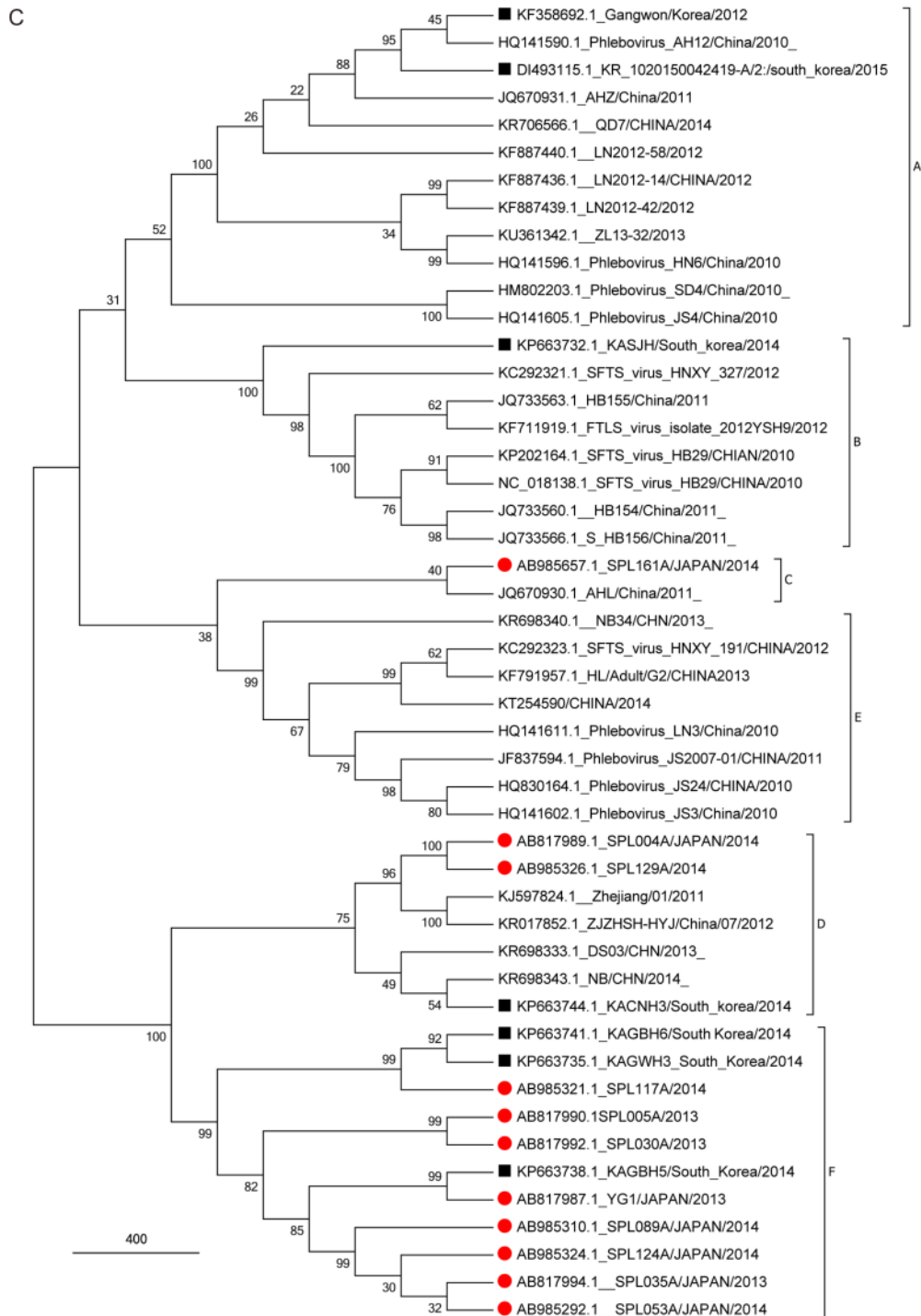


Figure 4. Phylogenetic analysis of the whole S (A), M (B), and L (C) segment sequences of SFTSV strains. The maximum likelihood trees were constructed using MEGA 6.06. GenBank accession numbers and strains are labeled on each branch. SFTSV was classified into six lineages (A–F) according to the genome segments. Red represents the isolates from Japan, and the black framing represents isolates from South Korea.

tor to forecast the outcomes of SFTS (Yoshikawa et al., 2016; Li et al., 2013). Li and colleagues (2016) reported that rapid diagnosis of SFTSV by AllGlo probe-based

real-time RT-PCR showed high sensitivity, specificity, and stability. SFTSV was detected by RT-nested PCR to amplify the S or L segment of the SFTS viral RNA gene

Table 2. Clinical symptoms of patients with laboratory confirmed disease in Hubei Province, 2011

Symptoms	Patients with symptoms (N = 68) No. (%)
Fever	68 (100.00)
Malaise	49 (72.06)
Fatigue	48 (70.59)
Anorexia	39 (57.35)
Nausea	21 (30.88)
Diarrhea	19 (27.94)
Vomiting	17 (25.00)
Dizziness	16 (23.53)
Headache	13 (19.12)
Throat congestion	13 (19.12)
Cough	12 (17.65)
Myalgia	8 (11.76)
Chill	7 (10.29)
Lymphadenopathy	7 (10.29)

(Wen *et al.*, 2011). Furthermore, a multiplex real-time RT-PCR assay could simultaneously detect four viral hemorrhagic fever pathogens (SFTSV, Hantaan virus, Seoul virus, and dengue virus) (Li *et al.*, 2013). A simple technique that incorporated RT-cross-priming amplification (RT-CPA) connected to a vertical-flow visualization strip was used to rapidly detect SFTSV infection (Chi *et al.*, 2012) (Table 3).

Specific antibodies to SFTSV are detectable from about 1 week after disease onset, and SFTSV-specific IgG antibodies can surge to peak levels by 6 months, remaining detectable for at least 5 years; however, SFTSV-specific IgM antibodies can surge to peak levels by 4 weeks and last for about 1 year after infection (Li, 2011; Lu *et al.*, 2015). Patients with SFTS show apparent loss of T, B, and natural killer (NK) cells during the first week of infection, which are rapidly recovered to standard levels. A markedly declined level of humoral immunity was observed simultaneously in patients with severe SFTS, particularly during the acute phase of the SFTSV infection (Lu *et al.*, 2015). SFTSV-specific IgG, IgM and total antibodies have been detected by in-house Mac-enzyme-linked immunosorbent assays (ELISAs), indirect ELISA assays, double antigen sandwich

Table 3. Comparison of various detection methods for SFTSV

Category	Detection methods	Minimum detection limit	Sensitivity	Specificity
SFTSV S segment	qRT-PCR (TaqMan)	10 copies/ μ L	98.6–100%	99–100%
SFTSV L segment	qRT-PCR (TaqMan)	5×10 copies/ μ L	NA	NA
SFTSV M segment	qRT-PCR (TaqMan)	2×10^2 copies/mL	NA	NA
SFTSV M segment	RT-LAMP	10 copies/test	NA	100%
SFTSV M segment	RT-CPA-VF	100 copies/test	94.1%	100%
SFTSV S segment	qRT-PCR (AllGlo)	1×10^3 copies/mL	NA	NA
SFTSV S&L segment	Nest RT-PCR	10 copies/ μ L	NA	55%
SFTSV antibody & RNA	ELISA+Nest RT-PCR	NA	NA	86%
SFTSV antibody	IFA	NA	95.6%	74.29%
SFTSV IgG	MLBI	NA	90.7%	66.67–100%
SFTSV total antibody	ELISA	NA	100%	99.57–100%
SFTSV RNA	Luminex	10^2 copies/ μ L	NA	NA
SFTSV IgM	ELISA	NA	90.59–96.67%	59–100%
SFTSV IgM	ICA	NA	98.4–100%	NA
SFTSV antigen	ELISA	0.117 mg	NA	NA
SFTSV RNA	qRT-PCR(MGB)	10 copies/ μ L	100%	99%
SFTSV IgG	ICA	NA	96.7–98.6%	NA

Note: NA, not applicable; ICA, immunochromatographic assay; RT-LAMP, reverse transcription-loop-mediated isothermal amplification; RT-CPA, reverse transcription-cross-priming amplification; MLBI, multiplexed luminex-based immunoassay; VF, vertical flow; MGB, minor-groove-binding (Yu *et al.*, 2015; Wang *et al.*, 2014; Cui *et al.*, 2012; Wu *et al.*, 2014; Li *et al.*, 2013; Wen *et al.*, 2011).

ELISAs, and immunofluorescence assays (IFAs) (Li et al., 2013; Lei et al., 2015; Jiao et al., 2011). These methods have higher sensitivity than neutralization tests, and no crossreaction among SFTSV, hantavirus, and dengue virus was observed (Jiao et al., 2011). Immunochromatographic assays (ICAs) may be suitable measure for rapid, on-site, and inexpensive detection SFTSV infection, and commercially available kits show good specificity for the diagnosis of SFTSV-specific IgM and IgG with no cross-reaction with positive serum samples in patients with infections of Japanese encephalitis virus, Dengue virus, Hantavirus, hepatitis C virus (HCV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), or *Mycobacterium tuberculosis* (Wang et al., 2014). Serum neutralization tests of SFTSV have been reported, e.g., 50% plaque reduction neutralization tests (PRNT50) and microtiter neutralization tests. Huang and colleagues (Huang et al., 2016) identified that hospitalized patients with SFTSV infection maintained neutralizing antibodies to SFTSV for 4 years after diagnosis.

CONCLUSION

SFTS is a severe disease found in many countries worldwide, including China, Japan, and South Korea, with central China as the main epidemic region. However, SFTSV is undergoing rapid evolution owing to gene mutation, reassortment, and recombination in tick vectors and animal hosts. The wide epidemic, rapid evolution, cross-species transmission, and the higher case fatality rates have made SFTS a significant public health problem. The role of climatic factors, cross-species transmission, and the development of vaccines and new drugs may be hotspots of future research.

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COMPLIANCE WITH ETHICS GUIDELINES

The authors declare that they have no conflicts of interest. The study was approved by the Ethics Committees of the Centers for Disease Control and Prevention of Hubei Province. Written consents were obtained from all participants involved in the study.

REFERENCES

- Bao CJ, Guo XL, Qi X, Hu JL, Zhou MH, Varma JK, Cui LB, Yang HT, Jiao YJ, Klena JD, et al. 2011. A family cluster of infections by a newly recognized bunyavirus in eastern China, 2007: further evidence of person-to-person transmission. *Clin Infect Dis*, 53:1208–1214.
- Chang MS, Woo JH. 2013. Severe Fever with Thrombocytopenia Syndrome: Tick-Mediated Viral Disease. *J Korean Med Sci*, 28: 795–796.
- Chi YY, Zhai SY, Wen HL, Wang L. 2012. SFTSV RNA detection in seropositive patients. *J Shandong Univ (Health Sci)*, 50: 118–121. (In Chinese)
- Cui L, Ge Y, Qi X, Xu G, Li H, Zhao K, Wu B, Shi Z, Guo X, Hu L, et al. 2012. Detection of severe fever with thrombocytopenia syndrome virus by reverse transcription-cross-priming amplification coupled with vertical flow visualization. *J Clin Microbiol*, 50: 3881–3885.
- Cui N, Liu R, Lu QB, Wang LY, Qin SL, Yang ZD, Zhuang L, Liu K, Li H, Zhang XA, Hu JG, Wang JY, Liu W, Cao WC. 2015. Severe fever with thrombocytopenia syndrome bunyavirus-related human encephalitis. *J Infect*, 70: 52–59.
- Peng C, Wang H, Zhang W, Zheng X, Tong Q, Jie S, Yang D, Zhou Y. 2016. Decreased monocyte subsets and TLR4-mediated functions in patients with acute fever with thrombocytopenia syndrome (SFTS). *Int J Infect Dis*, 43: 37–42.
- Ding NZ, Luo ZF, Niu DD, Ji W, Kang XH, Cai SS, Xu DS, Wang QW, He CQ. 2013. Identification of two severe fever with thrombocytopenia syndrome virus strains originating from reassortment. *Virus Res*, 178: 543–546.
- Gai ZT, Zhang Y, Liang MF, Jin C, Zhang S, Zhu CB, Li C, Li XY, Zhang QF, Bian PF, et al. 2012. Clinical progress and risk factors for death in severe fever with thrombocytopenia syndrome patients. *J Infect Dis*, 206: 1095–1102.
- Ge HM, Wang QK, Li ZF, et al. 2012. Survey of SFTSV carrying situation in rodents in SFTS epidemic area of Donghai County. *Jiangsu Prevent Med*, 23: 16–18. (In Chinese)
- Gong Z, Gu S, Zhang Y, Sun J, Wu X, Ling F, Shi W, Zhang P, Li D, Mao H, et al. 2015. Probable aerosol transmission of severe fever with thrombocytopenia syndrome virus in southeastern China. *Clin Microbiol Infect*, 21: 1115–1120.
- Guo X, Zhang L, Zhang W, Chi Y, Zeng X, Li X, Qi X, Jin Q, Zhang X, Huang M, et al. 2013. Human antibody neutralizes severe Fever with thrombocytopenia syndrome virus, an emerging hemorrhagic Fever virus. *Clin Vaccine Immunol*, 20: 1426–1432.
- Guan Y, Drosten C. 2016. Editorial overview: Emerging viruses: Interspecies transmission. *Curr Opin Virol*, 16: v-vi.
- He CQ, Ding NZ. 2012. Discovery of severe fever with thrombocytopenia syndrome bunyavirus strains originating from intragenic recombination. *J Virol*, 86: 12426–12430.
- Huang YT, Zhao L, Wen HL, Yang Y, Yu H, Yu XJ. 2016. Neutralizing antibodies to severe fever with thrombocytopenia syndrome virus 4 years after hospitalization, China. *Emerg Infect Dis*, 22: 1985–1987.
- Jiang XL, Zhang S, Jiang M, Bi ZQ, Liang MF, Ding SJ, Wang SW, Liu JY, Zhou SQ, Zhang XM, Li DX, Xu AQ. 2015. A cluster of person-to-person transmission cases caused by SFTS virus in Penglai, China. *Clin Microbiol Infect*, 21: 274–279.
- Jiao Y, Zeng X, Guo X, Qi X, Zhang X, Shi Z, Zhou M, Bao C, Zhang W, Xu Y, Wang H. 2011. Preparation and evaluation of recombinant severe fever with thrombocytopenia syndrome virus (SFTSV) nucleocapsid protein for detection of total anti-

- bodies in human and animal sera by double antigen sandwich ELISA. *J Clin Microbiol*, 50: 372–377.
- Jin C, Song J, Han Y, Li C, Qiu P, Liang M. 2016. Inclusion Bodies are formed in SFTSV-infected human macrophages. *Bing Du Xue Bao*, 32: 19–25. (In Chinese)
- Kawaguchi T, Matsuda M, Takajo I, Kawano A, Kariya Y, Kubo K, Miyauchi S, Umekita K, Nagatomo Y, Yano T, Yano K, Okayama A. 2016. Severe fever with thrombocytopenia syndrome with myocardial dysfunction and encephalopathy: A case report. *J Infect Chemotherapy*, 22: 633–637.
- Kim KH, Yi J, Kim G, Choi SJ, Jun KI, Kim NH, Choe PG, Kim NJ, Lee JK, Oh MD. 2013. Severe fever with thrombocytopenia syndrome, South Korea, 2012. *Emerg Infect Dis*, 19: 1892–1894.
- Lam TT, Liu W, Bowden TA, Cui N, Zhuang L, Liu K, Zhang YY, Cao WC, Pybus OG. 2013. Evolutionary and molecular analysis of severe fever with thrombocytopenia syndrome virus. *Epidemics*, 5: 1–10.
- Li DX. 2011. Summary of Severe Fever with Thrombocytopenia Syndrome Bunyavirus. *Chinese J Exp Clin Virol*, 25: 81–84. (In Chinese)
- Li J, Han Y, Xing Y, Li S, Kong L, Zhang Y, Zhang L, Liu N, Wang Q, Wang S, Lu S, Huang Z. 2014. 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*, 9: e91679.
- Li ZF, Hu JI, Bao CJ, et al. 2016. Rapid detection of severe fever with thrombocytopenia syndrome virus by AllGlo probe-based real-time RT-PCR. *Jiangsu Prev Med*, 27: 516–519. (In Chinese)
- Li Z, Cui L, Zhou M, Qi X, Bao C, Hu J, Shan J, Wu B, Wang S, Guo X, Jiao Y, Tang F, Wang H. 2013. Development and application of a one-step real-time RT-PCR using a minor-groove-binding probe for the detection of a novel bunyavirus in clinical specimens. *J Med Virol*, 85: 370–377.
- Li Z, Qi X, Zhou M, Bao C, Hu J, Wu B, Wang S, Tan Z, Fu J, Shan J, Zhu Y, Tang F. 2013. A two-tube multiplex real-time RT-PCR assay for the detection of four hemorrhagic fever viruses: severe fever with thrombocytopenia syndrome virus, Hantaan virus, Seoul virus, and dengue virus. *Arch Virol*, 158: 1857–1863.
- Liu JW, Wen HL, Fang LZ, Zhang ZT, He ST, Xue ZF, Ma DQ, Zhang XS, Wang T, Yu H, Zhang Y, Zhao L, Yu XJ. 2013. Prevalence of SFTSV among Asian House Shrews and Rodents, China, January–August 2013. *Emerg Infect Dis*, 20: 2126–2128.
- Liu JW, Zhao L, Luo LM, Liu MM, Sun Y, Su X, Yu XJ. 2016. Molecular Evolution and Spatial Transmission of Severe Fever with Thrombocytopenia Syndrome Virus Based on Complete Genome Sequences. *PLoS One*, 11: e0151677.
- Liu K, Cui N, Fang LQ, Wang BJ, Lu QB, Peng W, Li H, Wang LY, Liang S, Wang HY, Zhang YY, Zhuang L, Yang H, Gray GC, de Vlas SJ, Liu W, Cao WC. 2014. Epidemiologic features and environmental risk factors of severe fever with thrombocytopenia syndrome Xinyang, China. *PLoS Negl Trop Dis*, 8: e2820.
- Liu L, Chen W, Yang Y, Jiang Y. 2016. Molecular evolution of fever, thrombocytopenia and leukocytopenia virus (FTLSV) based on whole-genome sequences. *Infect Genet Evol*, 39: 55–63.
- Liu Q, He B, Huang SY, Wei F, Zhu XQ. 2014. Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. *Lancet Infect Dis*, 14: 763–772.
- Liu W, Lu QB, Cui N, Li H, Wang LY, Liu K, Yang ZD, Wang BJ, Wang HY, Zhang YY, 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.
- Liu Y, Li Q, Hu W, Wu J, Wang Y, Mei L, Walker DH, Ren J, Wang Y, Yu XJ. 2012. Person-to-person transmission of severe fever with thrombocytopenia syndrome virus. *Vector Borne Zoonotic Dis*, 12: 156–160.
- Lu QB, Cui N, Hu JG, Chen WW, Xu W, Li H, Zhang XA, Ly H, Liu W, Cao WC. Characterization of immunological responses in patients with severe fever with thrombocytopenia syndrome: a cohort study in China. *Vaccine*, 2015, 33: 1250–1255.
- Luo LM, Zhao L, Wen HL, Zhang ZT, Liu JW, Fang LZ, Xue ZF, Ma DQ, Zhang XS, Ding SJ, Lei XY, Yu XJ. 2015. Haemaphysalis longicornis Tick as Reservoir and Vector of Severe Fever with Thrombocytopenia Syndrome Virus in China. *Emerg Infect Dis*, 21: 1770–1776.
- Lei XY, Liu MM, Yu XJ. 2015. Severe fever with thrombocytopenia syndrome and its pathogen SFTSV. *Microbes Infect*, 17: 149–154.
- Ma T, Sun JM, Chen LF, Shi XG, Liu K, Gong ZY, Chen J, Zhang R, Ren JP, Jiang JM. 2015. A pediatric case of severe fever with thrombocytopenia syndrome in Zhejiang Province, China. *J Clin Virol*, 72: 85–87.
- McMullan LK, Folk SM, Kelly AJ, MacNeil A, Goldsmith CS, Metcalfe MG, Batten BC, Albariño CG, Zaki SR, Rollin PE, Nicholson WL, Nichol ST. 2012. A new phlebovirus associated with severe febrile illness in Missouri. *N Engl J Med*, 367: 834–841.
- Mishra AC, Mehta M, Mourya DT, Gandhi S. 2011. Crimean-Congo haemorrhagic fever in India. *Lancet*, 378: 372.
- Niu G, Li J, Liang M, Jiang X, Jiang M, Yin H, Wang Z, Li C, Zhang Q, Jin C, Wang X, Ding S, Xing Z, Wang S, Bi Z, Li D. 2013. Severe fever with thrombocytopenia syndrome virus among domesticated animals, China. *Emerg Infect Dis*, 19: 756–763.
- Ni H, Yang F, Li Y, Liu W, Jiao S, Li Z, Yi B, Chen Y, Hou X, Hu F, Ding Y, Bian G, Du Y, Xu G, Cao G. 2015. Apodemus agrarius is a potential natural host of severe fever with thrombocytopenia syndrome (SFTS)-causing novel bunyavirus. *J Clin Virol*, 71: 82–88.
- Park SW, Song BG, Shin EH, Yun SM, Han MG, Park MY, Park C, Ryou J. 2014. Prevalence of severe fever with thrombocytopenia syndrome virus in Haemaphysalis longicornis ticks in South Korea. *Ticks Tick Borne Dis*, 5: 975–977.
- Peng C, Wang H, Zhang W, Zheng X, Tong Q, Jie S, Yang D, Zhou Y. 2016. Decreased monocyte subsets and TLR4-mediated functions in patients with acute severe fever with thrombocytopenia syndrome. *Int J Infect Dis*, 43: 37–42.
- Plegge T, Hofmann-Winkler H, Spiegel M, Pöhlmann S. 2016. Evidence that processing of the Severe Fever with Thrombocytopenia Syndrome Virus Gn/Gc Polyprotein Is Critical for Viral Infectivity and Requires an Internal Gc Signal Peptide. *PLoS One*, 11: e0166013.
- Park SW, Han MG, Yun SM, Park C, Lee WJ, Ryou J. 2014. Severe Fever with thrombocytopenia syndrome virus, South Korea, 2013. *Emerg Infect Dis*, 20: 1880–1882.
- Park SW, Song BG, Shin EH, Yun SM, Han MG, Park MY, Park C, Ryou J. 2014. Prevalence of severe fever with thrombocytopenia syndrome virus in Haemaphysalis longicornis ticks in South Korea. *Ticks Tick Borne Dis*, 5: 975–977.
- Qu B, Qi X, Wu X, Liang M, Li C, Cardona CJ, Xu W, Tang F, Li Z, Wu B, Powell K, Wegner M, Li D, Xing Z. 2012. Suppression of the interferon and NF- κ B responses by severe fever with thrombocytopenia syndrome virus. *J Virol*, 86: 8388–8401.
- Richard ME, Benjamin B. 2014. Emerging phleboviruses. *Curr Opin Virol*, 5: 50–57.

- Stone R. 2010. Rival teams identify a virus behind deaths in central China. *Science*, 330: 20–21.
- Sun Y, Liang M, Qu J, Jin C, Zhang Q, Li J, Jiang X, Wang Q, Lu J, Gu W, Zhang S, Li C, Wang X, Zhan F, Yao W, Bi Z, Wang S, Li D. 2012. Early diagnosis of novel SFTS bunyavirus infection by quantitative real-time RT-PCR assay. *J Clin Virol*, 53: 48–53.
- Sun Q, Qi X, Zhang Y, Wu X, Liang M, Li C, Li D, Cardona CJ, Xing Z. 2016. Synaptogyrin-2 Promotes Replication of a Novel Tick-borne Bunyavirus through Interacting with Viral Nonstructural Protein NSs. *J Biol Chem*, 291: 16138–16149.
- Sun Y, Guo Y, Lou Z. 2012. A versatile building block: the structures and functions of negative-sense single-stranded RNA virus nucleocapsid proteins. *Protein Cell*, 3: 893–902.
- Takeshi K, Motohiro M, Ichiro T, Kawano A, Kariya Y, Kubo K, Miyauchi S, Umekita K, Nagatomo Y, Yano T, et al. 2016. Severe fever with thrombocytopenia syndrome with myocardial dysfunction and encephalopathy: A case report. *J Infect and Chem*, 22:633–637.
- Takahashi T, Maeda K, Suzuki T, Ishido A, Shigeoka T, Tomingaga T, Kamei T, Honda M, Ninomiya D, Sakai T, et al. 2014. The first identification and retrospective study of severe fever with thrombocytopenia syndrome in Japan. *J Infect Dis*, 209: 816–827.
- Tang X, Wu W, Wang H, Du Y, Liu L, Kang K, Huang X, Ma H, Mu F, Zhang S, Zhao G, Cui N, Zhu BP, You A, Chen H, Liu G, Chen W, Xu B. 2013. Human-to-human transmission of severe fever with thrombocytopenia syndrome bunyavirus through contact with infectious blood. *J Infect Dis*, 207: 736–739.
- Kawaguchi T, Matsuda M, Takajo I, Kawano A, Kariya Y, Kubo K, Miyauchi S, Umekita K, Nagatomo Y, Yano T, Yano K, Okayama A. 2016. Severe fever with thrombocytopenia syndrome with myocardial dysfunction and encephalopathy: A case report. *J Infect Chemother*, 22: 633–637.
- Wang M, Pennock DG, Spik KW, Schmaljohn CS. 2012. Epitope mapping studies with neutralizing and non-neutralizing monoclonal antibodies to the G1 and G2 envelope glycoproteins of Hantaan virus. *Virology*, 197: 757–766.
- Wang X, Zhang Q, Hao F, Gao X, Wu W, Liang M, Liao Z, Luo S, Xu W, Li D, Wang S. 2014. Development of a Colloidal Gold Kit for the Diagnosis of Severe Fever with Thrombocytopenia Syndrome Virus Infection. *Biomed Res Int*, 2014: 530621.
- Webster CG, Reitz SR, Perry KL, Adkins S. 2011. A natural M RNA reassortant arising from two species of plant and insect infecting bunyaviruses and comparison of its sequence and biological properties to parental species. *Virology*, 413: 216–225.
- Wen HL, Zhao L, Zhai S, Chi Y, Cui F, Wang D, Wang L, Wang Z, Wang Q, Zhang S, Liu Y, Yu H, Yu XJ. 2014. Severe fever with thrombocytopenia syndrome in Shandong Province, China, 2011. *Emerg Infect Dis*, 20: 1–5.
- Wu X, Qi X, Liang M, Li C, Cardona CJ, Li D, Xing Z. 2014. Roles of viroplasm-like structures formed by nonstructural protein NSs in infection with severe fever with thrombocytopenia syndrome virus. *FASEB Journal*, 28: 2504–2516.
- Wu W, Zhang S, Qu J, Zhang Q, Li C, Li J, Jin C, Liang M, Li D. 2014. Simultaneous detection of IgG antibodies associated with viral hemorrhagic fever by a multiplexed Luminex-based immunoassay. *Virus Res*, 187: 84–90.
- Xu B, Liu L, Huang X, Ma H, Zhang Y, Du Y, Wang P, Tang X, Wang H, Kang K, et al. 2011. Metagenomic analysis of fever, thrombocytopenia and leukopenia syndrome (FTLS) in Henan Province, China: discovery of a new bunyavirus. *PLoS Pathog*, 7: 1453–60.
- Yang G, Li B, Liu L, Huang W, Zhang W, Liu Y. 2012. Development and evaluation of a reverse transcription loop-mediated isothermal amplification assay for rapid detection of a new SFTS bunyavirus. *Arch Virol*, 157, 1779–1783.
- Yoshikawa T, Fukushi S, Tani H, Fukuma A, Taniguchi S, Toda S, Shimazu Y, Yano K, Morimitsu T, Ando K, et al. 2014. 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*, 52: 3325–3333.
- Yu FX, Du YH, Huang XY, Ma H, Xu BI, Ferdinand A, Daisuke H, Corazon C, Kouichi M. 2015 Application of recombinant severe fever with thrombocytopenia syndrome virus nucleocapsid protein for the detection of SFTSV-specific human IgG and IgM antibodies by indirect ELISA. *Virology J*, 8:12–117.
- Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, Zhang L, Zhang QF, Popov VL, Li C, et al. 2011. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl Med*, 364: 1523–1532.
- Yun SM, Lee YJ, Choi W, Kim HC, Chong ST, Chang KS, Coburn JM, Klein TA, Lee WJ. 2014. Molecular detection of severe fever with thrombocytopenia syndrome and tick-borne encephalitis viruses in ixodid ticks collected from vegetation, Republic of Korea, 2014. *Ticks Tick Borne Dis*, 7: 970–978.
- Yun Y, Heo ST, Kim G, Hewson R, Kim H, Park D, Cho NH, Oh WS, Ryu SY, Kwon KT, Medlock JM, Lee KH. 2015. 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*, 93: 468–474.
- Zhang L, Liu Y, Ni D, Li Q, Yu Y, Yu XJ, Wan K, Li D, Liang G, Jiang X, et al. 2008. Nosocomial transmission of human granulocytic anaplasmosis in China. *JAMA*, 300: 2263–2270.
- Zhang LP, Wang YC, Zhao Y, et al. Research Progress of Epidemiology and Detection Method of Severe Fever with Thrombocytopenia Syndrome Bunyavirus. *J of Inspec Quarantine*, 2014, 24: 67–71. (In Chinese)
- Zhang X, Liu Y, Zhao L, Li B, Yu H, Wen H, Yu XJ. 2013. An emerging hemorrhagic fever in China caused by a novel bunyavirus SFTSV. *Sci China Life Sci*, 56: 697–700.
- Zhang YX, Xie QX, Sun Y, et al. 2011. Isolation of novel bunyavirus using vero cell. *Anhui J Prev Med*, 18: 249–251.
- Zhang YZ, Xu JG. 2016. The emergence and cross species transmission of newly discovered tick-borne Bunyavirus in China. *Curr Opin Virol*, 16: 126–131.
- Zhang YZ, Zhou DJ, Qin XC, Tian JH, Xiong Y, Wang JB, Chen XP, Gao DY, He YW, Jin D, et al. 2012. The ecology, genetic diversity, and phylogeny of Huaiyangshan virus in China. *J Virol*, 86: 2864–2868.