



Review Article

Pathophysiology of severe fever with thrombocytopenia syndrome and development of specific antiviral therapy



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ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS) caused by SFTS virus (SFTSV), a novel phlebovirus, was reported to be endemic to central and northeastern PR China and was also to be endemic to South Korea and western Japan. SFTS is an emerging viral infection, which should be categorized as a viral hemorrhagic fever disease as Crimean-Congo hemorrhagic fever (CCHF) is caused by CCHF virus. SFTS is a tick-borne viral infection. SFTSV is maintained between several species of ticks and wild and domestic animals in nature. Patients with SFTS show symptoms of fever, general fatigue, and gastrointestinal symptoms such as bloody diarrhea. The severely ill SFTS patients usually show gastrointestinal hemorrhage and deteriorated consciousness. The case fatality rate of SFTS ranges from 5 to 40%. Pathological studies on SFTS have revealed that the mechanisms behind the high case fatality rate are virus infection-related hemophagocytic syndrome associated with cytokine storm, coagulopathy due to disseminated intravascular coagulation causing bleeding tendency, and multi-organ failure. Favipiravir was reported to show efficacy in the prevention and treatment of SFTSV infections in an animal model. A clinical study to evaluate the efficacy of favipiravir in the treatment of SFTS patients has been initiated in Japan. SFTSV is circulating in nature in PR China, Korea, and Japan, indicating that we cannot escape from the risk being infected with SFTSV. The development of specific therapy and preventive measures is a pressing issue requiring resolution to reduce the morbidity and mortality of SFTS patients.

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Abbreviations			
ALT	alanine aminotransferase	IL	interleukin
AST	aspartate aminotransferase	IP	interferon-γ-induced protein
CCHF	Crimean-Congo hemorrhagic fever	KO	knockout
CCHFV	CCHF virus	LDH	lactate dehydrogenase
CNS	central nervous system	MIP	macrophage inflammatory protein
DPRK	Democratic Peoples' Republic of Korea	NP	nucleocapsid protein
HLH	hemophagocytic lymphohistiocytosis	PE	Plasma exchange
IFN	interferon	PR China	the People's Republic of China
IFNAR	interferon alpha receptor	sCD40L	soluble CD40 ligand
IFNAR-KO mice	IFNAR-KO C57BL/6 mice	SFTS	severe fever with thrombocytopenia syndrome
IHC	immunohistochemistry	SFTSV	SFTS virus
		sIL-2RA	soluble IL-2 receptor alpha
		TCID ₅₀	50% tissue culture infective dose

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) was discovered as an emerging infectious disease epidemic to the People's Republic of China (PR China) [1,2], South Korea [3], and Japan [4,5]. SFTS is endemic to East Asia, PR China, South Korea possibly including the Democratic Peoples' Republic of Korea (DPRK), and Japan (Fig. 1). The causative agent of SFTS is a novel

phlebovirus of the family *Bunyaviridae*. It has been officially named SFTS virus (SFTSV) in the genus *Phlebovirus* of the family *Phenuiviridae* in the 10th Report released in 2016 from the International Committee on Taxonomy of Viruses (https://talk.ictvonline.org/ictv-reports/ictv_online_report/). Crimean-Congo hemorrhagic fever (CCHF) is also a tick-borne viral infection caused by CCHF virus (CCHFV, genus *Nairovirus*, family *Phenuiviridae*). CCHF is endemic to Africa, Europe, the

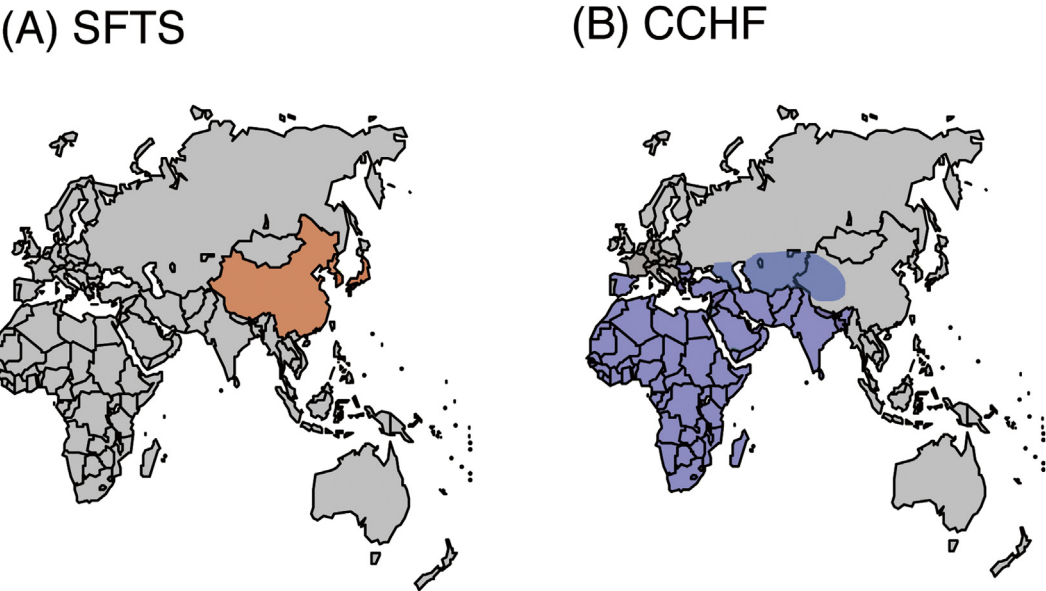


Fig. 1. SFTS- and CCHF-endemic regions. SFTS is endemic to East Asia whereas CCHF is endemic to Africa, Europe, the Middle East, and Central and South Asia, including the Xinjiang Uyghur Autonomous Region of PR China.

Middle East, and Central and South Asia (Fig. 1). SFTS is considered to be a disease similar to that of CCHF in terms of its virus characteristics, disease manifestations, mode of virus transmission to humans, pathophysiology, and high case fatality rate (CFR). SFTS can be classified under the disease category viral hemorrhagic fever, as CCHF also is. The CFRs in SFTS patients in PR China, South Korea, and Japan range from about 5% to over 40% [5–7].

Specific treatment with antiviral agents including antibodies to SFTSV for SFTS is urgently needed to reduce the morbidity and mortality as much as possible.

Recently, it was reported that the drug T-705 (favipiravir [Avigan®]; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide), which was developed by Furuta et al. of Toyama Chemical Co., Ltd., Tokyo, Japan [8], inhibits the replication of SFTSV in vitro and in vivo. Ribavirin also inhibits the replication of SFTSV in vitro, although its efficacy in vivo is limited [9]. The efficacy of favipiravir in the treatment of SFTSV infection was also shown in the STAT2-knockout (KO) hamster model [10].

In this review article, the epidemiology, the pathophysiology of SFTS studied by postmortem pathological examination, and the development of specific therapy with favipiravir for SFTS is described. The need for the development of specific therapies including the administration of antiviral agents such as favipiravir and that of preventive measures are also discussed.

2. Characteristics and life cycle of SFTSV and route of SFTSV infection to humans

2.1. Characteristics of SFTSV

SFTSV is a negative sense, single-stranded RNA virus classified in the genus *Phlebovirus* of the family *Phenuiviridae* and causes SFTS in humans. SFTSV is a spherically structured virus of approximately

100 nm in diameter and includes 3 segmented RNAs, S, M, and L segments, which encode the RNA-dependent RNA polymerase, membrane glycoprotein, and nucleocapsid protein (NP) and nonstructural protein, respectively. SFTSV is maintained in nature between several species of ticks and mammals (Fig. 2).

2.2. Tick species involved in SFTSV transmission to humans

Yu et al. reported that the tick species in which SFTSV genome RNA was detected in the SFTS-endemic regions was *Haemaphysalis (H.) longicornis*, suggesting that patients with SFTS might be infected with SFTSV through *H. longicornis* tick bites [2]. The SFTSV genome was also detected in the tick species *Amblyomma (A.) testudinarium* in South Korea and Japan [5,11,12]. The seasonality of SFTS is year-round, but most patients in Japan become ill between spring and autumn. According to the epidemiological data issued from the National Institute of Infectious Diseases (<https://www.niid.go.jp/niid/ja/sfts/sfts-idwrs/7415-sfts-nesid.html>, accessed on 18th June 2018), there was a bimodal distribution pattern in numbers of SFTS patients reported in 2013 and 2016.

The evidence of tick bites in patients with SFTS based on the detection of ticks on the skin surface and/or detection of possible tick-bite scars was not shown in one half of the SFTS patients in Japan [5]. Furthermore, *H. longicornis* and *A. testudinarium* play roles in transmitting SFTSV to humans in Japan, whereas in PR China and South Korea, the main vector involved in transmitting the virus to humans might be *H. longicornis* [11,13,14].

2.3. Human-to-human infections

Humans are also infected with SFTSV through a close contact with the body fluids of patients with SFTSV as a form of nosocomial and in-house infections [15–20]. The high risk of human-to-human

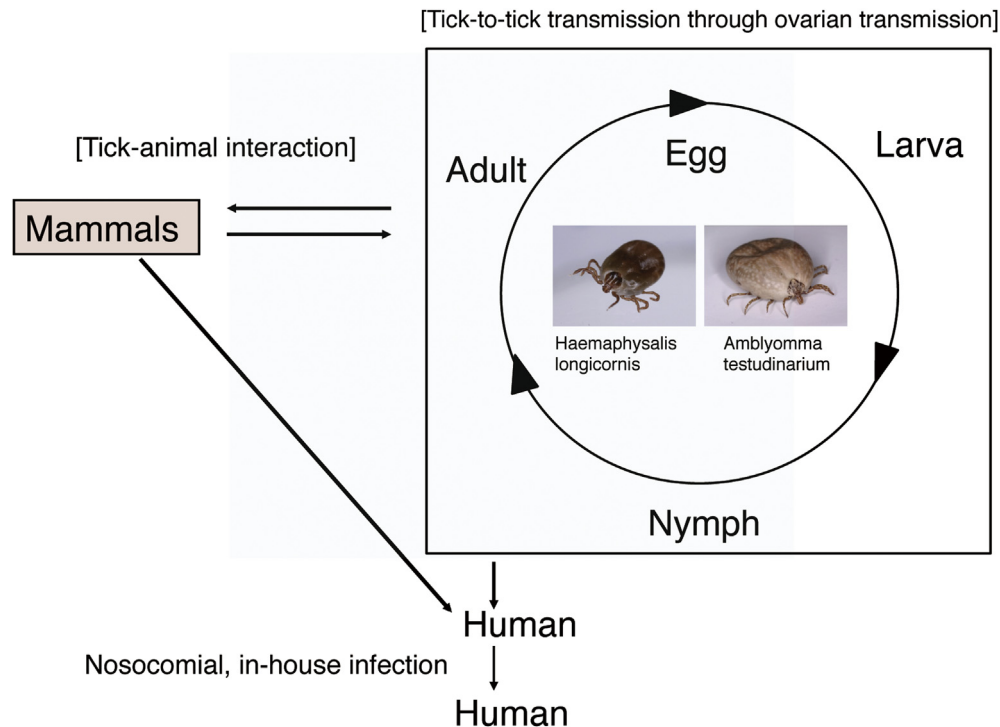


Fig. 2. Life cycle of SFTSV in nature and the route of SFTSV transmission to humans. SFTSV is transmitted from adult ticks to larva through ovarian transmission. Mammals such as deer and coconos are infected with SFTSV through tick bites causing a transit viremia. Ticks acquire SFTSV by biting viremic mammals. Thus, SFTSV is maintained in nature through the close interaction between several species of ticks such as *H. longicornis* and *A. testudinarium* and mammals. Humans are also infected with SFTSV through close contact with viremic patients with SFTSV shedding.

infections might be the direct contact with the body fluids, which might include hemorrhagic blood, of the patients in severe conditions. Not only the medical caregivers, but also the persons, who take care, should be protected from infections with SFTSV through a full personal protected equipment.

3. Clinical characteristics of SFTS

3.1. Clinical manifestations

The incubation time from the infection to the disease onset was reported to be generally 7–14 days, with an average of 9 days [21]. It was reported that incubation time from the exposure to the disease onset ranged from 7 to 13 days after exposure to the corpse of the index SFTS patient [17].

The major clinical manifestations of SFTS are rapid onset of high fever, gastrointestinal tract symptoms, and hemorrhagic tendency [4,5]. Those patients with hemorrhagic symptoms and/or deterioration in consciousness have a poor prognosis. Most patients show thrombocytopenia and leukopenia in their total blood cell counts. One patient with hematemesis, who was examined by gastrointestinal endoscopy to determine the cause of hemorrhage, had multiple ulcerative gastric lesions from which hemorrhagic oozing occurred [22].

3.2. Association between viremia level and prognosis

The association of viral copy number in blood specimens determined by quantitative real-time reverse transcription PCR with the patient prognosis was analyzed [23]. It was demonstrated that there was a statistically significant differences in the copy numbers between the patients with fatal and non-fatal outcomes. The mean viral copy number of the patients who died was higher than that of the patients who survived, with the mortality rate being higher in the patients with higher copy numbers.

3.3. Pathophysiology

The pathological findings of a patient who died of SFTS were reported for the first time in Japan [4]. In this patient and other patients in whom bone marrow aspiration was performed, hemophagocytic lymphohistiocytosis (HLH) (Fig. 3A) with or without bone marrow cell dysplasia was present. The patient's right axillary lymph node on computed tomography imaging was enlarged to 3.5 × 2.0 cm (Fig. 3B). SFTSV-NP antigen was detected in the cytoplasm of blastic cells and in necrotic regions in the cortical area of the right axillary lymph node. Severe necrotizing lymphadenitis with massive necrosis, depletion of small lymphocytes, and severe infiltration of the swollen right axillary and right cervical lymph nodes by histiocytes and immunoblasts were also observed [4]. Gastric ulceration, as was also reported in a case by [22], was also noted in the pyloric region (Fig. 3C), and hemorrhage was present in the colon and lung (Fig. 3D and E).

All pathological studies on SFTS have been reported by Japanese doctors at the autopsy stage [4,24–27]. The organs in which SFTSV-NP antigen was detected by immunohistochemistry (IHC) [4] in each of the examined patients are summarized in Table 1. Based on these reports, the pathological characteristics of SFTS can be summarized as follows. 1) All of the severely ill SFTS patients suffered from HLH. 2) SFTSV antigen was detected in lymph nodes of all patients tested. 3) There appears to be two distribution patterns of the SFTSV antigen: “Entirely SFTSV antigen-positive type”, in which the SFTSV antigen was detected in most organs tested (Patients 2-2 and 5-1), and “Localized SFTSV antigen-positive type”, in which the SFTSV antigen was detected in limited organs tested (Patients 1-1

and 3-1). 4) SFTSV antigen was detected in one patient (Patient 5-1) with pathological lesions in the central nervous system (CNS). 5) Fungal infection was incidentally detected in the lower respiratory tract and lung of 2 patients (Patients 2-2 and 4-1) [25,26].

Cytokine storm was reported to be one of the major pathophysiological features in SFTS patients that cause the case fatality rate to be high [28]. There have been the reports, in which the kinetics of cytokine and chemokine was studied in SFTS patients [28–32]. Based on these reports, interleukin (IL)-6, IL-10, interferon (IFN)- γ -induced protein (IP)-10, IFN-gamma levels increased generally in the early phase of the disease. Regulated on activation and normally T-cell expressed and secreted (RANTES) was reported to decrease in the early phase of the disease [28,30]. Kwon et al. reported that the IP-10 level in the early phase of the disease correlated with the SFTSV load [29], which was reported to be associated with the prognosis of SFTS patients [23]. This association between the IP-10 levels and the viremia levels was evaluated with only 10 patients, suggesting that further study is needed to address the association.

Ding YP et al. studied the association between the cytokine and chemokine levels and the platelet counts, serum chemistry such as AST, LDH and ALT in SFTS patients [31]. The platelet level tended to be lower when the soluble CD40 ligand (sCD40L) and platelet-derived growth factor (PDGF) BB levels decreased or when the IL-10, soluble IL-2 receptor alpha (sIL-2RA) and IP-10 levels increased. The serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were positively correlated with the cluster of cytokines or proteins including IL-10, sIL-2RA, heat shock protein 70, IP-10, IL-4, IFN- γ and tissue plasminogen activator inhibitor (tPAI)-1. The serum CK level was positively correlated with levels of IL-10, sIL-2RA, HSP70, IP-10, and IL-15. The lactate dehydrogenase (LDH) level was positively correlated with IL-10, sIL-2RA, HSP70, IP-10, IL-4, IFN- γ and IL-15 levels. In contrast, negative correlations existed between LDH and the cytokines soluble Fas ligand or sCD40L [31].

Cytokines IL-1 β , IL-8, macrophage inflammatory protein (MIP)-1 α , and MIP-1 β showed a unique pattern of elevation in fatal cases but not in nonfatal cases [28].

The levels of the serum chemistry were reported to be associated with the SFTSV genome loads and the severity of the disease [33]. These data indicate that the severity of cytokine storm, i.e. the severity of HLH, is one of the major pathophysiological factors and affects the severity of SFTS.

3.4. Mechanism of CNS-associated symptoms appearing in SFTS patients

It was thought that the deterioration of consciousness and other CNS-associated symptoms that appeared in the severely ill SFTS patients were a result of indirect effects induced by HLH associated with cytokine storm. However, the findings that pathological changes appeared in the CNS, into which SFTSV antigen-positive cells infiltrated, suggests that there might be cases of SFTS in which deterioration of CNS function is due directly to the SFTSV infection [24].

3.5. Pathophysiologies leading to a poor prognosis

The pathophysiologies leading to a poor prognosis for the patients with SFTS might include HLH associated with cytokine storm, hemorrhagic tendency caused by thrombocytopenia and disseminated intravascular coagulation, and multi-organ failure. The findings of fungal infections in the lungs of 2 of the 6 autopsied patients suggest that some patients with SFTS might be heavily immunosuppressed in a relatively short time from disease onset or from the infection with SFTSV.

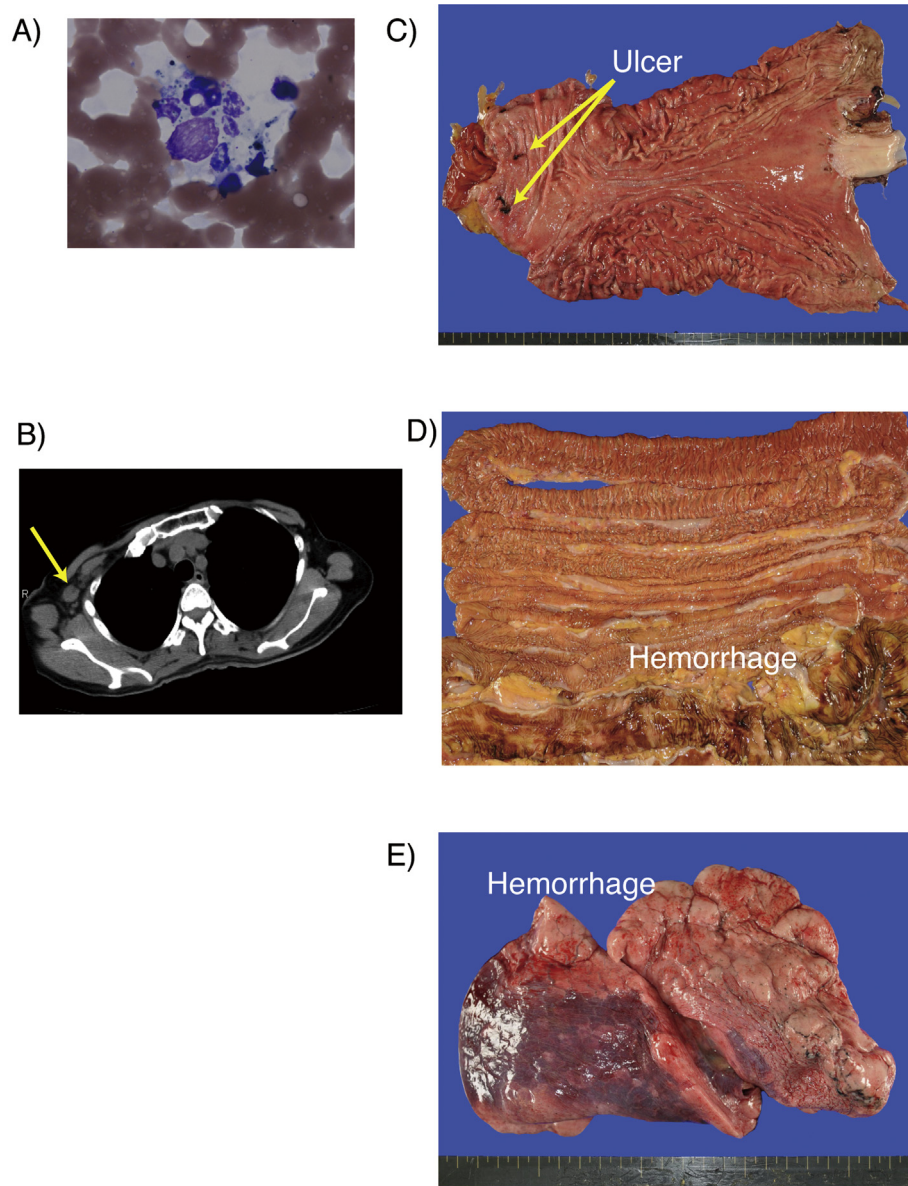


Fig. 3. The images shown in this figure are from the first patient diagnosed as having SFTS in Japan [4]. Hemophagocytes detected in the bone marrow indicate the presence of hemophagocytosis (A). Enlargement of the right axillary lymph node (arrow) was revealed on CT scan imaging (B). Ulcerative lesions were observed in the pyloric region (C, arrow). Hemorrhage was also seen in the colon (D) and the lungs (E). These images are used with the permission of Drs. Toru Takahashi and Toshiaki Kamei, Yamaguchi Grand Medical Center.

4. Animal model and evaluation of the efficacy of antiviral agents favipiravir and ribavirin in treating SFTSV infections

4.1. General issues

The antiviral agents that have been tested in animal models for an inhibitory effect on the replication of SFTSV in vitro and in vivo are ribavirin, favipiravir, antimalarial agent amodiaquine, and serum containing neutralizing antibody activity [9,34–37]. Ribavirin was shown to have an inhibitory effect on SFTSV replication in vitro and a partial effect in vivo [9,34,35,37]. However, it has not been possible to demonstrate a beneficial effect of ribavirin in the treatment of hospitalized SFTS patients in PR China [38,39].

The efficacy of favipiravir was assessed in vivo using interferon alpha receptor (IFNAR)-KO C57BL/6 mice (IFNAR-KO mice). The data presented in sections 4.2–4.4 are entirely based on the

previous report [9]. The efficacy of favipiravir in the treatment SFTSV infection was also reported using STAT2 KO hamsters [10].

4.2. In vitro antiviral activity of favipiravir against SFTSV

Favipiravir inhibited the replication of SFTSV in a dose-dependent manner (Fig. 4A). All 4 Japanese and Chinese SFTSV strains isolated in Japan and PR China showed sensitivities to favipiravir.

4.3. In vivo efficacy of favipiravir against SFTSV infection in IFNAR-KO mice

When the IFNAR-KO mice were infected with 1.0×10^6 50% tissue culture infective dose (TCID₅₀) of SFTSV subcutaneously, all mice died within 5–7 days after infection (Fig. 4B).

Table 1
SFTSV^a antigen-positive organs detected in patients who underwent autopsy.

Organs tested	Patients					
	Patient 1-1	Patient 2-1	Patient 2-2 ^b	Patient 3-1	Patient 4-1 ^b	Patient 5-1
	Female in her 50s	Female, 83 years	Male, 88 years	Male, 82 years	Female, 86 years	Male, 53 years
	Takahashi et al., 2014	Hiraki et al., 2014	Hiraki et al., 2014	Uehara et al., 2016	Nakano et al., 2017	Kaneko et al., 2017
Central nervous system	NR	Negative	NR	Negative	NR	Positive
Midbrain						Positive
Pons						Positive
Medulla						Positive
Basal ganglia						Positive
Cerebellum						Positive
Cerebrum						Positive
Stomach	Negative	Negative	Positive	NR	NR	Positive
Ileum/Colon	Negative	NR	Positive	NR	NR	Positive
Appendix	NR	NR	Positive	NR	NR	NR
Pancreas	NR	Negative	Positive	NR	NR	Positive
Spleen	Positive	Negative	Positive	Positive	Positive	Positive
Heart	Negative	Negative	Positive	NR	NR	Positive
Lung	Negative	Negative	Positive	Negative	NR	Positive
Liver	Positive	Negative	Positive	Positive	Positive	Positive
Kidney	Negative	Negative	Positive	Negative	NR	Positive
Thyroid	NR	Negative	Positive	NR	NR	Positive
Adrenal glands	Positive	Negative	Positive	Positive	NR	NR
Uterus	NR	Negative	NR	NR	NR	NR
Ovaries	NR	Negative	NR	NR	NR	NR
Bladder	NR	Negative	Positive	NR	NR	NR
Tonsils	NR	Positive	NR	Negative	NR	NR
Bronchi	NR	Negative	Negative	Negative	NR	NR
Esophagus	Negative	Negative	Positive	NR	NR	NR
Bone marrow	Positive	Negative	NR	Positive	Positive	Positive
Pituitary gland	NR	Negative	NR	NR	NR	NR
Gallbladder	NR	NR	Positive	NR	NR	NR
Testes	NR	NR	Positive	NR	NR	NR
Lymph nodes	Positive	Positive	Positive	Positive	NR	NR
Axillary	Positive	NR	NR	NR	NR	NR
Cervical	Positive	NR	NR	NR	NR	NR
Diaphragmatic	Negative	Negative	Positive	NR	NR	NR
Paratracheal	NR	Negative	Positive	NR	NR	Positive
Inguinal (Left)	NR	Negative	NR	Negative	NR	Positive
Inguinal (Right)	NR	Positive	NR	NR	NR	NR
Abdominal	NR	Negative	NR	NR	NR	NR
Paraortic	NR	Negative	Positive	Positive	NR	Positive

SFTSV: severe fever with thrombocytopenia syndrome virus; NR: not reported.

^a SFTSV was detected with immunohistochemical analysis using a polyclonal antibody raised against the nucleoprotein of SFTSV.

^b Fungal infection was seen in the lower respiratory tract (lung).

The efficacy of favipiravir in post-exposure treatment was examined using IFNAR–KO mice infected with SFTSV in comparison with that of placebo groups (Fig. 4B). Intraperitoneal administration of favipiravir at a dose of either 60 or 300 mg/kg/day for 5 days completely protected the mice from lethal SFTSV infection (Fig. 4B). Although the body weight of the mice treated with 300 mg/kg/day of favipiravir for 5 days did not show any decrease at all, the body weight of the mice treated with 60 mg/kg/day decreased slightly (Fig. 4B). Oral administration of favipiravir at either dose also completely protected the mice from lethal infection.

Surprisingly, the viremia level of the SFTSV-infected mice that were treated with favipiravir at the dose of 300 mg/kg/day became undetectable by highly sensitive SFTSV genome detection with real-time RT-PCR [23], even at 2 days after infection [9].

Histological and IHC analyses were performed with the placebo- and favipiravir-treated mice. SFTSV antigens were not detected by IHC analysis in any of the organs tested (cervical lymph nodes, spleen, liver, and kidney) in the favipiravir-treated mice, whereas those of the non-treated control mice were positive in all organs tested. The histology of the organs of the SFTSV-infecting IFNAR-KO mice remained normal.

4.4. Favipiravir therapeutic study

The therapeutic efficacy of favipiravir in the treatment of SFTSV infection was also evaluated in the IFNAR-KO mouse model (Fig. 4C). Favipiravir administration was initiated for the mice infected with 1.0×10^6 TCID₅₀ of SFTSV subcutaneously at 1, 2, 3, 4, and 5 days after infection. In this mouse model, the decrease in body weight began with no incubation time, that is, within 1 day after infection. Intraperitoneal administration of favipiravir at a dose of 300 mg/kg/day starting within 3 days after infection also completely protected the mice from lethal infections (Fig. 4C). Over 50% of the mice treated with favipiravir from 4 to 5 days after infection also survived, although they became very ill and showed weight loss of over 15%.

5. Specific and promising antiviral drug therapy for SFTS

Studies suggest that the efficacy of favipiravir in the treatment of patients with SFTS might be superior to that of ribavirin. SFTS is endemic to Japan, and the Japanese pharmaceutical company Toyama Chemical Co., Ltd. developed favipiravir [8]. With financial

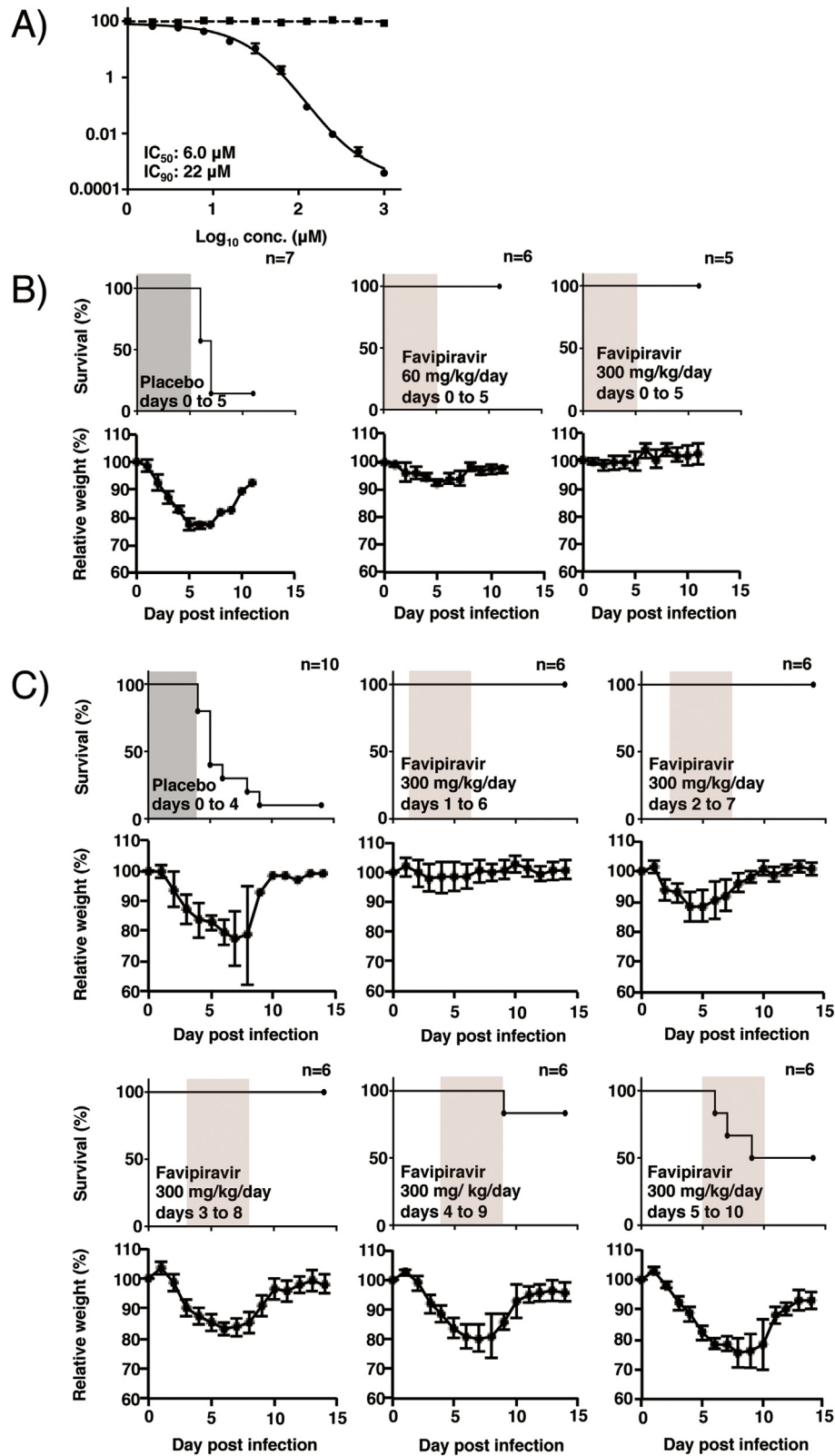


Fig. 4. Inhibitory effect of favipiravir on the replication of SFTSV in vitro and in vivo. The charts used in this figure are shown based on a previous report with some modification [9]. Favipiravir inhibited the replication of SFTSV in Vero cells in a dose-dependent manner (A). The IFNAR KO mice infected with 1.0×10^6 TCID₅₀ of SFTSV were administered favipiravir at the dose of 60 or 300 mg/kg/day from day 0 for 5 days. The treatment was administered to protect the mice from lethal infection (B). Furthermore, the efficacy of the favipiravir treatment for the SFTSV-infected mice at the dose of 300 mg/kg/day initiated on each of days 1, 2, 3, 4, and 5 after infection was also shown (C).

Table 2
Differences and similarities of disease characteristics between SFTS and CCHF.

Category	SFTS	CCHF
Virus	SFTSV (genus <i>Phlebovirus</i> , family <i>Phenuiviridae</i>)	CCHFV (genus <i>Nairovirus</i> , family <i>Phenuiviridae</i>)
Route of infection	Tick bite and close contact with viremic animals and patients with SFTS	Tick bite and close contact with viremic animals and patients with CCHFV
Endemic area	People's Republic of China, DPRK, South Korea, and Japan	Africa, Europe, Middle East, Central and South Asia
Tick species involved in virus transmission to humans	<i>Haemaphysalis longicornis</i> and <i>Amblyomma testudinarium</i>	<i>Hyalomma</i> spp. (<i>H. marginatum marginatum</i> , <i>H. asiaticum</i> , etc.) <i>Dermacentor</i> spp. (<i>D. marginatum</i> , etc.)
Pathophysiology	Generalized infection associated with multi-organ failure, hemophagocytosis, and coagulopathy	Generalized infection associated with multi-organ failure, hemophagocytosis, and coagulopathy
Case fatality rate	5–30%	5–40%

SFTS: severe fever with thrombocytopenia syndrome; CCHF: Crimean-Congo hemorrhagic fever; SFTSV: SFTS virus; CCHFV: CCHF virus; DPRK: Democratic Peoples' Republic of Korea.

support from the Japan Agency for Medical Research and Development (AMED), Tokyo, Japan, a clinical study to evaluate the efficacy of favipiravir in the treatment of SFTS patients was initiated since 2016. Partial data from the clinical study were presented at the 2nd International Conference on Crimean-Congo Hemorrhagic Fever, which was held in Thessaloniki, Greece, in September 2017 [40]. The study is still in progress.

6. Supportive therapies for SFTS patients

6.1. Steroid pulse therapy

Although there have been the patient reports, in which HLH was successfully treated with steroid therapy including a high dose corticosteroid pulse therapy, there are no prospective trials guiding treatment of HLH in adults [41]. Because the findings of HLH in bone marrow aspiration were demonstrated in most of the severe SFTS patients, some of the patients were treated with steroid pulse therapy, but some were not. The important therapy of HLH caused by infectious pathogens and the primary treatment should be focused on the treatment against the diseases caused by the pathogens. At this stage, there is no evidence that high dose corticosteroid pulse therapy is efficacious in the treatment of SFTS patients.

6.2. Plasma exchange

Korean scientists have recently reported the SFTS patients successfully treated with plasma exchange (PE) with or without ribavirin administration [42–44]. Furthermore, the efficacy of plasma exchange in the treatment of SFTS was evaluated with 53 SFTS patients, in whom 24 and 29 patients were treated with and without plasma exchange, respectively [45]. The mortality rate of the PE group did not differ from that of the non-PE group. In the 24 PE group patients, PE treatment was initiated within 7 days from the disease onset (early PE group) in 16 patients. The mortality of the early PE group patients did not differ from that of the non-PE group as well, but the early PE group patients survived longer than the non-PE group. Further study is needed to address the efficacy of PE in the treatment for SFTS patients.

7. SFTS and CCHF

There are many similarities in the disease characteristics of SFTS and CCHF as described above and summarized in Table 2. Although ribavirin inhibits the replication of CCHFV in vitro, its efficacy in the treatment of CCHF is still unknown. Oestereich et al. reported that favipiravir inhibits the replication of CCHFV in vitro and showed efficacy in the treatment of CCHFV infection in a mouse model in which IFNAR-KO mice (129Sv background) were used. Similarly to the efficacy of favipiravir in the treatment of SFTSV-infected IFNAR-KO mice

[9], the mice inoculated intraperitoneally with 100 focus-forming units of CCHFV survived completely when they were administered favipiravir at the dose of 300 mg/kg/day twice daily per os. In contrast, all of the mice in the control group died within 4 days after infection [46]. CCHF was discovered in the era of the First World War and has been studied by many researchers because of its long history, wider endemic areas, and the increase in the number of patients with CCHF. Specific therapy should be developed not only for SFTS but also for CCHF as research on the development of specific therapy for SFTS may also help in the development of novel therapy for CCHF.

8. Summary

SFTSV is circulating in nature in PR China, DPRK, South Korea, and Japan. Human-to-human infection of SFTSV has been reported as with CCHF infection [16–18,20]. The case fatality rate of SFTS is quite high. We cannot escape the risk of being infected with SFTSV in the endemic areas, and thus, it should be reiterated that the development of specific therapy for and prevention of SFTS with antiviral agents and vaccines, respectively, is urgently required. Reducing the morbidity and mortality of the SFTS patients can be achieved only through the development of efficacious antiviral drug-based therapy and vaccines. Presently, favipiravir is a promising antiviral drug for SFTS. Further study is needed for its evaluation in collaboration not only with domestic but also with international communities.

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