ORIGINAL ARTICLE

# Fever with Thrombocytopenia Associated with a Novel Bunyavirus in China

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## ABSTRACT

### BACKGROUND

Heightened surveillance of acute febrile illness in China since 2009 has led to the identification of a severe fever with thrombocytopenia syndrome (SFTS) with an unknown cause. Infection with *Anaplasma phagocytophilum* has been suggested as a cause, but the pathogen has not been detected in most patients on laboratory testing.

### METHODS

We obtained blood samples from patients with the case definition of SFTS in six provinces in China. The blood samples were used to isolate the causal pathogen by inoculation of cell culture and for detection of viral RNA on polymerase-chain-reaction assay. The pathogen was characterized on electron microscopy and nucleic acid sequencing. We used enzyme-linked immunosorbent assay, indirect immunofluorescence assay, and neutralization testing to analyze the level of virus-specific antibody in patients' serum samples.

### RESULTS

We isolated a novel virus, designated SFTS bunyavirus, from patients who presented with fever, thrombocytopenia, leukocytopenia, and multiorgan dysfunction. RNA sequence analysis revealed that the virus was a newly identified member of the genus phlebovirus in the Bunyaviridae family. Electron-microscopical examination revealed virions with the morphologic characteristics of a bunyavirus. The presence of the virus was confirmed in 171 patients with SFTS from six provinces by detection of viral RNA, specific antibodies to the virus in blood, or both. Serologic assays showed a virus-specific immune response in all 35 pairs of serum samples collected from patients during the acute and convalescent phases of the illness.

### CONCLUSIONS

A novel phlebovirus was identified in patients with a life-threatening illness associated with fever and thrombocytopenia in China. (Funded by the China Mega-Project for Infectious Diseases and others.)

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Between late March and mid-July 2009, an emerging infectious disease, which was identified as the severe fever with thrombocytopenia syndrome (SFTS), was reported in rural areas of Hubei and Henan provinces in Central China. The cause of the illness was unknown. The major clinical symptoms included fever, thrombocytopenia, gastrointestinal symptoms, and leukocytopenia, and there was an unusually high initial case fatality rate of 30%. In June 2009, an investigation was performed to identify whether the disease was caused by *Anaplasma phagocytophilum* or other pathogens. Although the clinical symptoms were considered to resemble those of human anaplasmosis,[1] neither bacterial DNA nor antibodies against this bacterium could be detected in blood samples from a majority of the patients. Instead, a novel virus was isolated from a patient's blood.

Since March 2010, there were frequent reports of a unique group of hospitalized patients who presented with clinical symptoms similar to those of SFTS in Central and Northeast China (Fig. 1). On the basis of data from a primary investigation in 2009, an enhanced surveillance was implemented in selected provinces in China to further investigate the cause and epidemiologic characteristics of SFTS. Here we describe the discovery and characterization of a novel phlebovirus in the Bunyaviridae family, designated SFTS bunyavirus (SFTSV), which is associated with SFTS. We also discuss the clinical manifestations of SFTS and the epidemiologic investigations.

## METHODS

### CASE DEFINITION AND SURVEILLANCE METHODS

Since 2009, we have implemented an active surveillance program in selected areas in Hubei and Henan provinces to identify patients with SFTS. The syndrome was characterized by acute fever (temperatures of 38°C or more) and thrombocytopenia (platelet count, <100,000 per cubic millimeter) of unknown cause.[2] We collected blood samples from hospitalized patients whose symptoms fulfilled the criteria of the case definition. We excluded patients whose symptoms fit these criteria but who had other clinical or laboratory-confirmed diagnoses.

We defined a laboratory-confirmed case as meeting one or more of the following criteria: the isolation of SFTSV from the patient's serum, the detection of SFTSV RNA in the patient's serum during the acute phase of the illness, or the detection of seroconversion or an elevation by a factor of four in serum IgG antibodies against SFTSV on enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay, or neutralization testing in serum obtained during the convalescent phase. If possible, we collected serum samples within 2 weeks after the onset of fever and again during the convalescent phase. We also collected serum samples from 200 patient-matched healthy persons living in the same areas and during the same time period. The research protocol was approved by the human bioethics committee of the Chinese Center for Disease Control and Prevention, and all participants provided written informed consent.

### ISOLATION OF AN UNKNOWN PATHOGEN

In June 2009, a blood sample in heparin anticoagulant was obtained on day 7 after the onset of illness from a patient from Xinyang City in Henan Province. Because the cause of the illness was unknown, we designed a strategy to isolate the pathogen by inoculating multiple cell lines susceptible to both viral and rickettsial agents, including human cell line HL60; animal cell lines DH82, L929, Vero, and Vero E6; and tick cell line ISE6. The patient's white cells were used to inoculate cell monolayers. The cells were cultured at 37°C in a 5% carbon dioxide atmosphere with media changes twice a week. In 2010, we used a related strategy to isolate an additional 11 strains of the virus by inoculation of serum or homogenized white cells onto Vero cells.

### ELECTRON MICROSCOPY

A DH82-cell monolayer that was infected with SFTSV in T25 flasks was fixed for transmission electron microscopy with Ito solution, as described previously.[3] Ultrathin sections were cut on a Reichert–Leica Ultracut S ultramicrotome, stained with lead citrate and examined in a Philips 201 or CM-100 electron microscope at 60 kV. Negative-stain electron microscopy was performed on virions purified from a clarified culture supernatant of infected Vero cells concentrated by a factor of 100.[4,5]

### GENETIC ANALYSIS

For the first SFTSV isolate, formalin-fixed cell culture was used to extract viral RNA using a High Pure FFPE RNA Micro Kit (Roche Applied Science). The virus was sequenced with the use of the


**Figure 1. Geographic Distribution of SFTS in Mainland China.**
Areas where SFTS surveillance was carried out and SFTS bunyavirus was isolated from patients are shown in red.

restriction-fragment–length-polymorphism assay with amplified complementary DNA, as described previously.[6] For the remaining 11 strains of the virus, the whole genomes were sequenced with the use of the sequence-independent, single-primer amplification (SISPA) method.[7] The 5′ and 3′ terminals of viral RNA segments were determined with a RACE Kit (Invitrogen). Phylogenetic analyses were performed with the neighbor-joining method with the use of the Poisson correction and complete deletion of gaps.

### NEUTRALIZATION ASSAY

For microneutralization testing, serial dilutions of serum samples were mixed with an equal volume of 100 median tissue-culture infectious doses of SFTSV (strain HB29) and incubated at 37°C for 1.5 hours. The mixture was then added to a 96-well plate containing Vero cells in quadruplicate. The plates were incubated at 37°C in a 5% carbon dioxide atmosphere for 12 days. Viral infection was detected on specific immunofluorescence assays in serum samples from patients with laboratory-confirmed infection. The end-point titer was expressed as the reciprocal of the highest dilution of serum that prevented infection.

### POLYMERASE CHAIN REACTION

RNA that was extracted from serum, whole blood, or homogenized arthropods was amplified with the use of a one-step, multiplex real-time reverse-transcriptase polymerase chain reaction (RT-PCR) with primers for SFTSV (Qiagen). The cutoff cycle-threshold value for a positive sample was set at

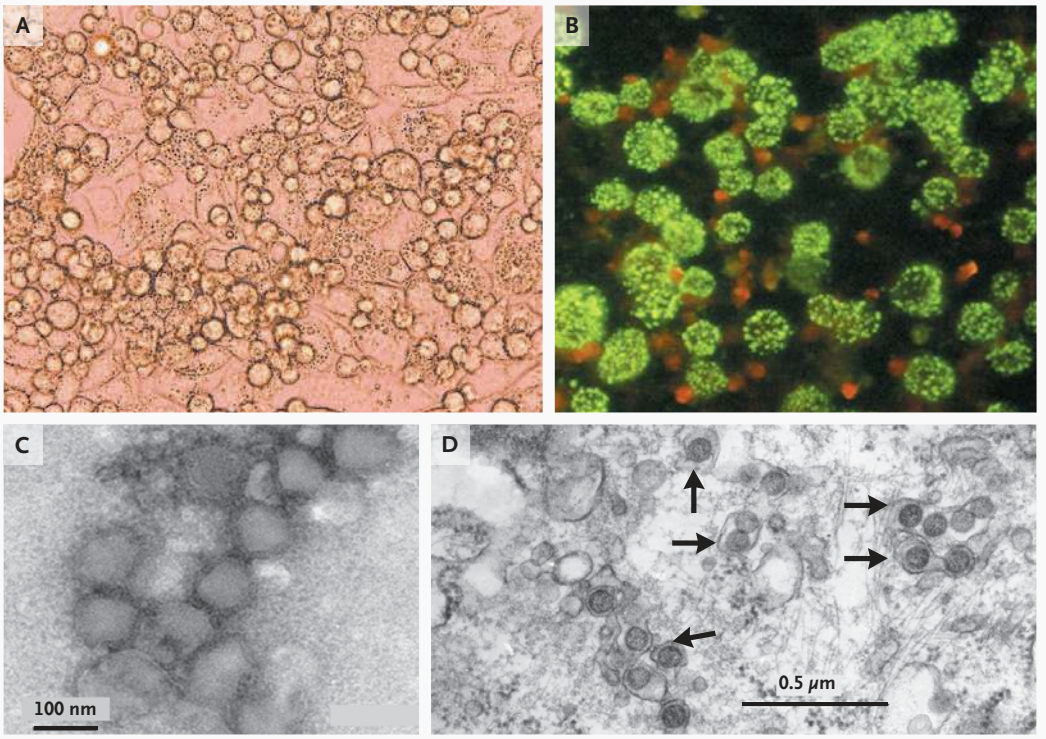


**Figure 2. Morphologic Features of SFTS Bunyavirus.**

Panel A shows virus-induced cellular changes that are visible on light microscopy (cytopathic effect) in DH82 cells infected with the severe fever with thrombocytopenia syndrome bunyavirus (SFTSV) 8 days after inoculation. The virus-infected DH82 cells are differentiated into macrophages with elongated pseudopodia with visible granular particles. Panel B shows virus grown in Vero cells and detected on immunofluorescence assay from a serum sample obtained from a patient with SFTSV infection. Panel C shows negatively stained virions purified from SFTSV-infected Vero cells. Panel D shows an image obtained on transmission electron microscopy of virus-infected DH82 cells (arrows).

35 cycles. Nested RT-PCR and sequencing were used to verify samples from which only one genomic segment was amplified.

## RESULTS

### VIRUS ISOLATION

The first SFTSV (strain DBM) was isolated from a 42-year-old man from Henan Province. A month after inoculation of cell monolayers with white cells obtained from the patient, virus-induced cellular changes visible on light microscopy (cytopathic effect) were observed in DH82 cells but not in the other cell lines. The morphologic features of infected DH82 cells changed from round monocytes to an elongated shape, which had granular particles in the cytoplasm (Fig. 2A). After several passages in culture, the cytopathic effect usually appeared on day 4 after inoculation of a fresh monolayer. Subsequently, 11 additional strains of the virus were isolated from serum samples obtained from patients during the acute phase of illness in six provinces with the use of Vero cells (Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). SFTSV can infect a variety of cells, including L929, Vero E6, Vero (Fig. 2B), and DH82 cells, but it resulted in the cytopathic effect only in DH82 cells. The viral particles were spheres with a diameter of 80 to 100 nm. Negative-stain electron microscopy of SFTSV particles that were purified from the supernatants of infected Vero cells revealed complex surface projections (Fig. 2C). Transmission electron microscopy revealed viral particles in the DH82-cell cytoplasm. The virions were observed inside vacuoles, presumably in the Golgi apparatus (Fig. 2D).

### MOLECULAR CHARACTERIZATION

Partial sequences were obtained from the first isolated virus strain DBM, and the complete genomes of 11 additional human isolates of SFTSV were determined. (GenBank accession numbers are provided in Table 1 in the Supplementary Appendix.) All isolates including strain DBM were closely related (96% homology of nucleotide sequences for all segments). The terminals of the three genomic segments of SFTSV were found to be similar to counterparts in other phleboviruses.[8] The L segment contains 6368 nucleotides with one open reading frame encoding 2084 amino acids. The M segment contains 3378 nucleotides with one open reading frame encoding 1073 amino acid precursors of glycoproteins (Gn and Gc). The S segment contains 1744 nucleotides of ambisense RNA encoding two proteins, the N and NSs proteins, in opposite orientations, separated by a 62-bp intergenic region.

Phylogenetic trees based on partial or complete viral genomic sequences of L, M, and S segments from strains DBM, HN6, and HB29 showed that SFTSV was related to prototypic viruses of the five genera of Bunyaviridae (Fig. 1 in the Supplementary Appendix). Among the genera orthobunyavirus, hantavirus, nairovirus, phlebovirus, and tospovirus, SFTSV belongs to the phlebovirus genus[8] but was more distantly related to prototypic viruses in the other four genera. To verify this finding, we carried out a phylogenetic analysis, using complete deduced amino acid sequences coding for RNA-dependent RNA polymerase, glycoproteins (Gn and Gc), and N and NSs proteins of SFTSV (strains HB29, HN6, AN12, LN2, JS3, and SD4) from six provinces in China, as compared with the other known phleboviruses (Fig. 3). The generated phylogenetic tree showed that all SFTSV isolates clustered together but were nearly equidistant from the other two groups,[9] the Sandfly fever group (Rift Valley fever virus, Punta Toro virus, Toscana virus, Massila virus, and Sandfly fever Sicilian virus) and the Uukuniemi group. This suggested that SFTSV is the prototype of a third group in the phlebovirus genus. A comparison of the similarity of amino acid sequences provided further evidence that SFTSV is distinct from the other phleboviruses (Table 2 in the Supplementary Appendix). Both RNA-dependent RNA polymerase and glycoproteins of SFTSV are slightly more closely related to counterparts in Uukuniemi virus. However, N proteins in SFTSV and Rift Valley fever virus had 41.4% similarity. In contrast, the amino acids in NSs proteins encoded by the S segment showed a similarity of only 11.2 to 16.0% with amino acids in other phleboviruses.

### SEROLOGIC ANALYSIS

We evaluated seroconversion against SFTSV in patients with SFTS using three different methods: immunofluorescence assay, ELISA, and microneutralization. We chose a cohort of 35 patients with RT-PCR–confirmed SFTSV infection who had serum samples from both acute and convalescent phases of the illness. An elevation in the antibody titer by a factor of four or seroconversion was observed in all 35 patients, as seen especially on microneutralization (Table 1). These results indicated that high levels of neutralizing antibodies were generated during the convalescent phase of the illness. An antibody titer of more than 1:25,600 on ELISA was present in 15 convalescent-phase serum samples, indicating a robust humoral immune response against SFTSV. Among the 35 seropositive samples, all SFTSV infections were confirmed on viral RNA sequencing, and 11 were confirmed on virus isolation. It is noteworthy that specific neutralizing antibodies against SFTSV persisted in some convalescent-phase serum samples even 1 year after recovery.

### CLINICAL SYMPTOMS

The first patient, a 42-year-old male farmer, presented with fever (temperatures of 39.2 to 39.7°C), fatigue, conjunctival congestion, diarrhea, abdominal pain, leukocytopenia, thrombocytopenia, proteinuria, and hematuria. Later, a unique group of hospitalized patients with acute high fever with thrombocytopenia was identified. We analyzed only 81 patients with laboratory-confirmed SFTSV infection who had a complete medical record for the clinical spectrum of SFTS. The clinical symptoms of SFTS were nonspecific, and the major symptoms included fever and gastrointestinal symptoms. Regional lymphadenopathy was also frequently observed (Table 2). The most common abnormalities on laboratory testing were thrombocytopenia (95%) and leukocytopenia (86%) (Table 3). Multiorgan failure developed rapidly in most patients, as shown by elevated levels of serum alanine aminotransferase, aspartate aminotransferase, creatine kinase, and lactate dehydrogenase. Proteinuria (in 84% of patients) and hematuria

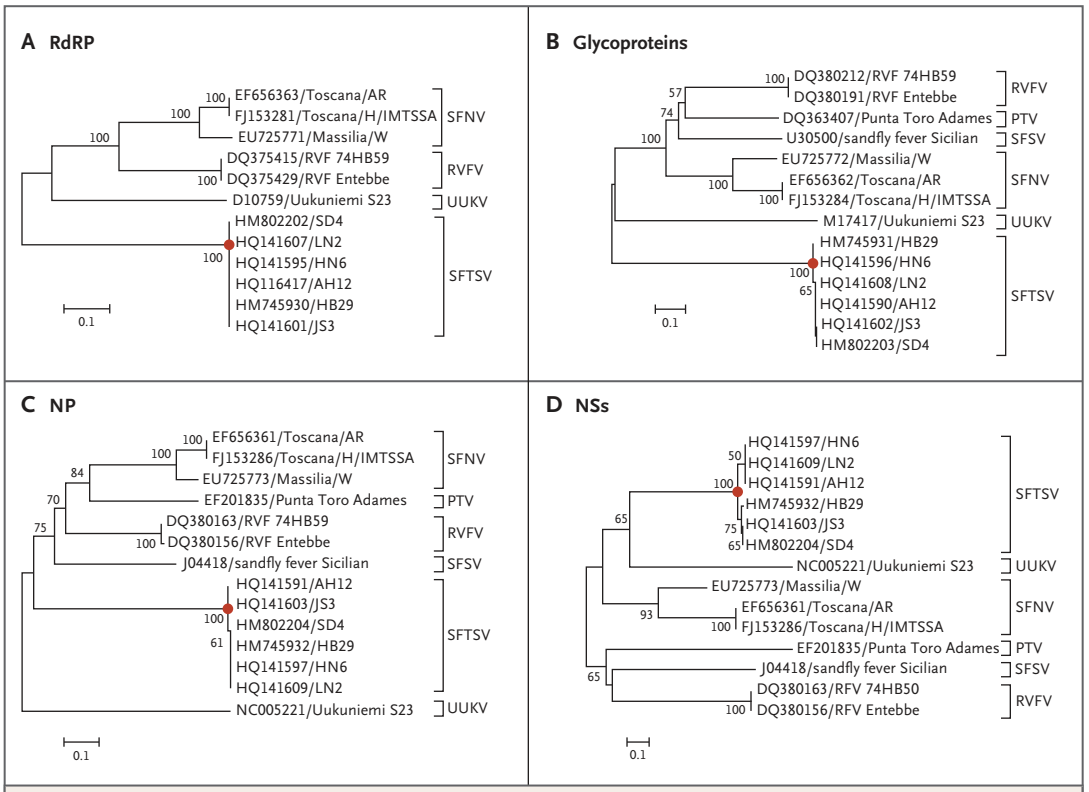


**Figure 3. Phylogenetic Analysis of SFTS Bunyavirus and Other Phleboviruses.**

The phylogenetic trees that are shown were generated by MEGA4 software from aligned amino acid sequences of six strains of phleboviruses, including the newly identified severe fever with thrombocytopenia syndrome bunyavirus (SFTSV). Coding regions for RNA-dependent RNA polymerase (RdRP) in the L segment (Panel A), for glycoproteins Gn and Gc in the M segment (Panel B), for N protein (NP) in the S segment (Panel C), and for NSs protein in the S segment (Panel D) were analyzed with the neighbor-joining method with the use of Poisson correction and complete deletion of gaps. Bootstrap testing (2000 replicates) was performed, and the bootstrap values are indicated. Sequences are identified by their GenBank accession numbers, followed by the virus name, according to the International Committee on Taxonomy of Viruses. The red dots indicate clusters of SFTSV strains. The scale bars in each panel indicate 0.1 substitutions per site. PTV denotes Punta Toro virus, RVFV Rift Valley fever virus, SFNV Sandfly fever Naples virus, SFSV Sandfly fever Sicilian virus, and UUKV Uukuniemi virus.

(in 59%) were also observed. Among the 171 confirmed cases, there were 21 deaths (12%). However, it is not clear how SFTSV caused these deaths.

### EPIDEMIOLOGIC INVESTIGATION

From June 2009 through September 2010, we detected SFTS bunyavirus RNA, specific antiviral antibodies, or both in 171 patients among 241 hospitalized patients who met the case definition for SFTS[2] in Central and Northeast China. These patients included 43 in Henan, 52 in Hubei, 93 in Shandong, 31 in Anhui, 11 in Jiangsu, and 11 in Liaoning provinces. In 2010, a total of 148 of 154 laboratory-confirmed cases (96%) occurred from May to July. The ages of the patients ranged from 39 to 83 years, and 115 of 154 patients (75%) were over 50 years of age. Of these 154 patients, 86 (56%) were women, and 150 (97%) were farmers living in wooded and hilly areas and working in the fields before the onset of disease. No SFTSV was identified on real-time RT-PCR and no antibodies against SFTSV were identified in serum samples that were collected from 200 patient-matched healthy control subjects in the endemic areas, from 180 healthy subjects from nonendemic areas, and from 54 patients with suspected hemorrhagic fever with renal syndrome. Mosquitoes and ticks were commonly found in the patients' home environment. However, viral RNA was not detected in any of 5900 mosquitoes tested. On the

**Table 1. Results on Serologic Testing and RT-PCR in 35 Patients with SFTS.***

| Patient No. | Province | Sex | Age | Days after Onset† | | RT-PCR | | IFA‡ | | ELISA‡ | | MNT‡ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | AP | CP | M Segment | L Segment | AP | CP | AP | CP | AP | CP |
| | | | *yr* | *no.* | | | | | | | | | |
| HB03 | Hubei | F | 56 | 7 | 40 | + | + | <20 | 160 | <100 | 6,400 | <10 | 640 |
| HB08 | Hubei | F | | 2 | 34 | + | + | <20 | 160 | <100 | 25,600 | <10 | 640 |
| HB10 | Hubei | F | 62 | 2 | 30 | + | + | <20 | 320 | 100 | 6,400 | <10 | 160 |
| HB11 | Hubei | F | 46 | 5 | 40 | + | + | <20 | >320 | <100 | 25,600 | <10 | 160 |
| HB12 | Hubei | F | 59 | 13 | 12 | + | + | 20 | >320 | 400 | 25,600 | <10 | 160 |
| HB14 | Hubei | F | 59 | 11 | 45 | + | + | <20 | >320 | <100 | 6,400 | <10 | 640 |
| HB16 | Hubei | F | 39 | 4 | 55 | + | + | 20 | >320 | 100 | 25,600 | 40 | 160 |
| HB18 | Hubei | F | 55 | 6 | 33 | + | + | <20 | 80 | 100 | 6,400 | <10 | 160 |
| HB20 | Hubei | F | 68 | 8 | 30 | + | + | <20 | 320 | 100 | 25,600 | <10 | 160 |
| HB24 | Hubei | M | 55 | 8 | 46 | + | + | <20 | >320 | 100 | 25,600 | 40 | 160 |
| HB29 | Hubei | F | 61 | 9 | 52 | + | + | <20 | 160 | <100 | 25,600 | 40 | 640 |
| SD02 | Shandong | M | 60 | 20 | 82 | + | + | >80 | >320 | 1600 | 6,400 | 40 | 640 |
| SD05 | Shandong | F | 52 | 12 | >360 | + | + | <20 | 160 | 100 | 25,600 | 40 | 160 |
| SD09 | Shandong | M | 83 | 15 | >360 | + | + | <20 | 40 | 400 | 6,400 | <10 | 160 |
| SD10 | Shandong | M | 50 | 8 | >360 | + | + | <20 | 20 | <100 | 1,600 | <10 | 160 |
| SD24 | Shandong | M | 74 | 8 | >180 | + | + | <20 | 20 | 100 | 1,600 | <10 | 640 |
| SD43 | Shandong | F | 60 | 11 | >360 | + | + | 40 | >320 | 100 | 25,600 | <10 | 640 |
| SD47 | Shandong | F | 75 | 3 | >360 | + | + | <20 | 20 | 100 | 6,400 | <10 | 640 |
| SD55 | Shandong | F | 51 | 8 | >360 | + | + | <20 | <20 | 100 | 100 | <10 | <10 |
| SD81 | Shandong | F | 55 | 6 | >360 | + | + | <20 | 320 | <100 | 25,600 | <10 | 160 |
| SD82 | Shandong | F | 70 | 4 | 40 | + | + | <20 | 320 | 400 | 25,600 | <10 | 160 |
| SD87 | Shandong | F | 37 | 12 | 40 | + | – | <20 | 160 | 100 | 6,400 | <10 | 160 |
| SD115 | Shandong | M | 51 | 5 | 34 | + | + | <20 | 80 | 400 | 6,400 | 40 | 160 |
| SD116 | Shandong | M | 78 | 3 | 37 | + | + | <20 | 80 | <100 | 160 | <10 | 160 |
| SD117 | Shandong | M | 41 | 2 | 30 | + | + | <20 | 160 | 100 | 1,600 | 10 | 160 |
| SD119 | Shandong | F | 78 | 7 | 55 | + | + | 20 | 160 | 100 | 1,600 | <10 | 160 |
| SD120 | Shandong | M | 68 | 14 | 62 | + | – | 40 | 320 | 1600 | 25,600 | <10 | 640 |
| SD121 | Shandong | M | 69 | 11 | 36 | + | + | <20 | –320 | 100 | 6,400 | 20 | 80 |
| HN02 | Henan | F | 59 | 6 | 51 | + | + | <20 | 320 | <100 | 25,600 | 10 | 160 |
| HN03 | Henan | F | 63 | 5 | 49 | + | + | <20 | 80 | <100 | 6,400 | 40 | 160 |
| HN04 | Henan | F | 61 | 5 | 45 | + | + | <20 | 80 | <100 | 25,600 | <10 | 160 |
| HN08 | Henan | F | 69 | 8 | 41 | + | + | <20 | 320 | 100 | 6,400 | 10 | 160 |
| HN09 | Henan | F | 48 | 5 | 36 | + | + | <20 | 80 | <100 | 1,600 | <10 | 160 |
| HN11 | Henan | F | 66 | 3 | 29 | + | + | <20 | 320 | <100 | 6,400 | <10 | 160 |
| HN12 | Henan | M | 76 | 3 | 28 | + | + | <20 | 320 | <100 | 25,600 | <10 | 160 |

* RT-PCR denotes reverse-transcriptase polymerase chain reaction.
† Indicated are the number of days after the onset of illness when samples were obtained from patients who were in the acute phase (AP) or the convalescent phase (CP) of the illness.
‡ The values for enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA), and microneutralization test (MNT) are the reciprocals of the serum dilution.

**Table 2. Clinical Symptoms of Hospitalized Patients with Laboratory-Confirmed SFTS.***

| Symptom | Patients with Symptoms (N=81) | Deaths (N=11) |
|---|---|---|
| | *no. (%)* | |
| Fever | 81 (100) | 11 (100) |
| Anorexia | 61 (75) | 7 (64) |
| Fatigue | 53 (65) | 6 (55) |
| Nausea | 56 (69) | 5 (45) |
| Abdominal pain or tenderness | 40 (49) | 4 (36) |
| Vomiting | 38 (47) | 4 (36) |
| Malaise† | 32 (46) | 7 (64) |
| Diarrhea | 34 (42) | 3 (27) |
| Lymphadenopathy† | 23 (33) | 2 (18) |
| Myalgia | 22 (27) | 2 (18) |
| Confusion | 18 (22) | 4 (36) |
| Headache | 10 (12) | NA |
| Throat congestion | 10 (12) | 2 (18) |
| Cough | 8 (10) | 2 (18) |
| Conjunctival congestion | 8 (10) | NA |
| Petechiae† | 5 (7) | 3 (27) |
| Apathy† | 6 (9) | 1 (9) |
| Slurred speech† | 4 (6) | 1 (9) |
| Coma† | 4 (6) | 3 (27) |

* Symptoms were evaluated in 81 patients with laboratory-confirmed SFTSV infection who had a complete medical record. NA denotes not available.
† This symptom was evaluated in 69 of the 81 patients.

other hand, 10 of 186 ticks (5.4%) of the species *Haemaphysalis longicornis* that were collected from domestic animals in the areas where the patients lived contained SFTSV RNA. The viruses in the ticks were isolated in Vero cell culture, and the RNA sequences of these viruses were very closely related but not identical to the SFTSV isolated in samples obtained from the patients (data not shown). There was no epidemiologic evidence of human-to-human transmission of the virus.

## DISCUSSION

Although we have not fulfilled Koch's postulates for establishing a causal relationship between a microbe and a disease in their entirety, our findings suggest that SFTS is caused by a newly identified bunyavirus. These data include epidemiologic, clinical, and laboratory findings and several lines of evidence that include virus isolation, viral RNA detection, and molecular and serologic analyses. SFTS has been identified in Central and Northeast China, which covers all six provinces where surveillance for SFTS was carried out. It is most likely that SFTS had been prevalent in China for some time, but it had not been identified. In previous studies, viral pathogens were cultured in Vero cells, in which SFTSV does not produce a cytopathic effect. We identified the virus by using several cell lines, including DH82, which is very sensitive to SFTSV.

SFTS needs to be differentiated from human anaplasmosis, hemorrhagic fever with renal syndrome,[8] and leptospirosis. Similar to patients with SFTS, patients with human anaplasmosis have fever and a decreased number of circulating white cells and platelets, but gastrointestinal symptoms are not common.[10] In the initial febrile phase, patients with hemorrhagic fever with renal syndrome may have gastrointestinal symptoms and abdominal pain resembling symptoms of SFTS, but the characteristic flushing of the face and V-area of the neck and thorax, conjunctival suffusion, and periorbital edema, hypotension, oliguria, polyuria, and bleeding disorders have not been observed in patients with SFTS.[11] Leptospirosis may be confused with SFTS because of the initial fever, chills, headache, myalgia, and abdominal pain, but common symptoms of leptospirosis, such as rash and jaundice,[12] are rare in patients with SFTS.

Most phleboviruses are associated with sandflies, and in such cases there is evidence of transovarial transmission.[13] The nonpathogenic Uukuniemi virus is a tickborne phlebovirus. Rift Valley fever is transmitted mainly by aedes species mosquitoes. SFTSV RNA was detected in some ticks in the Ixodidae family of the species *H. longicornis* that were obtained from animals, and these ticks may be a candidate vector of SFTSV. Regular hosts of *H. longicornis* include most mammals, including goats, cattle, sheep, yak, donkeys, pigs, deer, cats, rats, mice, hedgehogs, weasels, brushtail possums, and humans, along with some birds. *H. longicornis* is widely distributed in the Asia–Pacific region, including China, Korea, Japan, Australia, the Pacific Islands, and New Zealand.[14]

Our finding that SFTSV is the probable cause of a previously unknown severe febrile disease

**Table 3. Laboratory Findings in Patients with SFTS.**

| Result | Normal Level | Increased Level | Decreased Level |
|---|---|---|---|
| | | *no./total no. (%)* | |
| Platelet count | 4/73 (5) | 0/73 | 69/73 (95) |
| White-cell count | 8/74 (11) | 2/74 (3) | 64/74 (86) |
| Neutrophil count | 0/12 | 0/12 | 12/12 (100) |
| Lymphocyte count | 2/12 (17) | 0/12 | 10/12 (83) |
| Alanine aminotransferase | 11/64 (17) | 53/64 (83) | 0/64 |
| Aspartate aminotransferase | 4/63 (6) | 59/63 (94) | 0/63 |
| Ratio of albumin to globulin | 11/63 (17) | 0/63 | 52/63 (83) |
| Alkaline phosphatase | 39/53 (74) | 3/53 (6) | 11/53 (21) |
| Lactate dehydrogenase | 1/51 (2) | 49/51 (96) | 1/51 (2) |
| Creatine kinase | 21/49 (43) | 25/49 (51) | 3/49 (6) |
| Creatine kinase MB fraction | 19/47 (40) | 28/47 (60) | 0/47 |
| Activated partial-thromboplastin time | 7/12 (58) | 5/12 (42) | 0/12 |
| Proteinuria | 7/43 (16) | 36/43 (84) | 0/43 |
| Hematuria | 19/46 (41) | 27/46 (59) | 0/46 |
| Fecal occult blood | 15/19 (79) | 4/19 (21) | 0/19 |

is one of the fruits of heightened surveillance of infectious diseases in China. More research is needed to determine the extent to which this disease occurs in regions outside its area of identification.

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## APPENDIX

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