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Epidemiological and etiological investigation of a rare family cluster caused by severe fever with thrombocytopenia syndrome in Anhui Province in 2023

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Abstract

Background Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease discovered in the 21st century. Human-to-human transmission of the disease has been documented, but the mechanisms of transmission require further investigation.

Methods Epidemiological investigations and genetic analyses of the patients were conducted, and a retrospective cohort study was performed to analyze potential risk factors for person-to-person transmission.

Results According to epidemiologic investigations, 14 secondary cases had a clear history of exposure to blood and body fluids, and 3 secondary cases may have been exposed to aerosols in a poorly ventilated environment. Risk factor assessment revealed that the risk of SFTS was 6.778 times higher [RR = 6.778, 95%CI = 1.570-29.354] among those who had direct blood contact with the indicated patient compared to those who did not, and exposure to bloody secretions from the corpse was associated with a 12.800 times higher risk for SFTS [RR = 12.800, 95%CI = 1.479-110.789] compared to contact with the blood, bloody fluids, or secretions of living patients.

Conclusions Contact with the blood of a deceased individual during funeral rites was associated with secondary cases of SFTS. The cluster outbreak is suspected to be due to person-to-person transmission of SFTSV, likely through direct contact with the blood of an SFTS patient, while the spread of aerosols in enclosed environments is also an undeniable mode of transmission.

Keywords Severe fever with thrombocytopenia syndrome, Disease cluster, Epidemiologic investigations

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging hemorrhagic fever first confirmed in rural areas of east-central China in 2009. The earliest case was traced back to 1996 [1, 2]. The primary clinical manifestations include fever, thrombocytopenia, leukopenia, lymphadenopathy and gastrointestinal symptoms. The average case-fatality rate is approximately 12%, but it can reach as high as 30% [3], while the case-fatality rate in the epidemic situation is about 22% [4]. The SFTS virus (SFTSV) was identified as the causative agent and was officially renamed as Dabie Banda virus by International Committee on Taxonomy of Viruses (ICTV) in 2020 [5]. The virus is a segmented single-stranded negative-sense RNA virus. Its genome comprises three segments: large (L), medium (M) and small (S) [1]. The L segment is encoded by RNA-dependent RNA polymerase (RdRp), which can act as the viral transcriptase/replicase. The M segment encodes a 1073 amino-acid glycoprotein (Gn and Gc), and the S segment is an ambisense RNA that encodes the nucleocapsid protein (NP) and nonstructural protein (NSs) [6]. SFTS is mainly transmitted to humans through tick bites [7], but it can also be transmitted from person to person through direct contact with the blood of patients [8–10]. A recent cluster outbreak in Jiangsu suggested that individuals can be infected with SFTS through potential ocular exposure to infectious blood [11]. Additionally, aerosol transmission in closed environments is a potential mode of transmission [12, 13], although there is currently no definitive epidemiological evidence.

From late October to mid November 2023, an outbreak involving 18 clusters of suspected cases of SFTS occurred in Feidong County, Anhui Province, an endemic area of SFTS in China, resulting in four deaths, including the index patient and three secondary patients. In this study, we investigated these cases, analyzed the cause of the epidemic, the mode of transmission and risk factors, and further assessed the possibility of aerosol transmission in a closed environment. Additionally, molecular epidemiology methods were used to study the epidemiological characteristics and confirm the genetic homology among the secondary cases.

Methods

Subjects

In November 2023, a family cluster of SFTS in Feidong County, Hefei City, Anhui Province was reported through the public health emergency management information system. Based on the diagnostic criteria outlined in the Guidelines for the Prevention and Treatment of SFTS (2010 edition), we identified the infected individuals and close contacts associated with the cluster. Ultimately, a total of 18 cases were confirmed, and 44 close contacts were identified. Information was collected through in-person interviews or phone calls conducted simultaneously. Close contacts of SFTS were defined as individuals who had been exposed to the blood, bodily fluids, blood secretions, or excreta of an SFTS index patient. Additionally, the symptoms of the index case appeared on October 21.

Epidemiological investigation methods

We conducted retrospective epidemiological investigations on close contacts and utilized case definitions to perform case searches. A standardized survey form was used to collect epidemiological data from close contacts, exposed individuals, and infected cases. The primary information gathered during the investigation included demographic details, epidemiological contact history, and clinical characteristics.

Retrospective cohort methods

Based on the results of our preliminary interviews with close contacts, we hypothesized that exposure characteristics might have a potential impact on the eventual morbidity of close contacts. To validate this hypothesis, we conducted a retrospective cohort study on close contacts. Semi-structured data collection tools were used to gather potential exposure data.

Field collection of ticks

Ticks were collected from nearby farmlands, fields, grasslands, and hills in the vicinity of the index patient's location, based on epidemiological surveys conducted on November 15, 16, and 23, respectively. A white flannel cloth drape (1 m^2) was dragged over the plant-life to capture feeding ticks. The collected ticks were then sorted by species.

SFTSV RNA detection by RT-PCR

Venous blood (5 mL) was collected from close contacts and the surrounding population. The blood samples were centrifuged at 3000 rpm for 3 min to isolate the serum. RNA was extracted from the serum using a nucleic acid extraction instrument (TianLong, Xi'an, China). SFTSV RNA was detected using a fluorescent quantitative RT-PCR kit for SFTSV (BioGerm, Shanghai, China) on an ABI Q5 Systems (Applied Biosystems, Carlsbad, CA, USA).

Gene sequencing and phylogenetic analysis

The complete genome of SFTSV was sequenced and analyzed using RNA extracted from nucleic acid-positive samples. The whole genome of the SFTSV was sequenced using third-generation sequencing technology. The BAIYITECH New Bunia Virus Genome Capture Kit (item number: BK-WSFTSV024) and the Multi-Sample

DNA Library Construction Kit (item number: BK-AUX024) were used for reverse transcription amplification and library preparation. Sequencing was performed using the FLO-MIN106D chip from Oxford Nanopore Technologies. The sequencing results were assembled to obtain the complete genome sequence using the New Bunia Analysis Software (v5.0, BAIYITECH, Hangzhou, China) on the BAIYITECH platform. Six different genotypes (A–F) of SFTSV reference sequences were downloaded from GenBank (http://www.ncbi.nlm.nih.gov/genbank). Sequence alignment was performed using MAFFT v7.0.26 software, and a maximum likelihood phylogenomic tree was constructed using IQTREE v2.3.6 with the ModelFinder model selected automatically. Node support was calculated using the ultrafast bootstrap approximation method with 1,000 repetitions.

Statistical method

Adobe Illustrator was used to create the epidemic curve chart. The characteristic of this clustered epidemic was analyzed using descriptive epidemiological methods. Data analysis for this study was conducted with SPSS version 23.0. If the data followed a normal distribution, the mean and standard deviation were used for description; otherwise, the interquartile range (P25, P75) was used. Additionally, the Risk Ratio (RR) along with a 95% Confidence Interval (95% CI) was calculated. A *P*-value of less than 0.05 was considered statistically significant.

Results

Index patient

The index patient (patient A) was a 56-year-old man who lived alone in a small village in central Anhui Province. On October 21, 2023, he developed a fever and fatigue without any known reason. After 3 days, his condition worsened, and he visited the local village clinic to purchase medication for self-administration at home. However, no improvement was observed. On the afternoon of October 27, he was admitted to the local County Hospital A with a high fever of 39.0℃. At this time, the patient was noted to be confused and unable to speak. No focal neurological abnormalities were observed. Blood tests on admission revealed a decreased white blood cells count (WBC) count of 3.11×10^9/L (lower limit of normal: 4.0×10^9/L) and a platelet (PLT) count of 36×10^9/L (lower limit of normal: 100.0×10^9/L). The attending physician assessed that his condition was critical and recommended transfer to a hospital with better treatment capabilities. On the same day, the patient was transferred to the Hospital B with clinical symptoms of fever. Laboratory analysis of his blood revealed leukopenia (WBC count: 2.33×10^9/L), thrombocytopenia (PLT count: 27×10^9/L), ketoacidosis, and impaired liver and kidney function. On October 28, he visited County Hospital C, where he was diagnosed with "thrombocytopenia, renal insufficiency, and acidosis". The doctor recommended another referral to the provincial hospital headquarters. Due to a shortage of available beds, the patient was transferred to the Hospital D on October 29. His condition continued to deteriorate rapidly. Upon admission, his temperature was 39.0℃. Physical examination showed several enlarged lymph nodes in both the groin and behind the ears (maximum diameter: 8 cm×10 cm). Laboratory tests revealed a WBC count of 3.8×10^9/L, and a PLT count of 18×10^9/L. He was also found to have elevated liver-associated enzyme levels (serum lactate dehydrogenase: 3364 U/L; creatine kinase: 3374 U/L) and acute renal insufficiency (creatinine: 384.4 umol/L; urea nitrogen: 25.8 mmol/L). On October 30, a positive RT-PCR result for SFTSV was reported by the Municipal Hospital E. Considering his clinical condition, his family decided to discontinue intensive medical support and brought him home on November 2. The patient passed away on the same day. His body was cremated on November 4. All items he had used from the onset of illness until his death were discarded, and his home was disinfected after the funeral.

A retrospective investigation of the patient's family members revealed that he was a peasant. His yard lacked shrubbery, and he kept 15 chickens. He had a history of farm work in the dry land near his residence approximately 6 days before the onset of illness, but it was unclear whether he had been bitten by ticks. During his illness, his son cared for him day and night.

Epidemiological investigation for cases in the cluster

Of those who were in close contact with the index patient, we found 17 SFTS cases with RT-PCR positive results and typical symptoms of SFTS. These 17 cases were diagnosed as secondary patients from 5 to 11 days after the index patient died. Interviews were conducted with the 17 secondary cases, and a review of medical records helped reconstruct the timeline of relevant exposures and the onset of illness in the cluster (Fig. 1).

All secondary patients, including ten family members and seven relatives, reported no recent tick bites. However, they all reported attending the funeral of the index patient. The index patient died at home on November 2. Extensive blood was splashed when the catheters were removed from the trachea of the patient. The 14 secondary patients reported having wiped and dressed the corpse of the index patient and being exposed to the index patient's blood without personal protective equipment. Among them: patient B participated in removing the trachealtube, wiped blood from the corpse, and dressed the index patient without gloves, following local custom. Patients C and R were involved in removing the trachealtube and dressing the corpsed. Patients D,

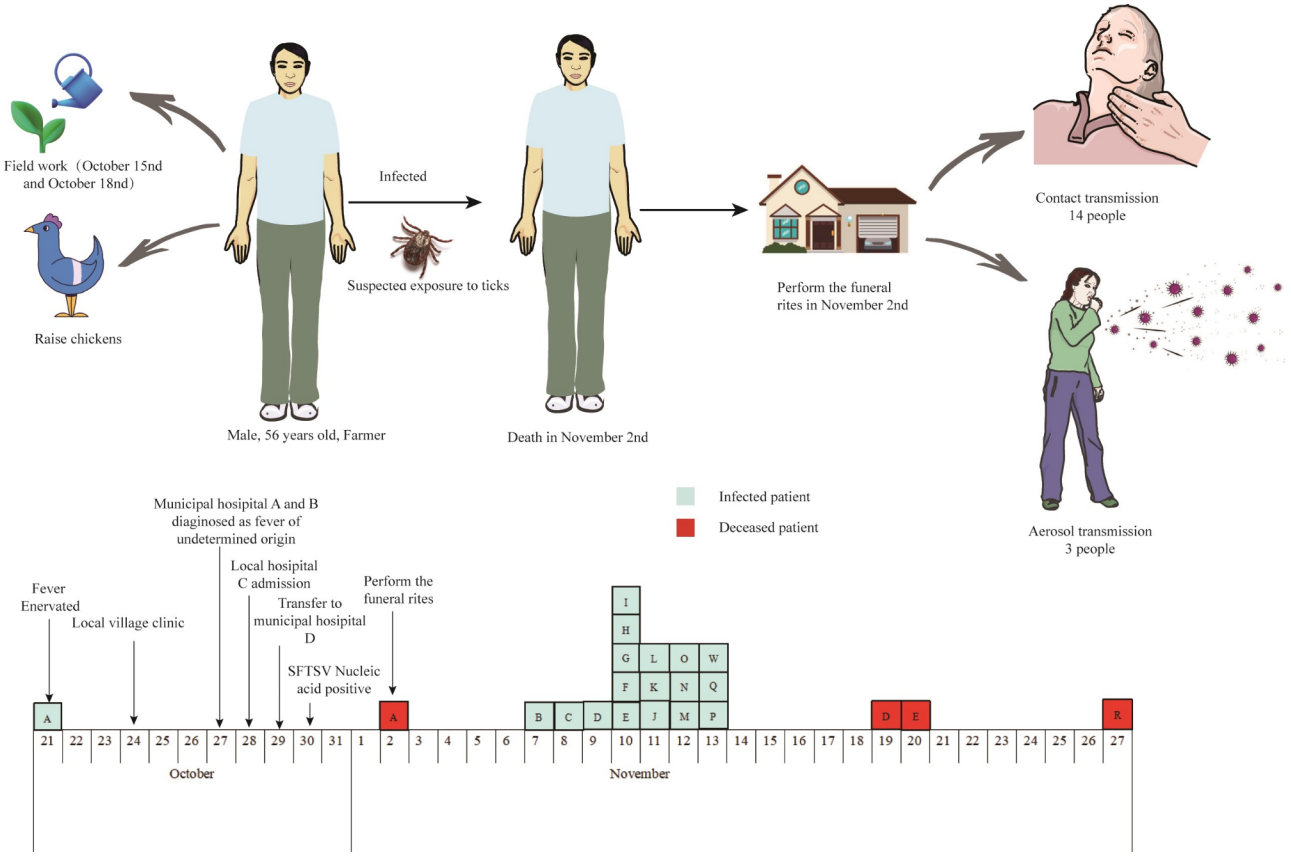

Fig. 1 Timeline of disease onset dates for a cluster of 18 SFTS (severe fever with thrombocytopenia syndrome) patients. Epidemic curve shows progression of critical symptoms during the index patient's illness, and the onset of SFTS in the eight clustered patients, of which the onset date ranged from 5 to 11 days after exposure to the dead body of the index patient, and clinical incubation time was mostly focused on 9 days ($n=17$)

M, E, F, L, and P participated in dressing and transporting the corpse of the index patient. Patient G took care of his father both in the hospital and at home. Patient Q changed the index patient's clothes after his death at home. Patients J, N, and O had direct blood contact with the corpse. The other 3 secondary patients, including patient H, I, and K, were suspected of being exposed to viral aerosols in an airtight environment at the funeral site.

The 17 secondary patients developed symptoms between November 7 and November 13 and were hospitalized between November 9 and November 16. Among them, the mean age was 59.1 years (ranging from 27 to 88 years), with eleven males and six females. In the occupation distribution, farmers account for the highest proportion (10/17). Unfortunately, patients D (80 years old), E (55 years old), and R (71 years old) progressed to severe disease during hospitalization, were transferred to the intensive care unit and died on November 19, November 20, and November 27, respectively. The case fatality rate of the secondary case was 17.6% (3/17). The demographic characteristics of the 17 secondary patients are displayed in Table 1.

Clinical characteristics

All 18 patients in the cluster developed a fever and exhibited clinical features of SFTS, including fatigue, nausea, myalgia, proteinuria, haematuria, thrombocytopenia, and leukocytopenia. Two of the four deaths had viral encephalitis and all four deaths were attributed to multiple organ failure. As shown in Table 2, laboratory tests showed elevated levels of liver enzymes (including ALT), myocardial enzymes (including LDH, and CK), and creatinine among the four deaths. These findings indicated that the deaths had significantly more severe impairment of liver, heart and kidney functions compared to the surviving SFTS patients.

Risk factors of person-to-person transmission of SFTSV

Based on the descriptive epidemiology findings and key informant interviews, we hypothesized the following potential exposures for this outbreak: direct contact with the index patient, exposure to bloody secretions from the corpse, and lack of standard protection. In the retrospective cohort study, we included all 44 close contacts of the index patient and persons exposed to the same space. We observed that the risk of SFTS was 6.778 times higher

Table 1 Demographic information of the 17 secondary patients

Variable	Total(n = 17)	Blood and body fluids exposure group (n = 14)	Aerosol exposure group (n = 3)	*P*
Sex				1.000
Male	11	9	2	
Female	6	5	1	
Age, years				0.641
Mean (SD)	59.1(18.7)	60.1(18.2)	54.3(25.0)	
Occupation				1.000
Farmer	10	8	2	
Bricklayer	2	2	0	
Housework and unemployment	2	1	1	
Sanitation worker	1	1	0	
Trucker	1	1	0	
Collect scrap	1	1	0	
Incubation time, days				0.520
Median (IQR)	9(2)	9(2.5)	8	
Period from onset to diagnosis, days				1.000
Median (IQR)	1(2.5)	1(2.25)	1	
Outcome				1.000
Discharge	14	11	3	
Death	3	3	0	
White blood cell count (Nadir), $\times 10^9$/L				0.157
Mean (SD)	2.6(1.3)	2.43(1.24)	3.60(1.26)	
Platelet count (Nadir), $\times 10^9$/L				0.743
Mean (SD)	96.9(41.1)	95.4(42.9)	104.3(37.4)	

[RR = 6.778, 95%CI = 1.570-29.354] among those who had direct blood contact with the index patient [56.0%, (14/25)] compared to those who did not [15.8%, (3/19)]. We also found that being exposed to bloody secretions of the corpse [51.6%, (16/31)] was associated with a 12.800 times higher risk [RR = 12.800, 95%CI = 1.479-110.789] for SFTS compared to contact with the living patients' blood, bloody fluids or secretion [7.7%, (1/13)]. All secondary cases occurred in the population without standard protection [50.0%, (17/34)]. See Table 3.

Investigation of the natural environment and biological vectors

An attempt was made to collect ticks in the fields near the patients' home on November 15, 16, and 23, respectively, but no ticks were captured. No ticks were found on the bodies of animals either.

SFTSV RNA detection

From November 15 to 20, 2023, a total of 187 blood samples were collected, including 184 human blood samples and 3 animal serum specimens (2 dog serum samples and 1 chicken serum sample). These samples were sent to the Anhui provincial CDC for SFTSV nucleic acid detection. Among them, 17 close contacts tested positive.

Sequencing and analysis of the complete SFTSV genome

On November 23, 2023, SFTSV whole genome sequences were obtained from secondary Patient K with a low Ct value (<30), and the complete S fragment sequences were successfully obtained from Patients I and N. According to the SFTSV typing method of China Center for Disease Control and Prevention, the L fragment of patient K belongs to genotype A, sharing similarity with the L fragment of AHZ2020-01(MT522608), JS2010-019(JQ317178) and Anhui-154 (MN509863). The L sequence similarity with AHZ2020-01(MT522608) was the highest (99.99%). The M fragment of patient K also belongs to genotype A, sharing similarity with the M fragment of HNXY-231(KC292313), JS2010-019(JQ317179), Gangwon (KF356892) and other sequences. The M sequence similarity with JS2010-019(JQ317179) was the highest (99.98%). The S fragment of patient K belongs to genotype A, sharing similarity with the S fragments of AHZ2011(JQ670933.1), HNXY-231(KC292286), HNXY-31(KC292283), and other sequences. The S sequence similarity with JS2010-019(JQ317179) was the highest (99.99%). The S fragment sequences of patients K, N and I showed 100% similarity. The L, M, and S fragments of patient K all belonged to genotype A, and no gene recombination was observed. Furthermore, the 100% similarity of the S fragment sequences among Patients K, N, and I indicates a close correlation between these cases (Fig. 2).

Discussion

This article reports an outbreak of human-to-human transmission of SFTS. A total of 18 individuals were involved in this outbreak. The first case was likely infected through a tick bite, as he had a history of outdoor work within 2 weeks before the onset of symptoms. Additionally, according to the results of SFTS surveillance over the years, the area where he lived is an endemic area. The first case was diagnosed with severe fever with thrombocytopenia syndrome 9 days after the onset of symptoms. Due to the atypical early symptoms, which only included fever and fatigue, the case was misdiagnosed multiple times. This ultimately affected the treatment and prognosis, a phenomenon also observed in other clusters of SFTS [14].

Therefore, early differential diagnosis, prompt detection, and timely treatment of SFTS cases are crucial [15]. Following the death of the index case, family members had insufficient awareness of the infectivity of the blood and body fluids of the corpse. As a result, within 5 to 11 days after the death of the first case, 17 individuals who

Table 2 Clinical symptoms and laboratory findings of a cluster of 18 patients with SFTS

Variables	Total (n = 18)	Death (n = 4)	Cured (n=14)
Clinical symptoms			
Fever	18(100)	4(100)	14(100)
Nausea	2(11.1)	1(25.0)	1(7.1)
Vomiting	2(11.1)	1(25.0)	1(7.1)
Fatigue	10(55.6)	2(50.0)	8(57.1)
Myalgia	2(11.1)	0(0)	2(14.3)
Multiple organ failure	4(22.2)	4(100)	0(0)
Tremors	1(5.6)	0(0)	1(7.1)
Viral encephalitis	2(11.1)	2(50.0)	0(0)
Proteinuria	12(66.7)	2(50.0)	10(71.4)
Haematuria	6(33.3)	1(25.0)	5(35.7)
Laboratory findings			
Platelet count (Peak), ($\times 10^9$/L)	48–385	55–385	48–223
Platelet count (Nadir), ($\times 10^9$/L)	17–173	17–106	47–173
White blood cell count (Peak), ($\times 10^9$/L)	1.7–47.41	1.77–47.41	1.7–12.99
White blood cell count (Nadir), ($\times 10^9$/L)	0.83–5.58	0.83–3.8	1.21–5.58
Alanine aminotransaminase (Peak), (u/ml)	10–595	10–595	28–114
Alanine aminotransaminase (Nadir), (u/ml)	10–595	10–595	13–92
Creatine kinase (Peak), (u/L)	29–21980	82–21980	29–4794
Creatine kinase (Nadir), (u/L)	20–3374	81–3374	20–383
Lactate dehydrogenase (Peak), (u/L)	197–26990	460–26990	197–814
Lactate dehydrogenase (Nadir), (u/L)	181–3364	191–3364	181–463
Creatinine (Peak), (mmol/L)	50.4–448	68.2–448	50.4–102.6
Creatinine (Nadir), (mmol/L)	42.7–220	68.2–220	42.7–91.9
Prothrombin time (Peak), (s)	10.1–38.6	11.4–22.8	10.1–38.6
Prothrombin time (Nadir), (s)	10.1–38.6	11.3–12	10.1–38.6
Activated partial thromboplastin time (Peak), (s)	15.4–146	15.4–146	17.8–63.3
Activated partial thromboplastin time (Nadir), (s)	15.4–60.2	15.4–60.2	17.8–51.6
Fibrinogen (Peak), (g/L)	1.77–3.63	2.32–3.44	1.77–3.63
Fibrinogen (Nadir), (g/L)	1.15–3.63	1.15–3.44	1.77–3.63

Table 3 The secondary rate of SFTS with different exposures with the index patient

Variables	The secondary rate of SFTS						*P*-Value	Relative risk	95% CI
	Exposed			Unexposed					
	Onset	Total	%	Onset	Total	%			
Direct blood contact with the index patient	14	25	56.0	3	19	15.8	0.007	6.778	1.570-29.354
Exposure to the blood of corpse	16	31	51.6	1	13	7.7	0.006	12.800	1.479-110.789
No standard protection	17	34	50.0	0	10	0	0.004	-	-

had close contact with the corpse developed related symptoms, and 3 of them died. The case fatality rate among secondary cases was 17.6%, which is almost equal to the polled case fatality rate of SFTS patients in China (16.6%) [16]. The intervals between exposure to blood and the onset of illness ranged from 5 to 11 (median: 9 days), which is consistent with other case clusters [14, 17].

In our study, a probable route for the person to person transmission of SFTSV was direct contact, which has been documented in other studies [18–20]. In certain rural areas of China, traditional funeral customs are still practiced. Families of patients who succumb to SFTS often request discharge from the hospital to manage funeral arrangements within their villages. In this case, after the death of the index patient, the tracheal tube was removed from the corpse at home, and bleeding from the body was still observed. 14 secondary cases, who did not take any personal protective measures, participated in handling the index patient's corpse and had close contact with the deceased's body surface, blood, or other secretions. We postulate that the index patient served as a significant source of viral transmission to those in close proximity during this period.

Probable aerosol transmission of SFTS was also observed in this cluster. Another 3 secondary patients (Patient H, I, and K) had no directly contact with the blood of the index patient but stayed in a poorly

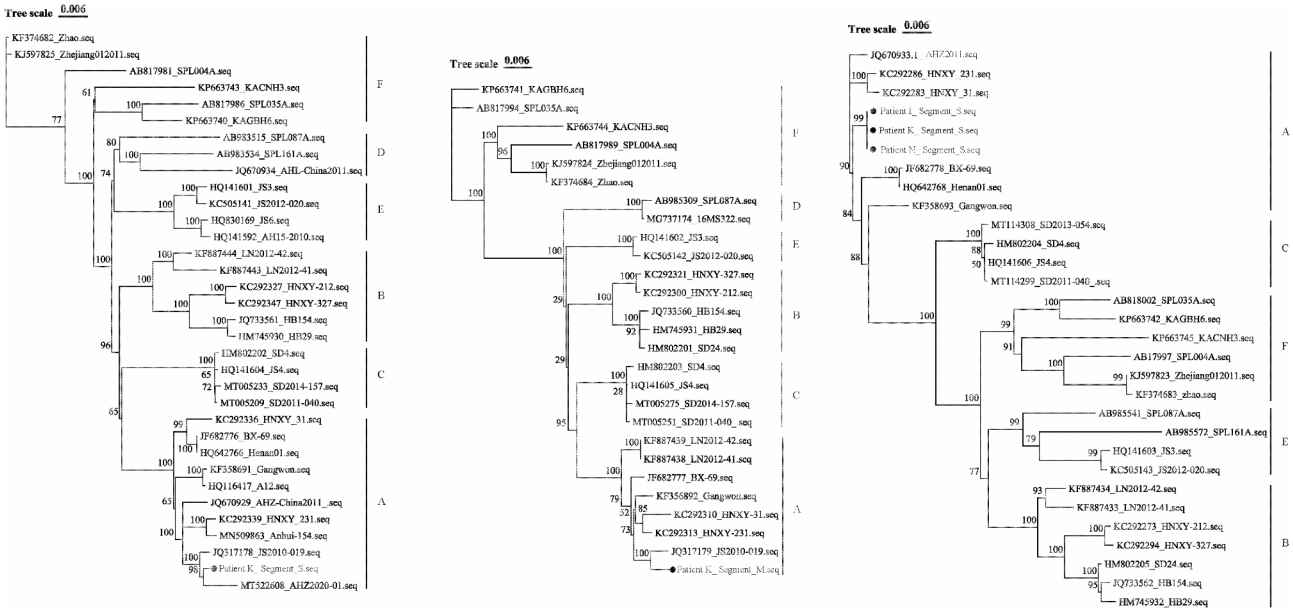

Fig. 2 The phylogenetic trees of the SFTSV genome for the L, M, S segments. The lack circle represents gene sequences in this study

ventilated room where the body was handled and stored for an extended period without personal protective measures. We believe that aerosol transmission is the most likely route in this scenario. Firstly, they had absolutely no direct contact with the blood of the corpse. Secondly, retrospective investigations revealed that all three had a history of staying in the mourning hall. One stayed for twenty minutes, while the other two stayed for several hours. Thirdly, the corpse was placed in a small, poorly ventilated room. Exposure to such an environment where the corpse was stored ($\chi^2 = 5.49$, $P = 0.019$) was significantly associated with SFTSV infection [12]. Fourthly, the timing of their illness was consistent with the exposure to the corpse. Fifthly, this is supported by the identical S fragments of patients K, N and I. Patient N had a clear history of contact with blood and body fluids. Lastly, concurrent investigations have indicated that aerosol transmission may also represent a viable route for person-to-person transmission of SFTSV [12, 21, 22]. Thus, we speculated that these 3 secondary cases may have been infected with SFTSV through aerosols in closed environment.

In addition, direct contact with blood poses a higher risk of transmission compared to exposure in an airtight aerosol environment. Furthermore, contact with a bleeding corpse presents a greater transmission risk than exposure to the blood of a living patient. An 11-year retrospective study in China showed that exposure to the blood of a deceased person during burial preparation was more likely to result in secondary cases than exposure to the blood of a living patient, and this retrospective cohort study provided further epidemiological evidence for this view (RR = 41.600, 95% CI = 5.063-341.831) [4]. Due to local funeral customs in rural China, elders in the family usually clean and dress the body of the deceased for burial, then stay in the family funeral hall for three days before burial. In addition, critically ill SFTS patients often present with bleeding from multiple orifices, which inevitably leads to contact with the bleeding corpse, significantly increasing the risk of secondary cases. At the same time, we found that all secondary cases occurred in individuals without standard protective measures. Conversely, none of the healthcare workers equipped with personal protective equipment were infected. Therefore, it is important to properly handle the corpses of patients who died from SFTS, and healthcare institutions should educate family members of patients preparing for discharge about necessary protective measures and provide a body-cleansing program.

There are some limitations to our study. Firstly, the unavailability of tick samples obtained from suspected infection sites poses a constraint on gathering additional evidence. Secondly, no serum sample of Patient A, was available for retrospective viral load detection. Lastly, we could not establish a dose-response relationship between the frequency of exposure to the index case and the risk of infection.

Conclusion

In this article, we conclude that this cluster outbreak was caused by person-to-person transmission. Direct contact with the patient's blood and body fluids may lead to SFTSV transmission. Additionally, transmission may also occur through aerosols in a poorly ventilated environment. The key lesson from this cluster of potential person-to-person transmission of SFTSV is that healthcare

institutions should educate family members of patients preparing for discharge about protective measures and provide a body-cleansing program.

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Author contributions
J-BW and X-XL: Investigation, Writing, Editing. NC, D-DS, W-HL, X-JC and H-BL: Methodology, Writing. WC, LG, and X-WT: Formal analysis, Data curation. W-WL, YS, X-ZC and ML: Software, Investigation, Writing. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This present research reported here has been approved by the Ethics Committee of Anhui Provincial CDC. Human research was carried out in accordance with the provisions of the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

Disclosure statement
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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