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A ten-year assessment of the epidemiological features and fatal risk factors of hospitalised severe fever with thrombocytopenia syndrome in Eastern China

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Abstract

Severe fever with thrombocytopenia syndrome (SFTS) virus has caused a large number of human infections since discovered in 2009. This study elucidated epidemiological features and fatal risk factors of SFTS cases accumulated up to ten years in Taizhou, a coastal prefecture of Zhejiang Province in Eastern China. A total of 188 hospitalised SFTS cases (including 40 deaths) reported to Taizhou Center for Disease Control and Prevention (CDC) during 2011–2020 were enrolled in the study. In the past decade, the annual incidence of SFTS increased over the years ($P < 0.001$) along with an expanding epidemic area, and the case fatality of hospitalised cases has remained high (21.3%). Although most cases occurred in hilly areas, a coastal island had the highest incidence and case fatality. The majority of cases were over the age of 60 years (72.3%), and both incidence and case fatality of SFTS increased with age. Multivariate logistic regression analysis showed that age (OR 7.47, 95% CI 1.32–42.33; $P = 0.023$), and haemorrhagic manifestations including petechiae (OR 7.76, 95% CI 1.17–51.50; $P = 0.034$), gingival haemorrhage (OR 5.38, 95% CI 1.25–23.15; $P = 0.024$) and melena (OR 5.75, 95% CI 1.18–28.07; $P = 0.031$) were significantly associated with the death of SFTS cases. Five family clusters identified were farmers, among four of which the index patients were female with a history of hypertension. Based on the study, age is a critical risk factor for incidence and case fatality of SFTS. With an increased annual incidence over the last ten years, SFTS remains a public health threat that should not be ignored. Further study is needed to look at the natural foci in the coastal islands.

Introduction

Severe fever with thrombocytopenia syndrome virus (SFTSV) is a novel tick-borne bunyavirus firstly discovered in 2009 in China [1]. In 2019, the virus was renamed as *Dabie bandavirus* and classified into *Bandavirus* genus, *Phenuiviridae* family, *Bunyavirales* order by the International Committee on Taxonomy of Viruses (ICTV) (https://talk.ictvonline.org/taxonomy). The major clinical symptoms of severe fever with thrombocytopenia syndrome (SFTS) patients include acute fever, gastrointestinal symptoms, haemorrhagic manifestations, central nervous system (CNS) manifestations, thrombocytopenia and leucopenia, followed with multiple organ dysfunctions [2]. SFTSV is mainly transmitted and maintained by *Haemaphysalis longicornis*, but also detected and isolated from other tick species [3, 4]. Both domestic and wild animals are regular hosts of SFTSV, as SFTSV antibodies or RNA have been found in several animal species including sheep, cattle, dogs, pigs, chickens, cats, rodents, hedgehogs and so on [5–8]. Person-to-person transmission has also occurred, via direct contact with blood or body fluid from infected patients [9–11]. SFTS cases have also been confirmed in Japan, South Korea and Vietnam, plus evidence in Pakistan and Myanmar [12–16].

From 2010 to 2018, SFTS cases had been reported in 25 provinces of China, with a case fatality of 10.5% [17]. SFTS cases were mainly distributed in central and eastern Chinese provinces including Henan, Hubei, Anhui, Jiangsu, Zhejiang, Shandong and Liaoning, and cases in these provinces frequently originated from rural, hilly regions [18–20]. The SFTS cases in Zhejiang Province were mainly clustered in eight counties during 2011–2015, of which three were located in Taizhou prefecture, suggesting that there were probable epidemics or outbreaks of SFTS [21]. Therefore, to solicit the epidemiological and clinical features of the SFTS epidemic in Taizhou, we reviewed and analysed the epidemiological and clinical data of reported SFTS cases in Taizhou during the past decade.

Materials and methods

Study site

Taizhou prefecture is located in the east area of Zhejiang Province, Eastern China (120°17′~121°56′ E, 28°01′~29°20′ N), near East China Sea (Supplementary Fig. S1). It has 9 counties or districts comprising 129 administrative townships with a total of 6.15 million residents. The total land area is 10050.43 square kilometres, of which 73% are mountainous and hilly areas under a warm and humid climate. It is one of the first regions reporting the SFTS cases in Zhejiang Province where 34% of all identified SFTS cases had been reported by Taizhou during 2011–2018 [22].

Data collection and management

According to the national guidelines, a laboratory-confirmed SFTS diagnosis satisfied one or more of the following criteria: (1) isolated SFTSV from patient's biospecimens, (2) detectable SFTSV RNA in serum or blood samples, (3) virus-specific IgG and/or IgM seroconversion or four-fold increase between acute and convalescent serum samples [23].

All laboratory-confirmed SFTS cases in Taizhou during 1 January 2011 to 31 December 2020 were subject to the analysis. The surveillance was performed at local CDC or visiting medical institutions. Following laboratory confirmation, an epidemiological investigation was administered immediately to each case. The information of cases was reported to local public health department, including the time of illness onset, confirmation and outcome. For the present study, demographic characteristics, exposure history, clinical symptoms and laboratory results of the cases were extracted from a structured questionnaire. Exposure history included agricultural activities, history of exposure to a tick, history of tick bite, skin breakdown, breeding domestic animals and contact animals within the month before their onset of symptoms. The study was approved by the Institutional Review Board of Fudan University School of Public Health, Shanghai, China.

Statistical analysis

The demographic, temporal and spatial distributions of the SFTS cases were described and tabulated using R software v4.0.2 (R Core Team 2013). The clinical and laboratory features of SFTS cases were analysed using the Statistical Product and Service Solutions software (SPSS v22; SPSS, Chicago, IL, USA).

All data were expressed as the percentage, mean ± standard deviation (S.D.) or median (range or interquartile range, IQR). To determine the difference between groups, means for continuous variables were compared using the independent-group student's *t* test when the data were normally distributed; otherwise, the Mann–Whitney *U* test and Kruskal–Wallis *H* test were used. Categorical variables were compared with a χ^2 test or Fisher's exact test. Spearman's correlation was calculated for the time from onset to confirmation and years. Univariate and multivariate logistic regression models were used to examine risk factors associated with death of SFTS cases. Variables with *P* value less than 0.10 in univariate analyses [24] or shown to be associated with fatal outcome in previous literature were included in multivariate analysis [2, 25, 26]. Age and sex were adjusted in the multivariate logistic regression model, while odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Significance for these analyses was defined at a *P* level of 0.05.

Results

Epidemiological characteristics

Temporal and populational distributions

From 2011 to 2020, a total of 188 laboratory-confirmed SFTS cases were reported. These cases met the criteria with a positive result for SFTSV RNA detected by real-time RT-PCR assay. Annual case numbers displayed striking variations and a sharp increase occurred in 2013–2015 (Fig. 1a). The annual incidence of SFTS increased over the years ($P < 0.001$). The SFTS epidemic curve followed an apparent seasonal pattern, and most cases occurred between April and October (81.4%, 163/188), with a major epidemic peak from May to July (60.1%, 115/188) (Fig. 1b). Among the total of 188 cases, 102 (54.3%) were male with an overall male-to-female ratio of 1.2:1 (Fig. 1a). The median age was 66 years with a range from 33 to 88 years, and the overall incidence increased with age ($P < 0.001$) in ten years (Fig. 1c). The majority of the cases lived in mountainous and hilly areas, and 94.7% were farmers. The median time from illness onset to confirmation was 7.5 days (ranged from 1 to 39 days), decreasing significantly ($r_s = -0.169$, $P = 0.021$) from 18 days in 2011 to 8 days in 2020 (Fig. 1d).

Among 188 laboratory-confirmed SFTS cases, a total of 40 deaths were reported, with an overall case fatality of 21.3%. The annual case fatality fluctuated between the highest (45.5%) in 2014 and the lowest (16.0%) in 2016. The median age of the deaths was 72 years with a range from 52 to 88 years, and the case fatality increased with age ($P = 0.001$) in ten years (Fig. 1c). Furthermore, the majority of deaths aged 60 years or older ($P = 0.005$), and the age of deaths was significantly higher than the survivals ($P < 0.001$). However, no significant differences ($P > 0.05$) were observed in gender, occupation, residence, comorbidities, smoking history and the intervals between illness onset and confirmation (Table 1).

Potential exposures

Most cases lived in mountainous or hilly areas, and engaged in agricultural activities. About 64.3% (117/182) of the cases had a history of farming within 2 weeks before illness onset. Within the past one month before illness onset, 47.2% (85/180) of the cases bred domestic animals, 65.7% (115/175) had been exposed to mice, but only 5 cases reported a history of exposure to wild animals. In addition, there were 62.6% (114/182) of the cases had noted ticks around the houses, and 51.4% (93/181) had seen the tick in the past one month before illness onset. Only 19.9% (36/181) reported a history of tick-bite, whereas 47.0% (85/181) cases were not certain whether they had been bit in the past one month before illness onset. In comparison to the survivals, the deaths were observed with a significant difference in mowing ($P = 0.021$) and tick bites ($P = 0.017$). Nevertheless, no significant differences were observed in wild or domestic animal contacts between the deaths and the survivals ($P > 0.05$).

Spatial distribution

The 188 SFTS cases were reported in 36 townships of six counties, including Linhai (42.6%), Tiantai (34.6%), Sanmen (10.1%), Xianju (8.5%) and Jiaojiang (2.7%), and Huangyan reported only sporadic SFTS cases (Supplementary Fig. S2). Among the six counties, Tiantai had the highest ten-year incidence of SFTS cases, followed by Linhai, Sanmen, Xianju, Jiaojiang and Huangyan, with the incidence being 16.0, 7.6, 5.4, 4.5, 0.7, 0.5 per 10^5 persons.

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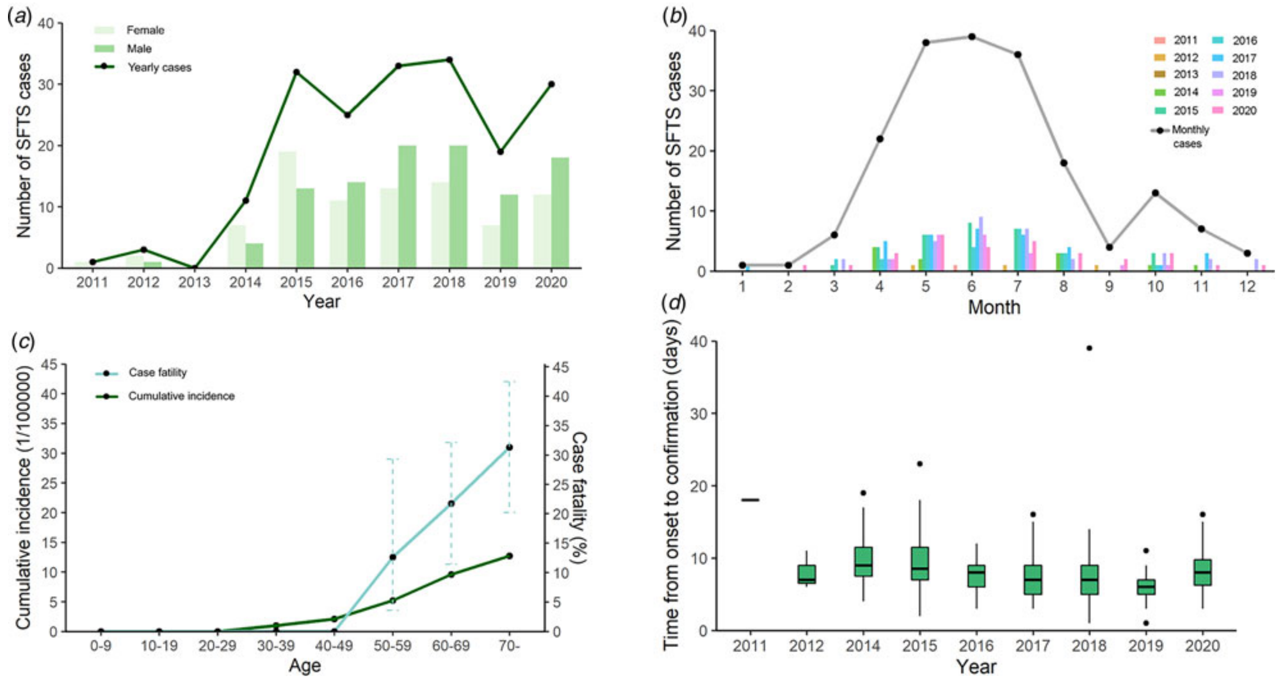

Fig. 1. Temporal and population distribution of the human SFTS cases in Taizhou, 2011–2020. (a). Annal number and sex distribution of the human SFTS cases in Taizhou from 2011 to 2020. Pale green indicates females, while dark green indicates males. (b). Monthly distribution of the human SFTS cases in Taizhou from 2011 to 2020. (c). Age distribution of the SFTS incidence and case fatality in ten years in Taizhou. Pale blue indicates cumulative incidence (1/100 000), while green indicates case fatality (%). (d). Trend of time from onset to confirmation of the SFTS cases in Taizhou from 2011 to 2020.

Although the SFTS cases mainly distributed in the northern and southern hilly areas of Taizhou prefecture, the township with the highest incidence and case fatality was Dachen island located in East China Sea, which were 127.58 per 10^5 persons and 60.0%, respectively. Although only about 3900 residents live in this island, SFTS cases have been annually reported in this island since 2016. To explore possible reasons of the high incidence and case fatality in Dachen island, we compared the age, seasonal distribution and history of exposure to ticks for the SFTS patients in Dachen and other townships. We found no significant difference was observed in terms of age and seasonal distribution between the patients in Dachen and other townships ($P > 0.05$), but the patients in Dachen island had a more intensive exposure to the tick bite in the past one month before illness onset ($P = 0.040$).

Clinical and laboratory features

182 cases reported from 2014 to 2020 were enrolled in the clinical and laboratory analyses. The major clinical symptoms included fever, anorexia, fatigue, chills, nausea and headache. Fever was the most frequent clinical complaint and a high fever over 39 °C was recorded in 64.8% of fever reporting cases. Fatal cases had a higher body temperature (≥39 °C) than non-fatal cases ($P = 0.044$). In comparison to the non-fatal cases, the fatal cases were not observed with a significant difference in gastrointestinal manifestations including nausea, vomiting, abdominal pain and diarrhoea. Meanwhile, 29% of cases had haemorrhagic manifestations including conjunctival congestion (14.9%, 27/181), petechiae (8.2%, 15/182), gingival haemorrhage (11.5%, 21/182), hematemesis (2.7%, 5/182) and melena (8.7%, 11/127). The occurrences of petechiae ($P = 0.005$), gingival haemorrhage ($P = 0.020$) and melena ($P = 0.012$) in fatal patients were more frequent than non-fatal patients, respectively (Supplementary Table S1).

About 92.8% of the cases had thrombocytopenia (platelets $< 100 \times 10^9$/l) and 91.7% had leucocytopenia (leucocytes $< 4 \times 10^9$ cells/l). The median platelet count was 47.5×10^9/l, and the fatal cases showed a lower platelet count than the non-fatal cases ($P < 0.001$). However, the leucocyte count was not significantly different between fatal and non-fatal patients.

To assess the risk factors for fatal outcome, logistic regression models were performed. The results of univariate analyses suggested that age and the symptoms of high fever (≥39 °C), petechiae, gingival haemorrhage and melena were significantly associated with fatal outcome (Table 2). In multivariate logistic regression analysis, age (OR 7.47, 95% CI 1.32–42.33; $P = 0.023$), and haemorrhagic manifestations including petechiae (OR 7.76, 95% CI 1.17–51.50; $P = 0.034$), gingival haemorrhage (OR 5.38, 95% CI 1.25–23.15; $P = 0.024$) and melena (OR 5.75, 95% CI 1.18–28.07; $P = 0.031$) still remained significantly associated with fatal outcome (Table 2).

Family clusters

Five family clusters were reported in Taizhou during the study period. Of the five clusters, all index patients and remanent patients were farmers, aged 52 years and older. The first cluster occurring in 2014 comprised three confirmed SFTS cases. The index patient and two following patients were sisters and they all died shortly after disease onset. For each of the other four family clusters (i.e. clusters A-D), the two confirmed SFTS cases were a couple. Of note, all four index patients were females with a history of hypertension. All four remanent patients were the index patient's husbands, who manifested symptoms after their index patients' disease onset. The interval time of clinical illness between index patient and secondary patient was 12 days in cluster A and 10 days in cluster D, respectively, but only 1–2 days in clusters B and C (Supplementary Table S2).

Table 1. Characteristics of SFTS patients in Taizhou, Zhejiang Province, 2011–2020

	Total (N = 188) No. (%)	Fatal (N = 40) No. (%)	Non-fatal (N = 148) No. (%)	P-value
Age, years, median (range)	66.0 (33–88)	72.0 (52–88)	64.0 (33–88)	<0.001
Age group, years				0.005
<60	52 (27.7)	4 (10.0)	48 (32.4)	
≥60	136 (72.3)	36 (90.0)	100 (67.6)	
Sex				0.411
Female	86 (45.7)	16 (40.0)	70 (47.3)	
Male	102 (54.3)	24 (60.0)	78 (52.7)	
Residence				1.000
Rural	186 (98.9)	40 (100.0)	146 (98.6)	
Urban	2 (1.1)	0	2 (1.4)	
Occupation				0.224
Famers	178 (94.7)	36 (90.0)	142 (95.9)	
Others	10 (5.3)	4 (10.0)	6 (4.1)	
Comorbidities[a]	73 (44.2)	18 (54.5)	55 (41.7)	0.183
Hypertension	50 (30.3)	13 (39.4)	37 (28.0)	0.204
Diabetes mellitus	6 (3.6)	1 (3.0)	5 (3.8)	1.000
Chronic respiratory disease	4 (2.4)	1 (3.0)	3 (2.3)	1.000
Smoking history	48 (29.3)	11 (32.4)	37 (28.2)	0.638
Time interval, days, median (range)				
From onset to confirmation	7.5 (1–39)	8 (3–19)	7 (1–39)	0.511
From onset to death	–	9 (2–28)	–	

Pearson χ^2 test or Fisher's exact test was used to compare categorical variables. Mann–Whitney U test was used to compared continuous variables.
$P < 0.05$ was considered statistically significant.
SFTS, severe fever with thrombocytopenia syndrome; IQR, interquartile range.
[a]Information was missing for 23 SFTS patients.

Table 2. Logistic regression analysis of clinical predictors of deaths among cases with SFTS

	Univariable		Multivariable[a]	
Variable	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (≥60, years)	4.32 (1.45–12.83)	0.008	7.47 (1.32–42.33)	0.023
Fever (≥39 °C)	10.12 (1.30–78.44)	0.027	2.31 (0.59–8.97)	0.227
Petechiae	7.90 (2.43–25.65)	0.001	7.76 (1.17–51.50)	0.034
Gingival haemorrhage	4.55 (1.51–13.73)	0.007	5.38 (1.25–23.15)	0.024
Melena	5.46 (1.38–21.61)	0.016	5.75 (1.18–28.07)	0.031

SFTS, severe fever with thrombocytopenia syndrome.
[a]Adjusting for sex and age; OR, odds ratio; CI, confidence interval.

Discussion

In the present study, we observed that the annual incidence of SFTS increased over the last ten years along with an expanding epidemic area, and the case fatality of hospitalised cases has remained high (21.3%). The majority of SFTS cases resided in the hilly regions, but the highest incidence and case fatality occurred in an eastern coastal island. Both of the incidence and case fatality of SFTS increased with age. Furthermore, age was also a risk factor associated with fatal outcome, as well as haemorrhagic manifestations including petechiae, gingival haemorrhage and melena.

By the end of 2018, a total of twenty-five provinces had reported over 11 000 SFTS cases in mainland China, with an annual incidence of 0.064 per 10^5 persons and a case fatality of 10.5% [17]. The annual incidence and case fatality we observed in Taizhou were higher than the overall average for China in 2018. The number of reported SFTS cases may be influenced by the improvement of diagnosis and detection capacity. The median time from onset to confirmation was 7.5 days, with a significant decrease from 18 days in 2011 to 8 days in 2020. At the beginning of the SFTS epidemic, the median time from onset to confirmation was longer, which seems to be related to lack of clinical experience with SFTS among physicians. However, a delayed diagnosis of the disease could affect the prognosis of the SFTS cases [27, 28]. To shorten the time from onset to confirmation and reduce case fatality rate, the capability to identify and cure SFTSV infection must be enhanced in hospitals.

Majority of the patients worked as farmers residing in mountainous and hilly regions [18, 29]. SFTS cases reported in Taizhou were also mainly distributed in the northern and southern hilly areas. However, the township with the highest incidence and case fatality was Dachen island. The island has abundant forest sources and the dominant tick species is *H. longicornis* [30]. Moreover, this island is close to the nearby Zhoushan islands, where some SFTSV strains isolated and classified into linage B might be transmitted from South Korea by migration birds [31]. A thorough investigation of the SFTSV transmission chain between ticks, animals and humans is needed in Dachen island.

Risk factors related to fatal outcome have previously been reported in a few studies, including elder age, high viral load, comorbidities, neurological manifestations, coagulopathy, respiratory symptoms and host immune responses [27, 32–35]. However, the majority of these results were assessed by univariate analysis. In our study, we used a multivariate logistic regression model to control confounding and estimate the direct effects of several possible causal risk factors. Our results showed that elder age was a critical risk factor for fatal outcome. In our study, most cases were over the age of 60 years, while both of the incidence and case fatality of SFTS increased with age. Elderly people with decreased immune function and comorbidities may suffer from severe clinical symptoms after SFTSV infections [36]. Remarkably, haemorrhagic manifestations including melena, gingival haemorrhage and petechiae were critical risk factors for fatal outcome in our study. Haemorrhagic manifestations are commonly observed among severely affected or dying patients [27, 37–39], and might be associated with a disorder of the internal and external coagulation pathways, such as the activated partial thromboplastin time (APTT) and prothrombin time (PT) prolonging [40]. As the vital clinical parameters were associated with fatal outcome of SFTS, the underlying mechanism of haemorrhagic manifestations need to be intensively studied.

Currently, family clusters have been reported in several provinces in China, which occurred probably due to person-to-person transmission and homologous SFTSV infection [9, 10, 41]. We identified five family clusters during 2011–2020, all patients were farmers. Notably, for each of the four family clusters of couple cases, all index cases were female with a history of hypertension. In agreement with previous studies [25], hypertension is one of the most prevalent comorbidities (30.5%) in SFTS cases, and we found that female SFTS cases were more likely to be living with hypertension than male cases. Furthermore, all family clusters occurred during April to June, when farmers particularly elderly female farmers were involved in seasonal activities such as picking teas and red bayberries.

The study has a couple of limitations. First, only hospitalised cases were identifiable and subject to the present analysis. Thus, the case fatality of SFTS reported in the study might be an overestimation and should not be applicable to asymptomatic cases or general conditions. Second, the obvious epidemiological disparities within the five family clusters remained unclear due to lack of thorough and timely epidemiological investigations. For example, detailed exposure behaviours and transmission patterns of the cases were unavailable.

In conclusion, our study for the first time reported epidemiological characteristics, clinical and laboratory features, and family clusters of SFTS cases in Taizhou, Zhejiang Province. We found a steady increased incidence along with an expanding epidemic area, and a high case fatality in the past decade. And both the incidence and case fatality of SFTS increased with age. Age and haemorrhagic manifestations were risk factors for fatal outcome. These findings have important implications for developing SFTS prevention and control strategy. Further research is warranted to solicit natural transmission mode of SFTSV among humans, hosts and vectors.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268822001108.

Author contributions. H. L. and N. H. contributed to the conception of the work and generally supervised the study. Z. Z. performed data analysis and drafted the manuscript. H. L. and N. H. critically revised the manuscript. Y. H., X. Z., C. C., Y. Z., Y. J. contributed to data collection, analysis or interpretation. All authors had access to and approved the final version of the manuscript.

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Conflict of interest. The authors declare that they have no competing interests.

Data availability statement. Readers may contact the authors for accessing data used in this study.

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