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MAJOR ARTICLE

Epidemiological Characteristics and Risk Factors of Severe Fever With Thrombocytopenia Syndrome in Yantai City, Shandong Province

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Background. To better understand the epidemiological characteristics and risk factors associated with the incidence of severe fever with thrombocytopenia syndrome (SFTS) in Yantai City, Shandong Province, China.

Methods. The SFTS data from 2010 to 2019 were obtained from the National Notifiable Disease Reporting System, and visualization was performed using ArcGIS 10. A community-based, 1:2 matched case-control study was conducted to investigate the risk factors for SFTS in Yantai City. Standardized questionnaires were used to collect detailed information about the demographics and risk factors for SFTSV infection.

Results. A total of 968 laboratory-confirmed SFTS cases were reported, 155 (16.01%) of which were fatal. The SFTS epidemic curve revealed that most cases occurred from May to August, accounting for 77.27% of all studied cases. The SFTS cases were mainly distributed in Lai Zhou, Penglai, Zhaoyuan, Haiyang, and Qixia from 2010 to 2019 (accounting for 83.47% of all cases). No differences in demographics were observed between the cases and controls. In the multivariate analysis, presence of rats in the household (odds ratio [OR] = 2.89, 95% confidence interval [CI] = 1.94–4.30), bitten by the ticks 1 month before the onset of symptoms (OR = 15.97, 95% CI = 5.36–47.60), and presence of weeds and shrubs around the house (OR = 1.70, 95% CI = 1.12–2.60) were found to be the risk factors for SFTS.

Conclusions. Our results support the hypothesis that ticks are important vectors of the SFTS virus. Education on SFTS prevention and personal hygiene should be imparted in high-risk populations, especially among outdoor workers living in SFTS-endemic areas, while vector management should also be considered.

Keywords. epidemiological; human infection; severe fever with thrombocytopenia syndrome; transmission.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease that was first reported in China in 2009 [1]. The causative virus, named the severe fever with thrombocytopenia syndrome virus (SFTSV), was isolated from an infected human. Since then, patients with confirmed SFTSV infection have been reported in 19 provinces of mainland China [2] as well as in other countries such as Japan, South Korea, the United States, and the United Arab Emirates [3–6]. Most cases were reported in China, with a high fatality rate of 12%–30% [1]. Severe fever with thrombocytopenia syndrome cases have been reported in 25 provinces in China from 2010 to 2019, with the numbers increasing annually [7].

Ticks are considered the most probable vectors of SFTSV transmission, and their derived sequences share high similarity with human- and animal-derived isolates [8, 9]. Severe fever with thrombocytopenia syndrome virus ribonucleic acid (RNA) has been detected in several tick species, including *Haemaphysalis longicornis*, *Haemaphysalis flava*, *Ixodes nipponensis*, and *Amblyomma testudinarium*, but it can only be isolated from *H. longicornis* ticks [9–11]. Zhang et al [12] reported that *H. longicornis* may be a major vector of SFTSV and that its geographic distribution and density may play a central role in the risk of SFTSV infection in humans. We aimed to understand the risk posed to humans living in areas where ticks are endemic not a specific species, thus we only mentioned *H. longicornis* once, and later we use the general term "ticks".

The national average mortality rate of SFTSV infection is 5.3%, with a higher rate in the elderly [7]. The main epidemic period is from May to July, with a peak in June [13]. Yantai has been the hardest-hit area in Shandong Province, where

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SFTSV has become endemic. The numbers of SFTS cases in Yantai in 2010 and 2011 were 44 and 81, respectively, accounting for 39.3% and 48.2% of the total number of SFTS cases in Shandong Province, respectively. There are many hills and mountains in Yantai City that host several tick species. Since 2007, some cases of fever of unknown cause have been reported successively, characterized by hemorrhagic fever and negative plasma antibody tests. Cases of fever and thrombocytopenia were studied in 2010 to detect the presence of novel Bunia virus nucleic acids in their serum. The results showed that the serum contained the same virus that was isolated from the ticks captured in Yantai. Although cases of SFTS have been detected in Yantai City for a long time, the epidemiological characteristics and risk factors for SFTS in Yantai City remain unclear. In this study, we conducted a systematic study to understand the epidemiological characteristics of SFTS and to explore the spatial and ecological risk factors for human SFTS from 2010 to 2019 in Yantai City.

METHODS

Ethical Approval

This study was reviewed and approved by the Ethics Committee of the Chinese Center for Disease Control and Prevention. According to the medical research of the National Health and Family Planning Commission of China, the commission uses international guidelines to ensure recognition, anonymity, and informed consent. Informed consent was obtained from all participants.

Patient Consent Statement

This study did not involve human participants and human experimentation. The only human materials used were blood samples collected from SFTS patients for public health purposes, and written informed consent for the use of their clinical samples was obtained from these patients.

Data Source

Data on laboratory-confirmed SFTS cases from January 1, 2010 to December 31, 2019 were extracted from the National Notifiable Disease Reposing System.

Case and Control Definition

According to the national guidelines for SFTS diagnosis (The Ministry of Health of People's Republic of China, 2010), patients with SFTS were defined as those who had positive real-time reverse-transcription polymerase chain reaction (RT-PCR) results for the SFTSV in this study. For each case, 2 controls were matched with negative laboratory test results for SFTS infection (RT-PCR). The controls were neighbors living in the same community or village with the case for more than 6 months, and their age was no more than 5 years older from that of the case.

Microbiological Analyses

Serum samples from suspected SFTS patients and identified matched controls were collected and transported in a cold box (4–8°C) to the laboratory of the Yantai Center for Disease Control and Prevention for testing. The RT-PCR was used to detect SFTSV RNA, according to the manufacturer's instructions.

Data and Sample Collection in the Community Case-Control Study

A structured questionnaire was designed by well trained interviewers to collect information from each case and identify matched controls (1:2 pair matching) using a face-to-face approach. Standardized questionnaires were used to collect detailed information on the cases and controls. The study participants were asked about their demographics (age, sex, nation, occupation, home address), exposure history within the 1 month before onset (eg, contact with a sick relative or neighbor, type of occupation, raising/contact with animals, tick or other insect bites, and preventative measures taken during outdoor activities), other possible risk factors (resting on a grass field, working with broken skin, and underlying diseases), and living and working environment (eg, presence of rats, weeds and shrubs, and ticks). The questionnaires were completed within 2 weeks after the laboratory diagnosis. All questionnaires were systematically verified for data completeness by the Shandong Center for Disease Control and Prevention (SDCDC) study coordinators. The geographical distribution of each confirmed SFTS case was analyzed according to the current living address and was linked to the town and county-level map of Yantai city using Geographic Information System (GIS) technology.

Statistical Analysis

The data were entered in Epidata 3.1, and a database consistency check was performed. SPSS version 18.0 (Statistical Product and Service Solutions, Chicago, IL) was used for all statistical analyses. The risk factors for SFTS were identified using univariate and multivariate conditional logistic regression models. A stepwise forward method was used to screen for independent risk factors in multivariate analysis. $P < .05$ was considered significant.

RESULTS

A total of 968 laboratory-confirmed SFTS cases were reported during the study period, 155 (16.01%) of which were fatal. The number of confirmed SFTS cases from 2010 to 2019 per year was 44, 81, 19, 44, 120, 127, 141, 89, 177, and 126, respectively. Confirmed cases were reported every month, except in January and February. The SFTS cases were reported began in April, after which the number of cases increased rapidly and then gradually declined in August. The number of cases reported from May to

Table 1. Summary of Epidemiological Characteristics of Severe Fever With Thrombocytopenia Syndrome in Yantai City, Shangdong Province, From 2010 to 2019

Characteristics	Total Cases (n = 968)	Deaths (n = 155)
Male, No. (%)	497 (51.34%)	92 (59.35%)
Age, mean ± standard deviation	63.68 ± 11.94	68.32 ± 9.48
Farmers (%)	841 (86.88%)	126 (81.29%)
Temporal Distribution	…	…
2010	44	6
2011	81	11
2012	19	5
2013	44	5
2014	120	25
2015	127	15
2016	141	16
2017	89	15
2018	177	31
2019	126	26
Epidemic Peak, No. (%)	May to August, 748 (77.27%)	May to August, 123 (79.35%)

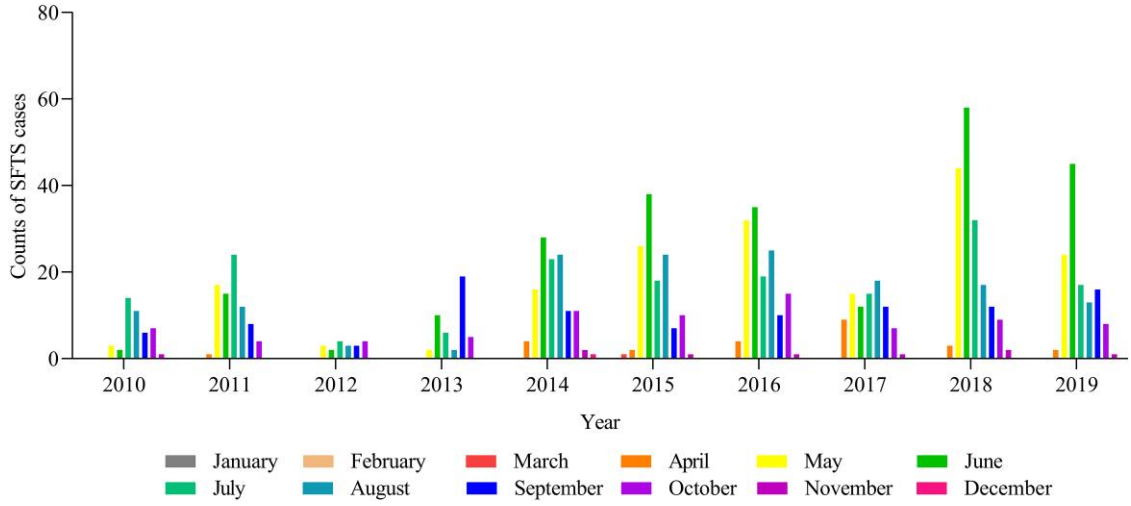

Figure 1. Monthly distribution of severe fever with thrombocytopenia syndrome (SFTS) cases from 2010–2019 in Yantai City. The horizontal axis represents January to December from 2010 to 2019. The vertical axis represents the number of cases.

August was the highest, accounting for 77.27% (Table 1, Figure 1). Deaths occurred from April to November, with the largest number occurring from May to August (79.35%) (Figure 2). Male-confirmed SFTS cases were 497 (51.34%) and the male-to-female ratio was 1.06:1. Most confirmed SFTS cases were farmers, which accounted for 86.88% (841 of 968) of the cases. The mean age was 63.68 years (ranging from 11 to 95 years), and 932 cases (92.37%) were mainly in the 45–85 years age group. Of the 155 fatal SFTS cases, 92 (59.35%) were men, with an average age of 68.32 years (range, 43–95 years).

From 2010 to 2019, the cumulative number of towns that reported SFTS cases increased from 18 to 126 (Figure 3). However, SFTS cases were still mainly distributed in Lai Zhou (225 cases), Penglai (209 cases), Zhaoyuan (155 cases), Haiyang (137 cases), and Qixia (82 cases), accounting for 83.47% (808 of 968), as shown in Figure 4*A*. Deaths were reported in 70 towns in Yantai and were mainly distributed in Penglai (38 cases), Zhaoyuan (32 cases), Laizhou (26 cases), Haiyang (20 cases), and Qixia (12 cases), accounting for 82.58% (128 of 155) of deaths, as shown in Figure 4*B*.

A total of 577 individuals participated in the study, including 199 cases and 398 matched controls. The matching ratio was approximately 1:2. All 199 cases showed positive results on PCR testing. No differences in demographics (eg, sex, nation, occupation, and age) were observed between the cases and controls. However, farmers were more frequently represented among the cases (91.96%) than among the controls (88.44%). All cases were of Han ethnicity (Table 2).

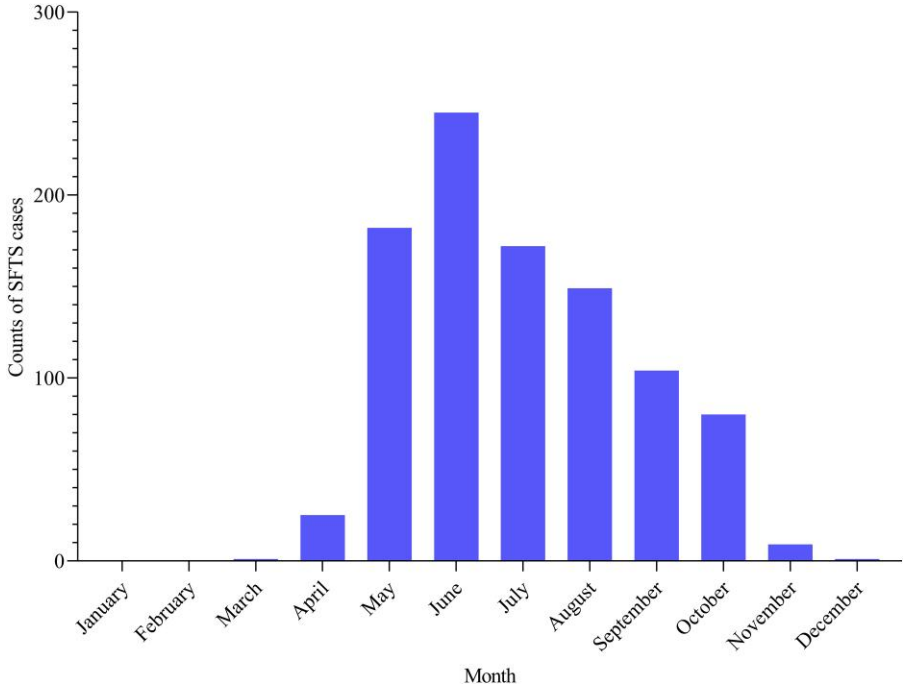

Figure 2. Monthly distribution of accumulative severe fever with thrombocytopenia syndrome (SFTS) deaths from 2010 to 2019 in Yantai City. The horizontal axis represents January to December. The vertical axis represents the number of deaths.

As shown in the univariate analysis, potential risk factors for SFTS included the presence of rats in the household, presence of ticks within 500 m of the living area, domestic animals bitten by ticks, bitten by the ticks 1 month before the onset of symptoms, presence of weeds and shrubs in working areas, presence of weeds and shrubs around the house, and resting on a grass field during work breaks (Table 3).

In the multivariate analysis shown in Table 3, the odds ratio (OR) for developing SFTS was 5.36- to 47.60-fold higher in patients who were bitten by ticks 1 month before the onset of symptoms ($P < .05$). Other independent risk factors included the presence of rats in the household ($P < .05$, OR = 2.89, 95% confidence interval [CI] = 1.94–4.30) and the presence of weeds and shrubs in the household ($P < .05$, OR = 1.70, 95% CI = 1.12–2.60).

DISCUSSION

High case-fatality rate and widespread epidemics of SFTS are a serious public health burden. The disease caused by the SFTSV was first reported in 2009 in China, where it is the most prevalent in Hunan, Hubei, and Shandong provinces [14]. Shandong Province has been carrying out SFTS case surveillance since 2010, and it was one of the first provinces in China to carry out SFTS case surveillance. As early as 2007, a fever of unknown cause was reported in Penglai and Laizhou in Yantai. In 2010, retrospective SFTSV detection was performed on stored samples from patients with a fever of unknown cause in 2008 and 2009 in Yantai City, and 70% of the patients were positive for SFTSV nucleic acid. Therefore, the Shandong Province selected Yantai for SFTS monitoring.

Severe fever with thrombocytopenia syndrome is an emerging infectious disease that has a high fatality rate [15]. The case fatality percentage of SFTS in Yantai was 16.01% (155 of 968) from 2010 to 2019, which is higher than the country-level statistics for China [7, 16]. The fatality rate of SFTS may be influenced by age, viral load, disease course, and local diagnosis and treatment levels [7]. In this study, the number of SFTS cases monitored showed a dynamic upward trend in Yantai City. The regional distribution of SFTS gradually expanded from 2 cities in 2010 to all cities in 2019. In addition, the mean age of the SFTS cases was 63.68 years old. The high incidence of SFTS in elderly people in China was presumed to be caused by the fact that the age distribution of the cases may only reflect the age demographics of the Chinese population in rural areas [15]. A high proportion of cases involved farmers, which is consistent with our findings [17, 18]. In this study, 841 (86.88%) cases were farmers living in rural areas where young people and their children had migrated to cities to work and go to school. In rural areas, husband-and-wife cooperation dominates the labor mode.

Age serves as related factors for SFTS infection, progression, and outcome [19]. Liu et al [20] found that the annual SFTS incidence increased with age. Plenty of studies supported the

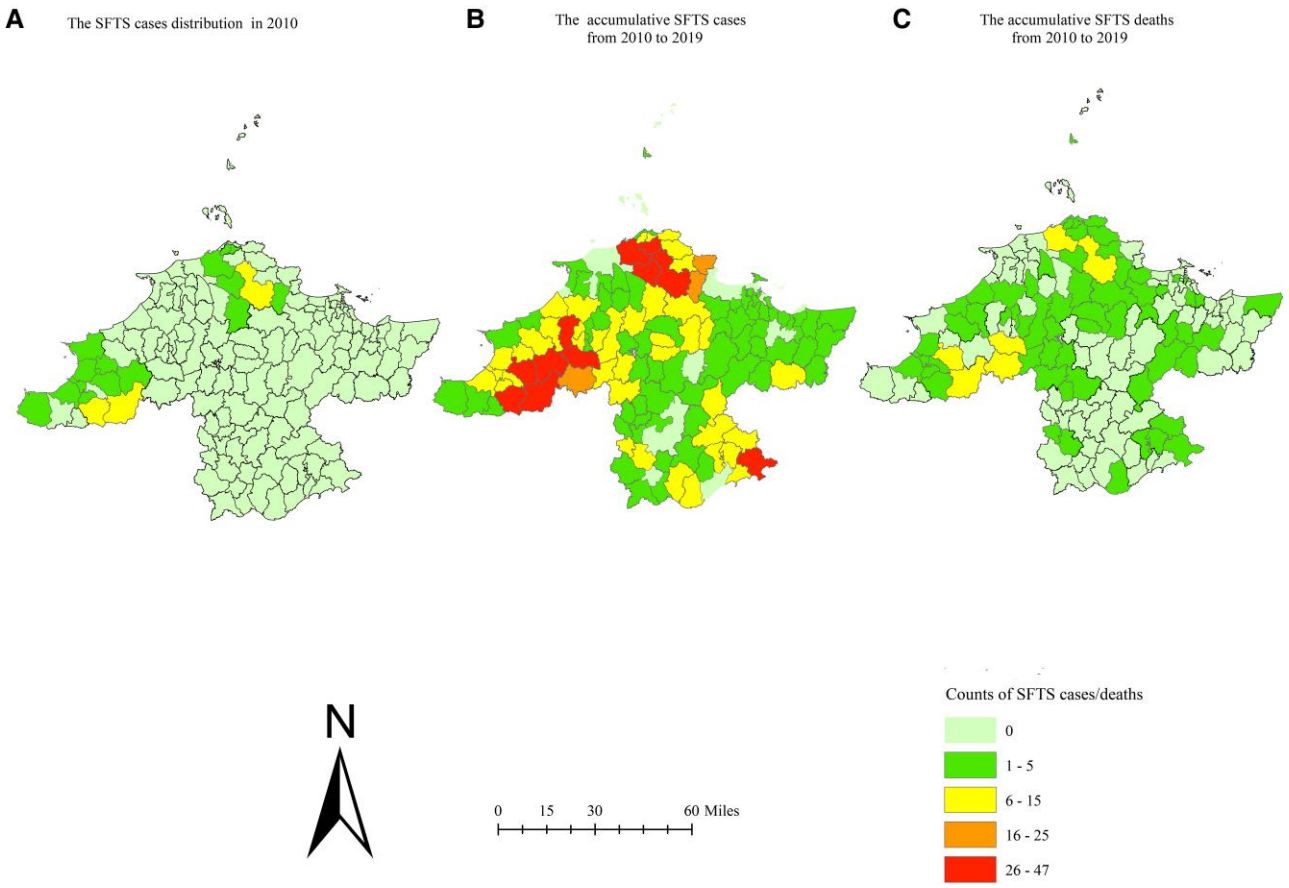

Figure 3. Town distributions of accumulative severe fever with thrombocytopenia syndrome (SFTS) cases and deaths in Yantai City from 2010 to 2019 (compared with SFTS cases in 2010). (*A*) Means of the town distribution of SFTS cases in Yantai City in 2010. (*B*) Means of the town distribution of accumulative SFTS cases from 2010 to 2019 in Yantai City. (*C*) Means of the town distribution of accumulative SFTS deaths from 2010 to 2019 in Yantai City.

evidence that elderly patients with SFTS have a greater risk of more severe outcomes [21–23]. In our study, there is no significant differences between cases and controls regarding age ($P > .05$). The reason may be that age is one of the matching factors in the 1:2 matched case-control study, which leads to similar age distribution between the 2 groups. However, most SFTS cases in our study occurred in individuals aged more than 60 years (68.34%), which was consisted with the epidemiological characteristic of many regions [7, 20, 24].

The spatial and temporal distributions of cases were consistent with the fluctuation of certain tick species in a given endemic area [25–28]. An ecological study reported that environmental changes, particularly those in the climate and landscape, may have promoted the spatial expansion of ticks and widespread dissemination of the SFTSV [29]. Jiang et al [30] explored the influence of climatic, environmental, and socioeconomic factors on SFTS occurrence in Shandong Province, and they found that temperature and precipitation had a nonlinear relationship with the risk of SFTS. High temperatures and precipitation could create more breeding sites in shrub or forest areas, increasing the egg productivity and hatch ratios of ticks, and thus increasing the population of ticks [31, 32]. Similar to these studies, in the present study, we found that the onset time of the disease was consistent with the active time of ticks. At the same time, the number of cases was higher in the season with higher tick activity and density, with the majority of cases occurring from May to August, and the number of cases increasing from May each year, peaking between May and August. Thus, it shows a unimodal distribution, with the number of SFTS cases rising in the high-temperature season and decreasing in low temperatures. An analysis of epidemiological characteristics from 2010 to 2019 in Mainland China found that SFTS cases occurred mainly from April to October, peaking in May and July [7]. The peak period of this study was longer than that of ours, which may be related to geographical and climatic differences as well as statistical methods.

Few studies have been conducted on the distribution, activity, and density curves of ticks in Yantai City. Wang et al [8] collected 3145 ticks from animals and vegetation in Yantai

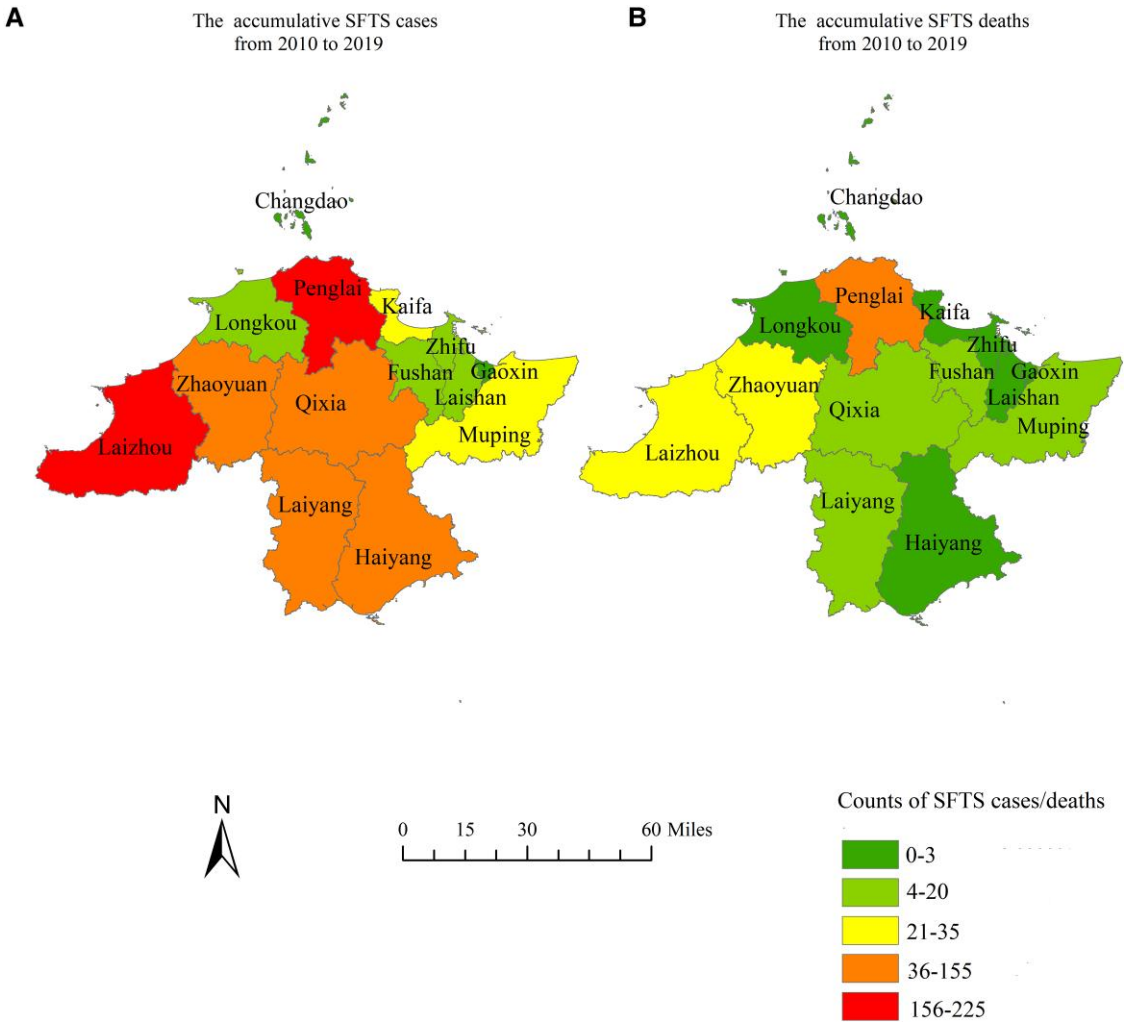

Figure 4. City distributions of accumulative severe fever with thrombocytopenia syndrome (SFTS) cases and deaths in Yantai City from 2010 to 2019 (compared with SFTS cases in 2010). (*A*) Means of the city distribution of accumulative SFTS cases from 2010 to 2019 in Yantai City. (*B*) Means of the city distribution of accumulative SFTS deaths from 2010 to 2019 in Yantai City.

City in 2011 and found 5 categories: 3048 (96.92%) *H. longicornis*, 73 (2.32%) *Rhinpicephalus sanguineus*, 10 (0.32%) *Boophilus microplus*, 9 (0.29%) *Haemaphysalis campanulata*, and 5 (0.16%) *Dermacentor sinicus*. The positivity rate of nucleic acids in 2044 samples was 6.16% (126 of 2044). In a study carried out in Jiaozhou County, Shandong Province, China (119°30′–120°30′, 35°35′–36°08′), which is adjacent to Yantai (119°34′–121°57′, 36°16′–38°23′), 3300 ticks were collected from vegetation and morphologically identified as *H. longicornis*. This study also indicated that ticks can serve as vectors and reservoirs for the SFTSV [33].

In the present community-based case-control study, we identified 3 risk factors for SFTSV infection: tick bites one month before disease onset, presence of weeds and shrubs around the house, and presence of rats in the household. Previous studies have also shown that "tick exposure" is a major risk factor for SFTSV infection [20, 34, 33]. Ticks infected with SFTSV can transmit the virus to host animals during feeding [8, 33], and the identified risk factors, such as the presence of rats in the household, suggest that ticks are the main vector of transmission.

The other identified risk factor was the presence of weeds and shrubs around the house, which was consistent with the fact that *H. longicornis* is known as a bush or scrub tick that is free-living in the environment, waiting for a suitable host (eg, small mammals, domestic animals, and wildlife). This further supports the belief that ticks are the main vectors of transmission. Furthermore, according to a previous study, 76.9% of 334 subjects, including 69 cases and 265 controls, had weeds and shrubs around their houses, demonstrating that the sanitary conditions of the environment in disease-endemic areas were very poor [35]. Consistent with our findings, Hu et al [35] found that weeds and shrubs around the house were risk

factors for SFTSV infection. Ding et al [36] conducted a case-control study in Henan, Hubei, and Shandong Provinces of China and reported that the presence of weeds and shrubs in the working environment was a risk factor for SFTSV infection.

Rodents are one of the hosts of the ticks, and their SFTSV positivity rate is higher than that of any other animal species [37]. Liu et al [38] demonstrated that SFTSV seropositivity in house mice and striped field mice was higher than that in other rodent species. An animal experiment confirmed that larvae could transmit the virus transstadially from infected mice to nymphs and adult ticks, and the latter could also transmit SFTSV to mice during feeding [33]. Therefore, the circulation of the SFTSV between ticks and rats may be necessary for SFTSV maintenance in nature. Similarly, our study found that rats in the household increased the risk of SFTS, which may suggest measures for preventing SFTSV infection.

Compared to previous studies, our study has several strengths. First, our data covered the period from 2010, when SFTS monitoring was carried out in Yantai City, to 2019, and the data were relatively complete. Second, the potential for selection bias was avoided because the age, sex, occupation, and neighborhood-matched design may have made cases and controls similar with regard to certain variables, including the residential area and possibly work place. Third, the study targeted behavioral risk factors and the results have definite implications for public health because the controls were recruited from all disease-endemic areas and resided in the same area as the cases.

Recall bias is inevitable when collecting information, and several measures were taken to minimize this problem. First, all questionnaires were systematically and objectively verified by SDCDC study coordinators for data completeness. Second, the questionnaires were completed within 2 weeks after laboratory diagnosis to ensure the accuracy of information. Third, all information from each participant was collected using a face-to-face approach by well trained interviewers.

Our study also has limitations. First, the SFTSV can be transmitted from person to person through contact with the infected patient's blood or mucus [39, 40]. However, we could not exclude these family clusters of SFTS cases. Second, we could not identify a dose-response relationship between the frequency of tick bites and occurrence of infection. Third, selection bias might have occurred because only laboratory-confirmed SFTS cases were included, and subclinical or mild infections with SFTSV may have been missed.

Table 2. Demographic Characteristics of the Cases and Controls in Yantai City, Shandong Province, From 2010 to 2019

Factors	Cases (%)	Controls (%)	χ^2	*P* Value
…	199	398	…	
Sex	…	…	0.34	.56
Male	86 (43.22)	182 (45.73)	…	
Female	113 (56.78)	216 (54.27)	…	
Nation	…	…	…	
Han	199 (100.00)	398 (100.00)	…	-
Other	0 (0.00)	0 (0.00)	…	
Occupation	…	…	…	
Farmer	183 (91.96)	352 (88.44)	1.76	.18
Nonfarmer	16 (8.04)	46 (11.56)	…	
Age Group	…	…	3.24	.66
<30	2 (1.01)	4 (1.01)	…	
30~39	0 (0.00)	5 (1.26)	…	
40~49	15 (7.54)	24 (6.03)	…	
50~59	45 (22.61)	90 (22.61)	…	
60~69	71 (35.68)	150 (37.69)	…	
≥70	66 (33.16)	125 (31.40)	…	

Table 3. Univariate and Multivariate Conditional Logistic Regression Analyses of Potential Risk Factors

			Univariate Analyses		Multivariate Analyses	
Exposure Factors	Cases n = 199 (%)	Controls n = 398 (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Patients among relatives or neighbors	5 (2.51%)	33 (8.29%)	3.51 (1.35~9.13)	.10	…	…
Owned domestic animals	96 (48.24%)	170 (42.71%)	1.25 (.89~1.76)	.20	…	…
Presence of rats in the household	142 (71.35%)	168 (42.21%)	3.41 (2.37~4.92)	.00	2.89 (1.94~4.30)	.00
Contacting with wild animals	94 (47.23%)	155 (38.94%)	1.40 (.99~1.98)	.053	…	…
Presence of ticks within 500 m of the living area[a]	95 (47.74%)	126 (31.66%)	1.97 (1.39~2.80)	.00	1.01 (.66~1.54)	.97
Domestic animals bitten by ticks	19 (9.60%)	19 (4.77%)	2.11 (1.09~4.08)	.027	2.00 (.92~4.35)	.080
Bitten by the ticks 1 month before the onset of symptoms	32 (16.16%)	4 (1.01%)	18.87 (6.57~54.21)	.00	15.97 (5.36~47.60)	.00
Worked in the field	138 (56.56%)	244 (61.31%)	1.43 (.99~2.05)	.054	…	…
Presence of weeds and shrubs in working areas	155 (77.89%)	255 (64.07%)	1.98 (1.33~2.93)	.001	1.44 (.89~2.33)	.14
Presence of weeds and shrubs around the house[b]	147 (73.87%)	225 (56.53%)	2.66 (1.55~4.57)	.00	1.70 (1.12~2.60)	.013
Resting on a grass field, during work break	92 (46.23%)	147 (36.93%)	1.47 (1.04~2.07)	.029	.93 (.60~1.43)	.73
Working with broken skins	17 (8.59%)	44 (11.06%)	.75 (.42~1.35)	.34	…	…

Abbreviations: CI, confidence interval; mo, month; OR, odds ratio.

[a]Presence of ticks within 500 m of the living area: the presence of ticks within a 500-m living radius within 1 month before the onset of severe fever with thrombocytopenia syndrome.

[b]Presence of weeds and shrubs around the house: there are weeds and shrubs in people's living areas and daily activity areas but they were not cleaned regularly.

CONCLUSIONS

In conclusion, our results support the hypothesis that ticks are important vectors of the SFTS virus. Integrated vector management should be implemented to reduce the density of ticks in the working and living environments. Moreover, education on tick bite prevention and personal hygiene should be implemented in high-risk populations, especially for outdoor workers in SFTS-endemic areas.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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