# Chapter 7
# Epidemiology of SFTS in China

**Hirofumi Kato and Masayuki Saijo**

**Abstract** Severe fever with thrombocytopenia syndrome (SFTS) is a novel emerging virus infection that was first found and reported in Peoples' Republic of China in 2009 and 2011, respectively. SFTS was later reported in Japan and South Korea, suggesting that SFTS is endemic to East Asian countries. Among these countries, the most SFTS cases have been reported in China. Geographically, SFTS cases have been mainly reported in rural and mountainous areas of the Eastern, Central, and North-Eastern China. So far, the number of SFTS cases has increased and the geographical distribution has expanded in China. From epidemiological studies, it was suggested that various factors including occupation, habit, tick bites, animal contact, environment, meteorological factor, demographic data, clinical symptoms, or laboratory data were associated with SFTS infection or fatal outcome. In this article, epidemiology of SFTS in China is described in detail to assess distributions over time, place, and person.

**Keywords** Epidemiology · Surveillance · Risk · Disease and geographical distribution · Demographical characteristics

## 7.1 Introduction

Severe fever with thrombocytopenia syndrome (SFTS) was formally found as a novel emerging virus infection in rural regions in Henan and Hubei Provinces in Peoples' Republic of China in 2009 and was reported in 2011 (Ministry of Health of People's Republic China 2010; Yu et al. 2011). However, it was later recognized that the first case was discovered in Anhui Province in the autumn of 2006 retrospectively (Zhang et al. 2008). At that time, these patients were improperly diagnosed with human granulocytic anaplasmois (HGA), due to similar clinical presentation (e.g. fever, leukopenia, thrombocytopenia, etc). Later, as the

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retrospective investigation was conducted, it was revealed that most of the patients suffered from SFTS, but not from HGA (Liu et al. 2012a). Successively, in 2007, multiple patients presenting fever, thrombocytopenia and leukopenia had emerged in local hospitals in Henan Province, especially around Xinyang City. A patient's family member reported the disease to the Henan Center for Disease Control and Prevention. The center, then, conducted a special epidemiological investigation. Based on the investigation, the relatively specific disease was found to be caused by a novel bunyavirus, which was later identified as SFTSV (Xu et al. 2011; Liu et al. 2014a). Since then, many epidemiological investigations were conducted in China resulting in obtaining various epidemiological findings. In this article, epidemiology of SFTS in China is described in detail by description to assess distributions over time, place, and person, based on these epidemiological investigations.

## 7.2 Surveillance System in China

In China, a national system of infectious disease surveillance has been established since 1959. After the severe acute respiratory syndrome (SARS) outbreak occurred in 2003, the Chinese government made the Law of Prevention and Control of Infectious Disease and improved its public health disease surveillance system, taking advantage of web-based system to build an integrated, effective, and reliable disease reporting system over the paper-based reporting system (Wang et al. 2017a). In the disease surveillance system, there are three major components (World Health Organization Western Pacific Region 2017; Vlieg et al. 2017; Zeng et al. 1998):

– National Disease Reporting System (NDRS); that is, notifiable disease surveillance. This surveillance involves the whole population living in all counties, prefectures, and provinces in Mainland China. There are 38 notifiable infectious diseases, which are classified into 3 groups (Group A, B, and C). Groups A and B represent categories of diseases with high risk of causing outbreaks or that are likely to result in rapid spread once an outbreak occured. Group A diseases should be reported within 2 h of diagnosis, while Group B and C diseases should be within 24 h.

  Group A: plague, cholera
  Group B: SARS, measles, rabies, malaria, syphilis, etc.
  Group C: influenza, rubella, hand-foot-mouth disease, etc.

– Nationwide Disease Surveillance Points (DSPs); that is, sentinel disease surveillance. This surveillance is used when high-quality data are required about particular diseases that cannot be obtained through the notifiable disease surveillance (World Health Organization n.d.). The sentinel system involves only a limited network of carefully selected reporting sites. In China, approximately 150 report-

ing units are randomly selected from all medical facilities in 30 province-level divisions, which covers for about 1% of the entire facilities. The information of patients are obtained from these selected facilities.
- Surveillance system for specific infectious diseases, occupational diseases, foodborne diseases, etc.

SFTS is included in the last surveillance system, which is regarding specific infectious diseases. As SFTS is identified in 2009, a hospital-based sentinel surveillance for SFTS has been established since 2010 in endemic areas: Liaoning, Shandong, Henan, Hubei, Anhui, and Jiangsu provinces (Yu et al. 2011; Xiong et al. 2012). SFTS has been added to the list of national reported diseases that requires reporting within 24 h as regulated by the national guideline for prevention and control of SFTS (Ding et al. 2014a). SFTS cases were detected in hospitals and reported to Centers for Disease Control and Prevention (CDC) at prefectural, municipal, provincial, and national levels through the electronically operating China Information System for Diseases Control and Prevention (CISDCP) (Liu et al. 2015; Guo et al. 2016).

## 7.3 Case Definition of SFTS

According to the national guideline for prevention and control of SFTS (Ministry of Health of People's Republic China 2010; Ding et al. 2014a), a probable SFTS case is defined as a patient with acute fever (≧38 °C), accompanying symptoms (e.g. gastrointestinal symptoms, bleeding), epidemiological risk factors (occupational history including farmer or exposure to ticks 2 weeks before disease onset) and laboratory data consisting of thrombocytopenia and leukocytopenia. A confirmed case is defined by laboratory evidence meeting one or more of the following criteria (Wang et al. 2017a; Sun et al. 2017):

1. A positive SFTSV culture
2. A positive result for SFTSV RNA by molecular detection
3. Seroconversion or a four-fold increase in specific IgG antibody titers to SFTSV between the acute and the convalescent serum samples collected at least 2 weeks apart

Probable SFTS cases are not well defined because approximately 30% of probable cases of SFTS cannot be confirmed by laboratory tests (Yu et al. 2011; Wen et al. 2011a).

## 7.4 Disease and Geographical Distribution

SFTS cases have been mainly reported in rural areas of the Eastern, Central, and North-Eastern China, where *Haemaphysalis longicornis* and *Rhipicephalus microplus* ticks are prevalent (Liu et al. 2015; Liu et al. 2014b). The number of SFTS cases is relatively lower in urban areas than in rural areas. Using the average evolutionary rate, it was sought that SFTSV may have appeared 20–87 years ago in the Dabie Mountains, China and it was possible that SFTSV might spread to some other regions of China, Japan, and South Korea (Liu et al. 2016). In China, based on the national surveillance data in 2011, 571 laboratory-confirmed cases were reported from 13 Province, including 59 fatal cases (Liu et al. 2014b). However, there might be more potentially probable cases at the early stage of discover.

By the end of 2016, a total of 5360 laboratory-confirmed cases were reported (Sun et al. 2017). It is obvious that the number and notification rate of SFTS cases has increased gradually year by year (Zhan et al. 2017a). Besides, clinically-diagnosed and the laboratory-confirmed cases were reported in 23 and 18 Provinces, respectively. The geographical distribution has also been gradually expanding to date (Zhan et al. 2017a). Although the reasons are not known, the number of cases has increased and the geographical distribution has expanded. Several factors may contribute the epidemiological evidence. First, the number of SFTS patients might has truly increased and the SFTS-endemic areas might has spread more widely due to the spread of the animal hosts and/or vectors. Second, medical staffs might have become aware of the disease and find more cases through intensive education and trainings. Third, systems including disease monitoring and detection capacity of the pathogen likely have improved (Sun et al. 2017; Wang et al. 2017b).

According to the previous reports, the national case-fatality proportion was reported to be 7.3%, ranging from 6.3% to 30.0% (Liu et al. 2014a). In the early stage of SFTS discovery, the case-fatality proportion showed about 30%. However, as the SFTS cases have increased, the case-fatality proportion has gradually decreased. In the most recent report, the proportion was 4.8% (355/7419) (Zhan et al. 2017a) (Fig. 7.1).

## 7.5 Geographical Distribution

SFTS cases have mainly been reported in rural areas of the Eastern, Central and North-Eastern China. According to the spatial-temporal cluster analysis to reveal detail endemic areas, three clusters of SFTS cases were identified; cluster 1 was located around the Dabie Mountains, where was at the junction region of Henan, Hubei, and Anhui Provinces, cluster 2 was located in Jiaodong peninsula of

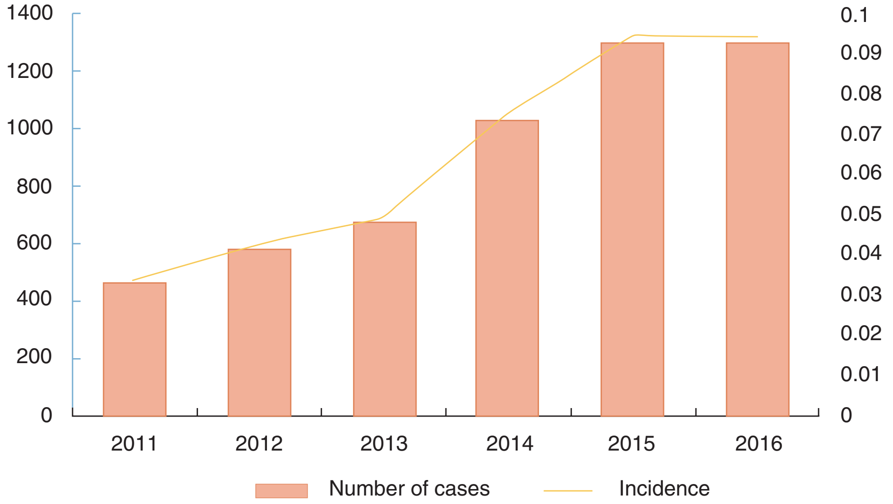

**Fig. 7.1** Annual numbers and notifications of SFTS cases in China, 2011–2016 (Sun J, et al. Sci Rep 2017; 7: 9236)

Shandong Province, and cluster 3 was located in the central part of Shandong Province (Liu et al. 2015).

By October 2016, laboratory-confirmed cases had been found in 18 provinces: Heilongjiang, Jilin, Liaoning, Beijing, Hebei, Shandong, Jiangsu, Anhui, Zhejiang, Henan, Hubei, Fujian, Jiangxi, Hunan, Shaanxi, Sichuan, Guizhou, and Yunnan. Additionally, probable cases had also been reported from 5 Provinces: Shanxi, Guangxi, Guangdong, Xinjiang, and Gansu (Zhan et al. 2017a). So far, no case has been confirmed in Taiwan, which locates across the sea between Fujian Province in Mainland China and Okinawa prefecture in Japan, in both of which laboratory-confirmed SFTS cases were reported (Fig. 7.2).

Among these provinces, there have been the hot spots, where more than 95% of laboratory-confirmed cases have been reported, in 7 provinces of Henan, Shandong, Hubei, Anhui, Liaoning, Zhejiang, and Jiangsu (Xing et al. 2017). From 2010 to October 2016, SFTS cases in China were the most frequently reported in Henan, followed by Shandong, Anhui, and Hubei; the percentage of SFTS cases of these provinces in China was 37%, 27%, 14%, and 13%, respectively (Zhan et al. 2017a). As well, notification rates by province showed the similar trends. Until the end of 2013, Henan reported the highest notification of SFTS, followed by Shandong, Hubei, Liaoning, Anhui, and Zhejiang; the notifications were 0.73, 0.53, 0.38, 0.27, 0.20, and 0.12 per 100,000 person-years, respectively (Fig. 7.3) (Liu et al. 2015). Not only the numbers but also the notifications from most provinces have increased annually since 2011 (Sun et al. 2017; Zhan et al. 2017b).

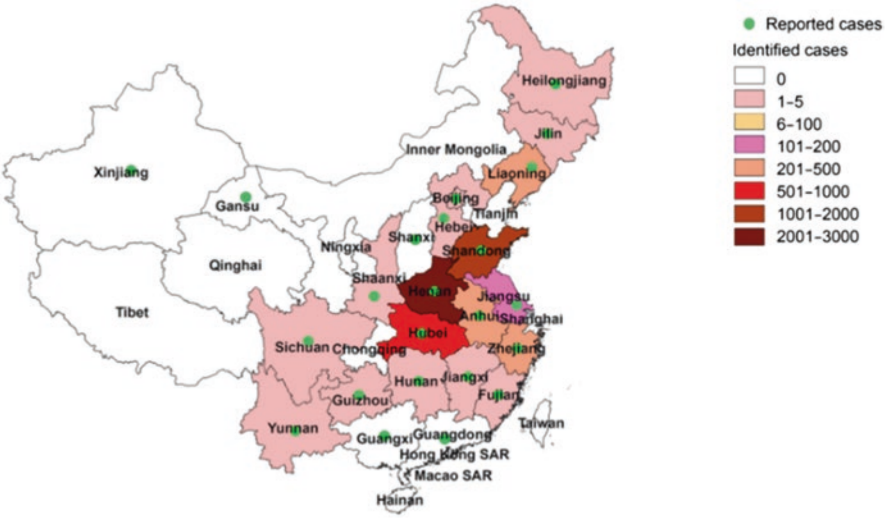

**Fig. 7.2** Geographical distribution of SFTS reported and confirmed cases in China, from 2010 to October 2016 (Zhan J, et al. Virol Sin 2017; 32: 51–62)

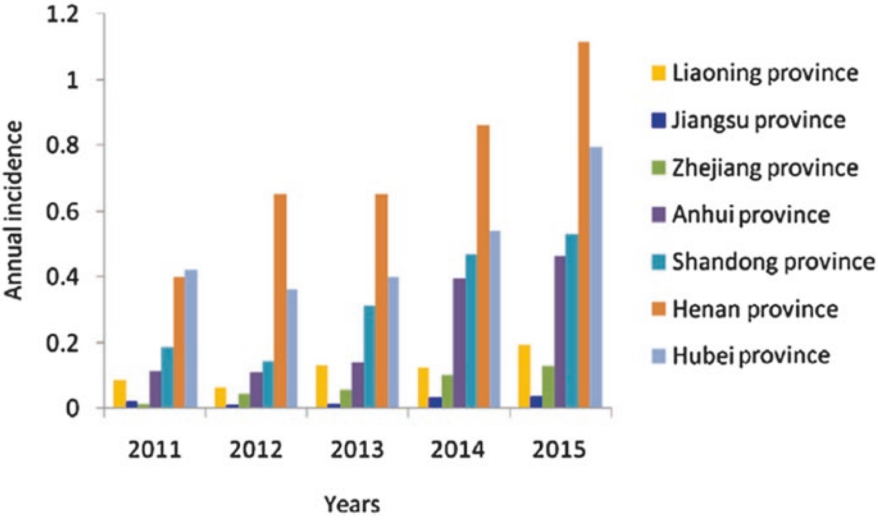

**Fig. 7.3** The annual notification of SFTS cases in China by province, 2011–2015 (Zhan J, et al. Virus Res 2017; 232: 63–8)

### *7.5.1 Henan Province*

Henan Province is located in central China, adjacent to Hubei and Anhui Province, which is an SFTS-endemic area. During 2007–2011, a total of 1021 cases were reported in Henan. The number was the highest among those in each province in

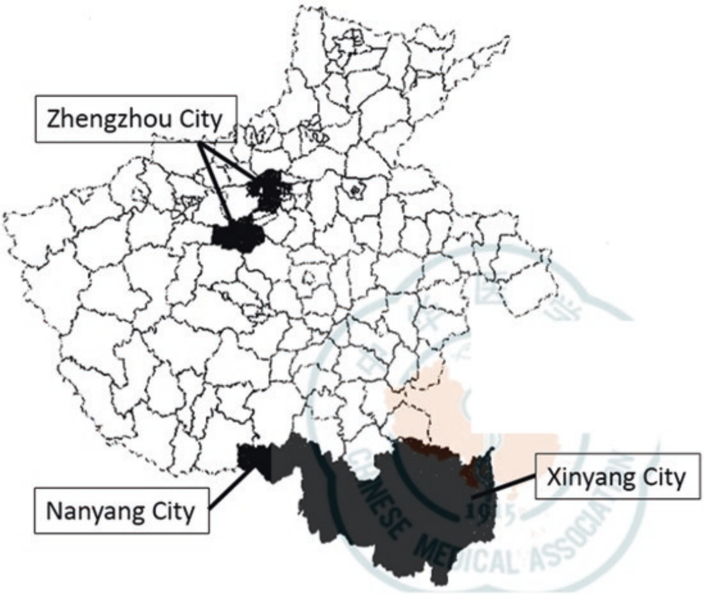

**Fig. 7.4** Geographical distribution of SFTS cases in Henan Province, 2007–2011 (Kang K, et al. Chin J Prev Med 2012; 46: 106–109)

China (Kang et al. 2012). The total reported cases in Henan Province accounted for 48% of SFTS cases in entire China during 2011–2012 (Ding et al. 2013).

In Henan Province, SFTS cases were reported in 13 counties of 3 cities including Xinyang City, Nanyang City, and Zhengzhou City during 2007–2011 (Kang et al. 2012). Xinyang City, where is the southern part, is the most endemic area, which reported 99% of SFTS cases in Henan Province (Fig. 7.4). Of Xinyang City, the number of cases in Shangcheng County, Shihe County, Guangshan County, and Pinggiao County was 394 (34%), 169 (17%), 147 (14%), and 126 (12%), respectively (Kang et al. 2012) (Fig. 7.5). These regions are characterized by its distinct natural landscapes, with the northern part mainly comprising plains and the southern part stretching across the Dabie Mountain range (Liu et al. 2014c).

### 7.5.2 *Shandong Province*

Shandong Province is located in eastern China of a coastal region. Shandong Province reported the second highest notification of SFTS by the end of 2013 (Liu et al. 2015). From January 2010 to April 2013, a total of 416 laboratory-confirmed cases were reported in the province (Du et al. 2014). SFTS is highly endemic to the northeast area, where is mainly Jiaodong peninsula, and central area (Fig. 7.6) (Liu et al. 2015). Several epidemiological research were conducted in the rural areas of

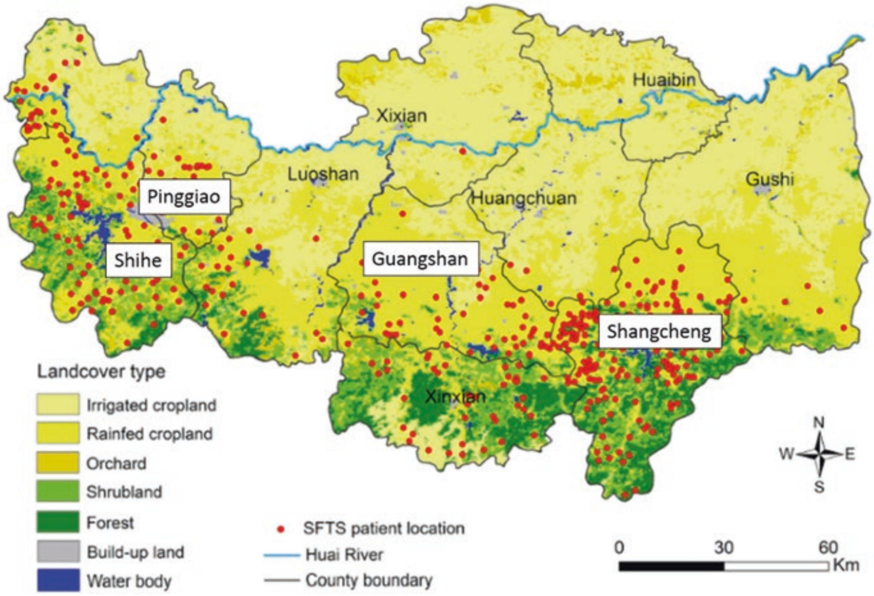

**Fig. 7.5** Geographical distribution of confirmed SFTS cases in Xinyang City, 2011–2012 (Liu K, et al. PLoS Negl Trop Dis 2014; 8: e2820)

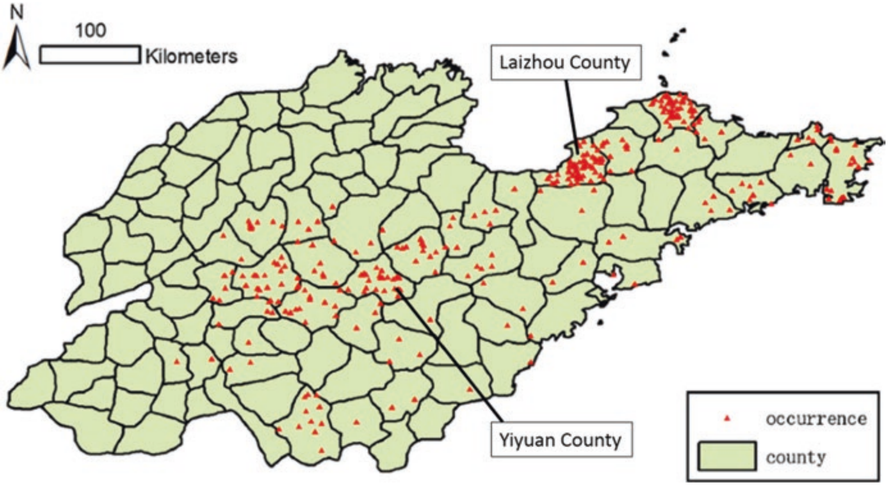

**Fig. 7.6** Geographical distribution of reported SFTS cases in Shandong Province from January 2010 to April 2013 (Du Z, et al. Int J Infect Dis 2014; 26: 1–8)

Yiyuan County, located in central area, and Laizhou County, located in Jiaodong peninsula (Ding et al. 2014b; Wen et al. 2011b; Cui et al. 2013). There are low-lying hills with forests and grasslands in Yiyuan County, and there are hills and mountains in the southeast and plains in the northwest in Laizhou County. These reports showed that the notification was 4.1/100,000 person-years in Laizhou County, which was similar to that in Yiyuan County (Ding et al. 2014b).

### 7.5.3 Hubei Province

Hubei Province is located in central China, adjacent to Henan and Anhui Province, to which SFTS is endemic. In Hubei Province, a total of 521 laboratory-confirmed cases were reported during 2011–2016 (Wang et al. 2017b). Of the confirmed cases, most cases were found in the Dabie mountainous area (Zhan et al. 2017b). Specifically, the cases were more clustered in the northeast in the cities of Suizhou, Xiaogan, and Huanggang, bordering Xinyang City of Henan Province (Fig. 7.7) (Wang et al. 2017b; Liu et al. 2012b). The SFTS cases were reported from 164 townships in 15 cities, covering 11.5% of the total area (1424 townships) of Hubei Province (Wang et al. 2017b). Of these 164 townships with confirmed cases, 50 had an annual SFTS notification of more than 10.00 per 100,000 people (Wang et al. 2017b).

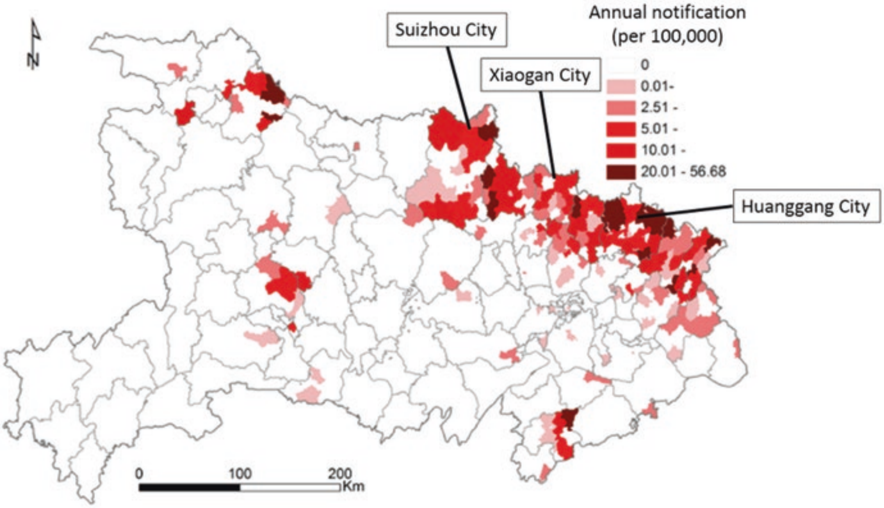

**Fig. 7.7** Geographical distribution and annual notification of SFTS cases at the township level in Hubei Province, 2011–2016 (Wang T, et al. Front Microbiol 2017; 8: 387)

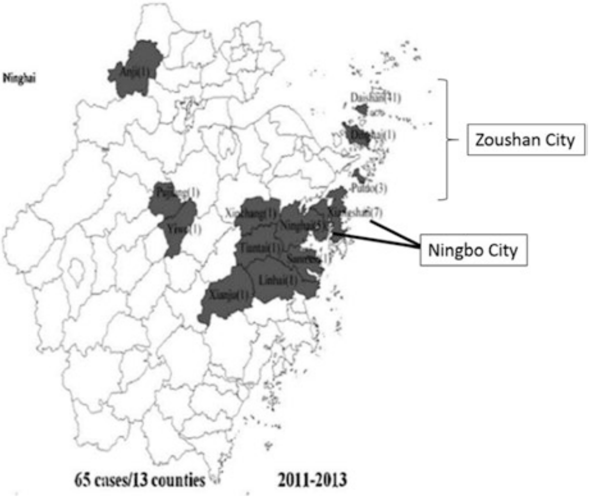

**Fig. 7.8** Geographical distribution of SFTS cases in Zhejiang Province, 2011–2013 (Sun J, et al. Int J Infect Dis 2014; 25: 180–5)

### 7.5.4 *Zhejiang Province*

Zhejiang Province is located in the coastal region of southeastern China, adjacent to Jiangsu and Anhui Province, to which SFTS is endemic. During 2011–2013, a total of 65 laboratory-confirmed cases were identified in Zhejiang Province (Sun et al. 2014) (Fig. 7.8), demonstrating that all cases occurred in 13 counties, and the number of counties had increased anually. The highest reported cases occurred in Zhoushan (69%) and Ningbo City (18%), located in the northeastern and eastern Zhejiang Province. Of these, most cases were identified in Daishan County of Zoushan City, characterized by mountainous areas of the island. A few cases were reported in Anji and Pujiang, where were the western and central Zhejiang (Sun et al. 2014).

### 7.5.5 *Liaoning Province*

Liaoning Province is located in northeastern China, where SFTS cases were found across 19 counties of 5 cities. A total of 167 laboratory-confirmed cases were reported during 2010–2013. The SFTS cases were mainly distributed in Dandong City, accounting for 57% (95/167) of all cases, followed by Dalian City (33%, 55/167), Fushun City (4.8%, 8/167), Yingkou City (3.0%, 5/167) and Benxi City (2.4%, 4/167). By county, the SFTS cases were reported in Kuandian Manchu Autonomous County of Dandong City, accounted for 29% (48/167) of the total cases, followed by Fengcheng County (25%, 41/67), Dandong County, (16%, 26/167), Pulandian County of Dalian City (7.2%, 12/167), and Zhuanghe County of Dalian City (4.8%, 8/167) (Wang et al. 2016).

### 7.5.6 *Anhui and Jiangsu Province*

Anhui Province is located in eastern-central China. Jiangsu Province is on the east of Anhui Province and located in a coastal region. Anhui Province has a high proportion of SFTS patients, accounting for approximately 12% (342/2949) of the total laboratory-confirmed case number in China from January 2011 to July 2014 (Lyu et al. 2016). According to another study, a total of 286 confirmed cases were reported in Anhui and Jiangsu Provinces from January 2010 to December 2015 (Li et al. 2017). SFTS cases distributed in the border area of Anhui and Jiangsu Province, where are mountainous landscapes, and in the western region, which is located at the northern foot of the Dabie Mountains (Lyu et al. 2016; Li et al. 2017).

## 7.6 Seasonal Distribution

The epidemic curve showed seasonality. Based on the combined numbers of SFTS in China, the epidemic season of SFTS starts from spring and ends in late autumn with the highest peak of occurring between May and July (Fig. 7.9) (Liu et al. 2015; Liu et al. 2014b). However, the epidemic curve revealed a slightly different charac-

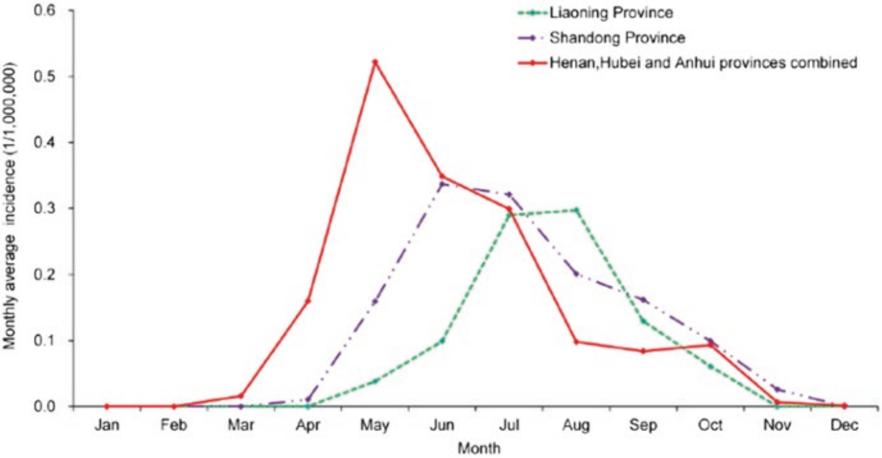

**Fig. 7.9** Seasonal epidemic curves of SFTS notification in the severely affected provinces. (Liu K, et al. Sci Rep 2015; 5: 9679)

teristics by area; that is, it peaked later in provinces with higher latitudes. In Henan, Anhui and Hubei Provinces, where are the central region, the peak months were from May to July, while those in Shandong Province, the eastern region, and in Liaoning Province, the northeastern region, were between June and July and between July and August, respectively (Liu et al. 2015).

Seasonality of SFTS occurrence may be attributed to the activity level of both the hosts and the vectors. From spring to summer, the outdoor activity or field work of the farmers such as picking tea and clearing weeds increased, subsequently elevating the potential risk of exposure to the putative vectors. Outdoor activities in rural areas, such as camping and hiking, are also a potential risk factor for exposure to vectors (Liu et al. 2014a). Additionally, during the same period, a tick density and activity also increased and absorb their hosts' blood in order to grow and proliferate between May and August (Xu et al. 2011; Liu et al. 2014b; Sun et al. 2014). In fact, it showed that the SFTSV infections were highly correlated with the tick density curve, and the peak of tick density occurred prior to the peak of human infection cases (Wang et al. 2017b; Du et al. 2014; Liu et al. 2012c).

## 7.7 Population Distribution

Although there is variation among reports, the median age of SFTS cases was 61 years, ranging from 1 to 93, being the majority 50 years of age or more (Fig. 7.10) (Liu et al. 2015; Liu et al. 2014b; Zhan et al. 2017a). The female-to-male ratio was slightly higher than 1, but no obvious difference was found (Liu et al. 2015; Liu et al. 2014b; Zhan et al. 2017a). Age distribution demonstrated that the annual noti-

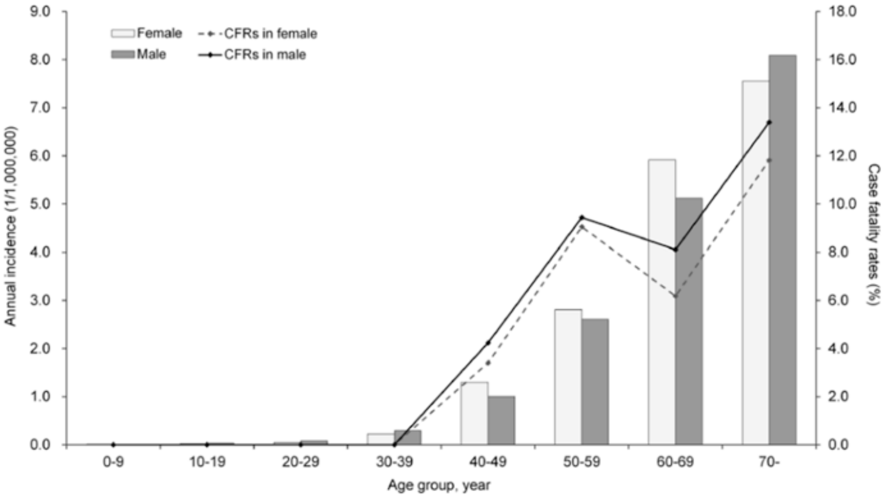

**Fig. 7.10** Age and sex distribution of the SFTS notification and case-fatality proportions in China (Liu K, et al. Sci Rep 2015; 5: 9679)

fications increased gradually from younger to older age groups (Liu et al. 2015; Liu et al. 2014c). Several pediatric cases under the age of 18 were reported, and they remained to be rarer compared with adult cases (Zhu et al. 2017; Wang et al. 2014). This may be because the child cases show relatively milder clinical symptoms and better prognosis than those of the elderly cases (Zhu et al. 2017; Wang et al. 2014). The high notification of elderly patients may be due to the physiological factors related to ageing, such as decreased in immune function and the presence of comorbidities with chronic diseases. However, this may also be associated with demographic characteristics of residents in wooded or mountainous areas, where SFTS cases occur (Sun et al. 2014). Generally, the younger generation attend to the main commerce and industrial work in urban area in China, instead of agriculture in rural area. On the other hand, the older generation attend to farming or stock-farming activities (growing various crops, cultivating fields, cutting glasses, and breeding animals, etc), especially tea-picking activity, which was carried out by elderly women (Liu et al. 2014c). These specific social factors may contribute to population distribution in China.

## 7.8 Potential Risk Factors of Infection Associated with SFTS

### *7.8.1 Occupation and Habit*

Occupation and habit are associated with SFTS suffering. Because SFTS is a tick-borne disease, occupation and habit with frequently exposure to ticks seem to be potential risk factors. Agricultural tea pluckers, farmers, forest workers, and residents who live in rural areas, where is wooded and hilly areas, are the occupational risk factors (Liu et al. 2014a; Liu et al. 2015; Zhao et al. 2012). In a seroepidemiological survey conducted in non-endemic areas of Anhui Province, multivariate analysis revealed that the odds ratio for tea pluckers was 3.7 folds higher than non-tea pluckers (95% CI: 1.033–13.582) with a statistical significance (Huang et al. 2017). Several descriptive reports revealed that farmers in endemic area accounted for around 85% or more of SFTS cases, and those residing in mountainous areas did for 95% or more. They might be a major high-risk population (Ding et al. 2014a; Zhan et al. 2017a; Liu et al. 2014c). In the case-control study, the odds ratio for workers in the field was 2.3 folds higher (95% CI: 1.3–4.0) in the cases than the controls. In the other studies on seroprevalence, odds ratios for farming, farm work time (>3–6 h a day), and grass mowing were also significantly higher (OR: 4.919, 95% CI: 1.269–19.058; OR: 3.24, 95% CI: 1.49–7.05; OR: 14.05, 95% CI: 5.53–35.70, respectively). To the contrary, a case-control study suggested that there was no significant difference in occupations between the cases and controls (Xing et al. 2017). Probably, farming would be a potential risk factor, but it has still been unclear whether farmers have truly a higher risk or not. The majority of workers in rural area are farmers, which may influence the conclusions. In addition to these factors, one review article described that tourists, who might be more susceptible, were also often suffered to SFTS (Hu et al. 2016).

### *7.8.2 Tick Bites*

*Haemaphysalis longicornis* and *Rhipicephalus microplus* are the major potential vectors to transmit SFTSV to humans, based on the evidence that SFTSV was isolated from these ticks in endemic areas (Liu et al. 2014b; Zhang et al. 2012a).

Epidemiological surveys support that tick bites or presence of ticks are identified as one of potential risk factors associated with SFTSV infection. In multivariate analysis of the case-control studies, it was demonstrated that the odds ratios of history of tick bites in case-group were significantly 4.5 (95% CI: 1.6–12.9) and 6.6 (95% CI: 2.9–15.0) folds higher than the control-group selected from the same hospital and that from outside of the hospital, respectively (Ding et al. 2014a; Sun et al. 2016). The seroprevalence study demonstrated that tick bites was one of potential risk factors (OR: 3.81, 95% CI: 1.22–11.85) (Li et al. 2014a). In the case-control study focusing on the detail tick-exposures were classified into four groups of "see ticks", "contact ticks", "catch ticks", or "bitten by ticks". The multivariate conditional logistic regression analysis of tick exposure sources showed that "bitten by environmental ticks" and "contact with cattle ticks" including touching ticks, catching ticks, or bitten by ticks, were the potential risk factors for acquiring SFTSV infection. The odds ratio for "bitten by environment ticks" and that for "contact with cattle ticks" were 12.00 (95% CI: 1.44–99.67) and 7.70 (95% CI: 1.64–36.21), respectively (Xing et al. 2017). However, it was also reported that tick bites was only noticed by approximately 15% of the cases (Ding et al. 2014a; Sun et al. 2016). The reason may be that SFTS cases usually do not notice whether they had a history of being bitten by ticks or not, because tick bites are commonly painless. It is possible that history of tick bites might be under-reporting; therefore, it is assumed that tick bites would be more important potential risk factor than expected (Ding et al. 2014a).

In the epidemiological surveys regarding other possible vectors, it was suggested that there was no evidence of SFTSV being isolated from vectors except ticks, especially mosquitoes, captured in the human affected areas (Yu et al. 2011; Xiong et al. 2012). In accordance with the results, there would be little possibility that other arthropods including mosquitoes act as vectors for SFTSV transmission to animals including humans (Liang et al. 2017).

### *7.8.3 Animal Contact*

The natural reservoir hosts of SFTSV has not yet been clarified, but it is suggested that various domestic and wild animals in the endemic area play a role in the maintainance of SFTSV in nature. To investigate the role of domestic and wild animals as reservoir hosts, a study was conducted in Laizhou and Penglai counties of Shandong Province, demonstrating that SFTSV RNA was detected in the serum samples of sheep, cattle, pigs, dogs, and chickens, ranging from 1.7% to 5.3% (Niu et al. 2013). Besides, SFTS-specific antibodies were also detected in a wide range of animals, including goats, sheep, cattles, dogs, pigs, chickens, geese, rodents, and hedgehogs (Niu et al. 2013; Li et al. 2014b; Ding et al. 2014c). Epidemiological studies have provided the knowledge on the risk of contact of humans with animals. In the descriptive study, the number of bred domestic animals and exposure to a mouse was 20 (31%) and 37 (57%) among 65 SFTS cases, respectively (Sun et al. 2014). In the case-control study, it was suggested that cat and cattle ownership was a potential risk factor; adjusted odds ratios were 2.1 (95% CI: 1.2–3.9) and 2.6 (95% CI: 1.4–4.8), respectively (Ding et al. 2014a). According to the multivariable logistic regression analysis in another case-control study, the odds ratio of breeding domestic animal was 1.7 (95% CI: 1.0–3.0) (Sun et al. 2016). In the seroprevalence study focusing on Jiangsu Province, a multiple variable logistic regression analysis showed that raising goats, raising cattles, and grazing were potential risk factors for SFTSV infection, whose odds ratios were 7.27 (95% CI: 1.29–40.89), 11.51 (95% CI: 2.18–60.67), and 40.154 (95% CI: 6.385–252.530), respectively (Xing et al. 2017; Li et al. 2014a; Liang et al. 2014). Additionally, density of cattle was found to be the independent potential risk factor for the presences of SFTS in Hubei Province, whose adjusted notification rate ratio was 2.03 (95% CI: 1.38–3.00) (Liu et al. 2015; Wang et al. 2017b).

From these results, Xing X, et al. have discussed that cattle might be a major amplifying and reservoir hosts in maintaining SFTSV in the endemic regions (Xing et al. 2017). Similarly, Liang S, et al. speculated that goats are the potential reservoir for SFTSV (Liang et al. 2014). However, it is difficult to specify the animals, which might be the true amplifiers or reservoirs. Therefore, more additional studies are needed.

### *7.8.4 Environment*

Environmental factors also involve SFTSV infection. In multivariate analysis of the case-control study, the presence of weeds and shrubs in the working areas was a potential risk factor, with an odds ratio 1.91 (95% CI: 1.0–3.5) (Ding et al. 2014a). In another report, the Poisson regression analysis demonstrated that SFTS notification was associated with shrub, forest, and rain-fed cropland areas (Liu et al. 2014c).

Coverage of shrub, forest, and rain-fed cropland are highly associated with tick density, because these seem to be ideal habitats for ticks. According to spatial-temporal clusters, the boosted regression tree model identified forest coverage and *Haemaphysalis longicornis* ticks density as important potential risk factors for SFTSV infection (Liu et al. 2015).

### 7.8.5 *Meteorological Factor*

It has still been unclear how meteorological factors contribute to SFTS occurrence, because there is only a few research about these factors. It is considered that meteorological factors influence the distribution of tick vectors and animals. It was reported that meteorological factors affected SFTS occurrence by the analyses using ecological model for predicting the distribution. In the study, the key environmental factors were temperature, precipitation, and duration of sunshine (Du et al. 2014). It was also revealed that temperature and relative humidity were associated with SFTS notification, whose adjusted notification rate ratios were 0.83 (95% CI: 0.71–0.97) and 1.72 (95% CI: 1.18–2.50), respectively (Wang et al. 2017b). Furthermore, according to the spatial-temporal clusters analysis, it was reported that temperature, rainfall, relative humidity, sunshine hours, and altitude as important potential risk factors for human infection with SFTSV by the boosted regression tree model (Liu et al. 2015).

Epidemiologically, these meteorological factors play an important role in the transmission of SFTSV to humans. First, meteorological factors are mainly impacting the ecological dynamics of the vectors, ticks; the comfortable temperature can promote the activities and growth of vectors, giving the reservoirs and hosts more opportunities to be infected with SFTSV. Second, they influence the behaviors and ecological characteristics of both the wild and domestic animals as reservoirs. Third, they also affect behavioral pattern of people in endemic area; optimum weather condition can promote outdoor activities (Du et al. 2014).

## 7.9 Potential Risk Factors of Fatal Outcome Associated with SFTS

### 7.9.1 *Demographic Data – Age, Sex, Body Mass Index (BMI), and Period*

Various potential risk factors for fatal outcome were suggested by epidemiological surveys. Several studies pointed out that aging was one of the potential risk factors of a fatal outcome, although there were a few reports, in which it was described that older age was not a potential risk factor for SFTS fatal outcome. The age distribution was similar between the patients died and those survived (Sun et al. 2016). According to the investigation conducted soon after the disease discovery, the median age of fatal cases was significantly higher than that of the non-fatal cases (62.1 vs 52.9 years; $p = 0.011$). In the large-population-based investigation, the multivariate discriminate analysis also demonstrated the indicators of the fatal outcome was the older age (Cui et al. 2014). Furthermore, the integrated data analysis suggested that fatal outcome was associated with the age (Guo et al. 2016). This might be because that higher fatality among elderly patients may be due to physiological factors related to ageing, such as decreased immune function and the presence of comorbidities with chronic diseases.

Most studies indicated that no significant differences were demonstrated in sex between fatal and non-fatal cases; therefore, sex was not considered to be a potential risk factor of a fatal outcome (Sun et al. 2016; Gai et al. 2012a).

As other demographic factors, body mass index (BMI) and intervals from illness onset to the confirmation and/or hospital admission were the potential risk factors for poorer prognosis. In the case-control study, multivariable logistic regression analysis demonstrated that a significant difference was observed in BMI between fatal and non-fatal cases (OR: 3.886, 95% CI: 1.275–11.84) (Sun et al. 2016). This study mentioned that BMI $< 18.5$ or $> 24$ should be paid attention as a useful predictor of fatal outcome (Sun et al. 2016). Presumably, BMI may represent body condition of persons and normal BMI suggest better immunological status. Additionally, in the study, it was mentioned that a significant difference was observed in intervals from the disease onset to diagnosis between fatal and non-fatal cases (OR: 1.956, 95% CI: 1.139–3.361) (Sun et al. 2016). The integrated data also suggested that longer delay from the disease onset to the hospital admission was significantly associated with a fatal outcome (Guo et al. 2016) (Table 7.1).

**Table 7.1** The seropositive rates of SFTS cases in healthy subjects and estimated SFTS case incidence and case-fatality proportion (Guo CT, et al. Epidemiol Infect 2016; 144: 1345–54)

| Variable | Seroprevalence[a] mean (95%CI) | P value† | Case incidence rate (per $10^5$) | P value[b] | Case-fatality proportion (%) | P value[b] |
|---|---|---|---|---|---|---|
| Age, years | | <0.01 | | <0.01 | | <0.01 |
| < 40 | 3.3 (1.1–6.5) | | 0.01 | | 6.8 (4/59) | |
| 40–50 | 3.4 (1.3–6.5) | | 0.121 | | 4.9 (8/165) | |
| 50–60 | 2.3 (0.3–4.9) | | 0.281 | | 9.2 (24/261) | |
| 60–70 | 3.7 (1.5–6.9) | | 0.575 | | 15.1 (35/392) | |
| ≥ 70 | 7.1 (5.8–8.6) | | 0.592 | | 19.5 (55/282) | |
| Sex | | 0.92 | | 0.47 | | 0.26 |
| Male | 3.3 (1.4–5.9) | | 0.136 | | 14.3 (133/931) | |
| Female | 3.3 (1.2–6.6) | | 0.153 | | 12.5 (124/989) | |
| Area | | <0.01 | | <0.01 | | 0.42 |
| High endemic | 3.9 (2.5–5.5) | | 0.567 | | 13.9 (161/1159) | |
| Middle endemic | 2.6 (0.9–5.1) | | 0.067 | | 12.6 (96/761) | |
| Recruitment year | | <0.01 | | <0.01 | | 0.03 |
| 2010 | 2.2 (0.7–4.5) | | 0.004 | | 25.3 (61/241) | |
| 2011 | 3.1 (0.8–6.7) | | 0.034 | | 13.9 (71/510) | |
| 2012 | 3.0 (0.3–8.2) | | 0.046 | | 10.4 (59/569) | |
| 2013 | 6.5 (5.6–7.4) | | 0.052 | | 8.4 (37/439) | |
| Total | 3.0 (1.6–4.9) | | 0.144 | | 12.2 (257/1920) | |

[a] SFTSV-specific IgG antibody-positive proportion by meta-analysis

[b] Using $\chi^2$ test

### 7.9.2 Clinical Symptoms

Here, potential risk factors of severity and fatality associated with clinical symptoms are described.

By using the integrated several observational studies, it was suggested that deterioration in the central nerve system (CNS) and hemorrhagic manifestations were associated with severity and fatality (Sun et al. 2016; Gai et al. 2012b; Liu et al. 2013). In multivariate analysis of the observational study, it was also revealed that the independent predictors of risk for severity was the presence of neurological manifestations (OR, 7.70; 95% CI, 3.28–62.24) (Deng et al. 2013a); while it was controversial whether gastrointestinal symptoms were associated with those. Another study reported that the severity was associated with abdominal pain (OR, 21.95; 95% CI, 2.32–208.11) and gingival bleeding (OR, 122.1; 95% CI, 6.41–2328) (Sun et al. 2016; Ding et al. 2014d). However, in the univariate analysis, fatal outcome was not associated with the following symptoms: body temperature (level of fever), fever duration, flu-like symptoms (e.g. headache, fatigue, lymphadenopathy, and conjunctival congestion), and gastrointestinal symptoms (e.g. anorexia, nausea, vomiting, abdominal pain, abdominal distension, and diarrhea) (Guo et al. 2016; Sun et al. 2016; Gai et al. 2012b). Besides, it was reported that fatality was not associated with tick bite (Chen et al. 2017).

### 7.9.3 Laboratory Data

Here, potential risk factors of severity and fatality associated with laboratory data is described. For details about clinical characteristics, see the chapter on laboratory diagnosis of SFTS.

The major clinical laboratory data of SFTS include leukopenia, thrombocytopenia, and elevation of liver enzyme. Several observational studies suggested that thrombocytopenia, the elevation of liver enzyme, and coagulation disorders were associated with severity and/or fatality, but leukocytosis was not associated (Cui et al. 2014; Chen et al. 2017). However, it is very difficult to exclude bias completely and identify laboratory data as potential risk factors for fatal outcome accurately; therefore, it varies depending on reports.

In the integrated data analysis, it was described that thrombocytopenia was found to be increased in fatality by univariate analysis; however, this association disappeared after multivariate adjustment (Guo et al. 2016). In the univariate analysis regarding other parameters, it was suggested that the severity was significantly associated with the elevations of AST, CK and LDH (Ding et al. 2014d). In multivariate analysis, it was demonstrated that the independent predictors of risk for severity were: albumin $\leq$30 g/l (OR, 8.09; 95% CI, 2.58–25.32), APTT $\geq$66 seconds (OR, 14.28; 95% CI, 3.28–62.24), and sodium $\leq$130 mmol/l (OR, 5.44; 95% CI, 1.38–21.40) (Deng et al. 2013b). In another multivariate analysis, the independent

**Table 7.2** Clinical manifestation and laboratory parameters in correlation with fatal SFTS cases during 2010–2013 using the integrated dataset in China (Guo CT, et al. Epidemiol Infect 2016; 144: 1345–54)

| | | | Crude | | | Adjusted∗ | | |
|---|---|---|---|---|---|---|---|---|
| Variable | Fatal | Non-fatal | OR | 95% CI | P | OR | 95% CI | P |
| Age, years, mean ± S.D. | 66.1 ± 10.7 | 59.7 ± 13.2 | 1.04 | 1.03–1.06 | <0.01 | 1.05 | 1.02–1.06 | <0.01 |
| Sex, male | 79 (51.6%) | 512 (48.5%) | 1.13 | 0.81–1.59 | 0.92 | 0.95 | 0.65–1.40 | 0.81 |
| Days from onset to admission, mean ± S.D. | 6.0 ± 3.2 | 5.2 ± 2.9 | 1.07 | 1.02–1.13 | <0.01 | 1.09 | 1.02–1.17 | 0.01 |
| Platelet, $10^9$/L | 64.6 ± 58.0 | 72.2 ± 35.7 | 0.99 | 0.99–1.00 | 0.03 | 1.00 | 0.99–1.00 | 0.32 |
| White blood cell, $10^9$/L | 2.9 ± 2.4 | 3.0 ± 2.4 | 0.99 | 0.91–1.07 | 0.72 | 0.98 | 0.90–1.07 | 0.63 |
| Weakness | 134 (87.6%) | 933 (88.4%) | 0.92 | 0.55–1.55 | 0.76 | 0.80 | 0.45–1.44 | 0.46 |
| Lymphadenopathy | 61 (40.0%) | 364 (34.5%) | 1.26 | 0.89–1.78 | 0.20 | 1.34 | 0.92–1.96 | 0.13 |
| Conjunctival congestion | 8 (5.2%) | 38 (3.6%) | 1.48 | 0.67–3.23 | 0.33 | 1.57 | 0.55–4.49 | 0.40 |
| Gingival bleeding | 87 (5.2%) | 31 (2.9%) | 1.82 | 0.82–4.04 | 0.41 | 1.58 | 0.60–4.21 | 0.36 |
| Anorexia | 110 (71.9%) | 774 (73.4%) | 0.93 | 0.64–1.36 | 0.70 | 0.92 | 0.54–1.46 | 0.74 |
| Nausea | 80 (52.3%) | 540 (51.2%) | 1.05 | 0.74–1.47 | 0.80 | 0.78 | 0.48–1.27 | 0.32 |
| Vomitting | 51 (33.3%) | 326 (30.9%) | 1.12 | 0.78–1.60 | 0.54 | 1.34 | 0.80–2.25 | 0.27 |
| Haematemesis | 3 (2.0%) | 18 (1.7%) | 1.15 | 0.34–3.96 | 0.82 | 0.82 | 0.18–3.77 | 0.80 |
| Abdominal pain | 13 (8.5%) | 136 (12.9%) | 0.63 | 0.35–1.14 | 0.13 | 0.54 | 0.27–1.09 | 0.09 |
| Diarrhoea | 43 (28.1%) | 268 (25.4%) | 1.15 | 0.79–1.68 | 0.58 | 1.21 | 0.79–1.86 | 0.39 |

OR, odds ratio; CI, confidence interval; S.D., standard deviation.
∗Multiplevariable logistic regression analysis was performed

predictors of risk for fatality were presence of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) (HR, 4.59; 95% CI, 1.48–14.19) and disseminated intravascular coagulation (DIC) (HR, 4.24; 95% CI, 1.38–13.03) (Deng et al. 2013b) (Table 7.2).

## 7.10 Person-to-Person Transmission

Person-to-person transmission of SFTSV was described through epidemiological investigations in China. For details about prevention and control, see the chapter on infection control of SFTS in hospitals and at home.

A main transmission route of SFTSV to humans is supposed to contact with vectors. However, probable person-to-person transmission in hospitals and among family members was also provided under detail epidemiological investigations. In person-to-person transmission, most primary-index cases were fatal with a high viral load in blood. Secondary cases were infected with the virus through the direct contact of the mucous membranes or fragile skin with blood or bloody secretions of the primary cases without effective personal protection. Several reports revealed that the viral strains isolated from the secondary cases were identical to the sequence of the virus isolated from the primary-index case by complete genomic sequencing (Yu et al. 2011; Bao et al. 2011). Other than blood, it was reported that the viral RNA could be detected in urine, throat, and fecal samples of a substantial proportion of patients, suggesting that these excretions could be the potentially infective (Zhang et al. 2012b).

Of the secondary cases, most were family members, relatives, neighbors, medical care providers, and mortuary beauticians (Liu et al. 2014b). Generally, in the rural areas in China, medical care in terminal stage and burial has been taken by family members and/or relatives. Thus, these persons have high opportunities of the close contact with blood and/or bloody secretions, suggesting that they may be high risk population for person-to-person transmission. In fact, the odds ratio of burial was 17.98 (95% CI: 4.35–74.26) folds higher (Li et al. 2014a).

So far, no tertiary case has been reported, suggesting that the risk of person-to-person transmission might not be so high. Besides, there is no evidence that suggests that airborne and fecal–oral transmission play a role in person-to-person transmission (Gai et al. 2012a; Li 2015). Taking account of these data, SFTSV is not likely to be transmitted among humans. No stockbreeding- and/or slaughtering-associated professional infections of SFTS have been reported (Gong et al. 2015), although the transmission route is highly likely as in the case of Crimean-Congo hemorrhagic fever. Blood and secretions of subclinical animals might become a source of infection, but the risk would be relatively low (Zhan et al. 2017a).

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