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Original Article

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Seroprevalence of Severe Fever with Thrombocytopenia Syndrome in the Agricultural Population of Jeju Island, Korea, 2015–2017

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ABSTRACT

Background: Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne zoonotic disease that is caused by the SFTS virus (SFTSV), and exhibits an overall mortality rate of approximately 20.0% in Korea. Most cases of this disease have been reported in Korea, East China, and Japan, and it mostly affects outdoor workers and farmers. This study aimed to investigate the seroprevalence of SFTSV among healthy farmers on Jeju Island, Korea.
Materials and Methods: In this prospective cross-sectional study, we analyzed 421 blood samples obtained from 254 farmers (mean age, 59.9 years; 68.9% male) to determine the seroprevalence of SFTSV in 16 rural areas of the Jeju Special Self-Governing Province over a period of 3 years (January 2015–December 2017). We used an enzyme-linked immunosorbent assay to detect immunoglobulin (Ig) G antibodies against SFTSV in the collected samples.
Results: The seroprevalence of the SFTSV IgG among farmers on Jeju Island was observed to be 2.4%. One subject showed seropositivity over the entire 3-year study period. The areas with the highest SFTSV IgG seropositivity rates were Seonheul-ri in Jocheon-eup, followed by Namwon-eup. Fruit farmers were at a higher risk of exposure to SFTSV than other farmers.
Conclusion: The seroprevalence of SFTSV in the healthy agricultural population of Jeju Island was not high. However, personal hygiene management should be implemented for the agricultural population in the endemic areas. Surveillance of mild or asymptomatic infections is required in the endemic regions.

Keywords: Severe fever with thrombocytopenia syndrome; *Phlebovirus*; Seroprevalence; Epidemiology; Korea

INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne zoonosis that is caused by the SFTS virus (SFTSV) [1, 2]. Recently, confirmed cases of SFTS have been reported in East China, Japan, and Korea [3-6]. Between 2013 and 2016, the disease showed an overall mortality rate of approximately 20% in Korea [7]. The SFTS prevalence rate in this country

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Conflict of Interest
No conflict of interest.

Author Contributions
Conceptualization: JRY, KHL. Data curation: SWS, JWB, MYK. Formal analysis: JRY, STH. Funding acquisition: JRY. Investigation: SWS, JWB. Methodology: KHL. Project administration: JRY. Resources: SWS, KHL. Software: SWS, KHL. Supervision: JRY, KHL. Validation: STH. Visualization: STH, MYK. Writing - original draft: JRY. Writing - review & editing: JRY, KHL.

was 1.19 per 100,000 inhabitants on the mainland and 8.66 per 100,000 inhabitants on Jeju Island from 2013 to 2018 [7].

The SFTSV has been detected in several species of ticks including *Haemaphysalis longicornis*. Person-to-person transmission of the SFTSV is possible through close contact between healthcare workers and family members [8-10]. SFTSV and anti-SFTSV antibodies have been identified among ticks, domestic and wild animals, and humans in nature in endemic areas [11, 12]. Most patients with SFTS are elderly farmers living in rural areas [2, 6, 13, 14]. According to recent seroepidemiological studies, the seroprevalence of SFTSV varies in endemic countries [13, 15, 16], with a higher prevalence among Chinese farmers and a lower prevalence in the healthy population of Japan than in that of Korea [13-15, 17].

Jeju Island comprises predominantly of grazing land and woodlands and has the largest farmer population in Korea. However, the seroprevalence of SFTSV in this population has not been evaluated. In this study, we assessed the seroprevalence of SFTSV-immunoglobulin (Ig) G among farmers on Jeju Island.

MATERIALS AND METHODS

1. Subjects

We performed a cross-sectional seroepidemiological study of SFTSV among healthy farmers from various rural areas of Jeju Island over a period of three years from January 2015 to December 2017 (**Fig. 1**). Jeju Island (33°0′ N, 126°0′ E) is the largest island located off the

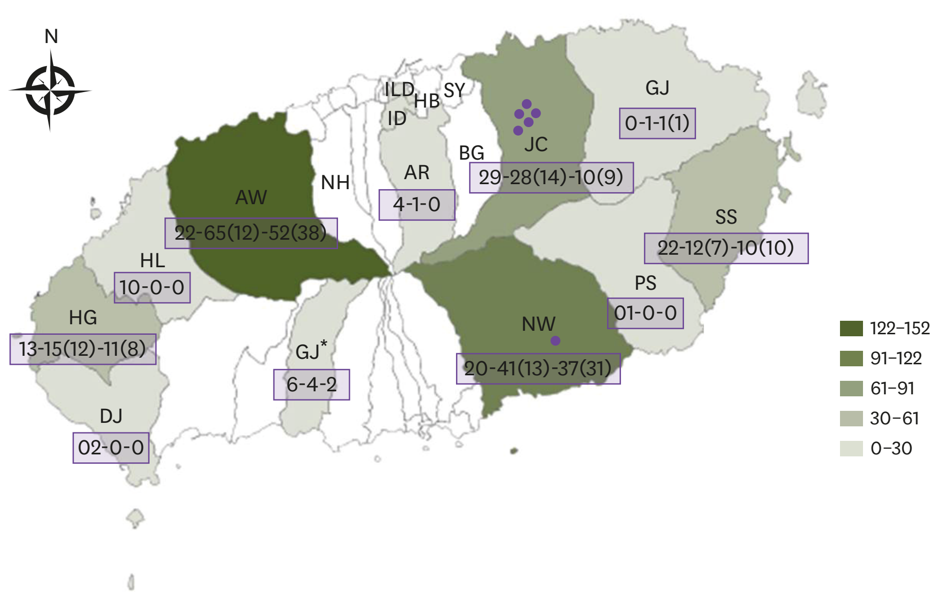

Figure 1. Geographic distribution of 421 samples obtained from subjects and the distribution of SFTSV IgG seropositivity among agricultural and livestock workers on Jeju Island, South Korea, 2015–2017. Violet dots indicate the location of seropositive SFTSV IgG subjects. The number of samples is shown in the boxes [2015–2016(repeat number)–2017(repeat number)].
HL, Hanlim-eup; AW, Aewol-eup; NH, Nohyeong-dong; ILD, Ildo-dong; ID, Ido-dong; AR, Ara-dong; HB, Hwabug-dong; SY, Samyang-dong; BG, Bonggae-dong; JC, Jocheon-eup; GJ, Gujwa-eup; SS, Seongsan-eup; WP, Wolpyeong-dong; GJ*, Ganjeong-dong; DJ, Daejeong-eup; HG, Hangyeong-myeon; DR, Daeryun-dong; SH, Seohong-dong; NW, Nanwon-eup; PS, Pyoseon-myeon

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coast of the Korean Peninsula. It has a humid subtropical climate and is warmer than the rest of Korea (daily mean temperature: 15.8–16.6°C). The climate in winter is moderate with temperatures rarely falling below 0°C (32°F). A total of 650,000 people reside on the island, about 15% of whom are farmers.

The study subjects were farmers living on the Jeju Island who were some of the participants of the Prevention for Agricultural Injury of Farmers study which was conducted by the Center for Farmers' Safety and Health at Jeju National University Hospital. Along with the team of the Prevention for Agricultural Injury of Farmers study, we recruited participants and sequentially tested them from 2015 to 2017, using a three-step protocol. In the first step, ten rural villages were selected based on the type of agriculture and distance from urban areas; a total of 400 farmers (50 from each village) were selected. In the second step, 377 of these 400 farmers verbally consented to participate via telephone. In the third step, trained researchers visited each village and conducted face-to-face interviews among the participants. Three hundred and twenty-four farmers were enrolled in the cohort and 53 were excluded because they refused to participate in the face-to-face interviews. Finally, 254 farmers agreed to provide blood samples for SFTSV antibody tests and were included in the study. All subjects provided written informed consent. The study protocol was approved by the Institutional Review Board of Jeju National University Hospital (IRB no. 2015-11-002-004).

Data regarding sociodemographic status, medical history, occupation, type of farming, history of tick bites, history of SFTS, history of contact with SFTS patients, and other relevant information were collected via standardized questionnaires and interviews. The team analyzed blood samples collected from subjects for the presence of SFTSV antibodies.

2. Antibody detection in sera

Serum samples obtained from the subjects were stored until serologic analyses could be performed. SFTSV IgG was detected using an enzyme-linked immunosorbent assay (ELISA), as previously described [9]. In our previous study, the sensitivity and specificity of ELISA were comparable to those of the immunofluorescence assay (IFA); samples that tested positive for the IgG in the ELISA also showed positive results in the IFA. Huh7 cells were infected with SFTSV strain HB 29 (multiplicity of infection = 0.1) and incubated at 37°C for 48 h. The cells were collected and washed with phosphate-buffered saline (PBS) and lysed with PBS containing 1% NP-40. The cell lysates were centrifuged at 8000 rpm for 10 min at 4°C, and the supernatant was collected and used as a source of SFTSV antigens for the IgG ELISA. Huh7 cell lysates of uninfected cells were used as a negative control. A Nunc-Immuno Plate (Thermo Fisher Scientific, Waltham, MA, USA) was coated with a predetermined optimal quantity of cell lysates from SFTSV-infected or uninfected Huh7 cells (1:800 dilution with PBS) and incubated overnight at 4°C. The cut-off value was set as the average value obtained in the control sera (serum samples obtained from healthy donors) plus thrice the standard deviation (SD) (mean ± 3 × SD). An absorbance reader (Sunrise, Tecan's Magellan™, Männedorf, Switzerland) was used to measure the absorbance in the ELISA. A sample was considered antibody-positive if it yielded an optical density (OD) above the predetermined cut-off value at 405 nm (OD_{405}). The average OD values for the negative and positive controls were ~0.12 and ~1.06, respectively. The antibody-positive serum of an SFTS patient who was admitted at our hospital was used as a positive control (OD_{405} = 1.06). The SFTSV IgG antibody levels in the specimens obtained from the cohort were higher than that in the positive control (OD_{405} = 1.06).

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3. Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The results for categorical variables are presented as frequencies or proportions and were compared using the chi-square test. P <0.05 was considered statistically significant. The results for continuous variables are presented as the means ± standard deviations or medians and ranges. Regional annual incidences were calculated using the annual number of cases of SFTS reported in the Disease Web Statistics System, Korea Centers for Disease Control and Prevention (http://is.cdc.go.kr) and population statistics based on resident registration (http://www.kosis.kr).

RESULTS

1. Demographic characteristics

A total of 254 healthy subjects were enrolled in the study, and 421 samples were collected. **Figure 1** shows the geographic distribution of all the healthy subjects. Many of the subjects had resided in the same location for at least 10 years. Five samples were obtained in Jeju-si, 67 in Jocheon-eup, 139 in Aewol-eup, 98 in Nanwon-eup, 39 in Hangyeong-myeon, 44 in Seongsan-eup, 2 in Daejeong-eup, 10 in Hanlim-eup, 2 in Gujwa-eup, 1 in Pyoseon-myeon, and 12 in Gangjeong-dong. All samples were subjected to ELISA for SFTSV detection. We obtained 131 samples in 2015, 167 in 2016, and 123 in 2017. Tests were performed once for 142 subjects, twice for 83 subjects, and thrice for 72 subjects from 2015 to 2017. The mean age of the participants was 59.9 years (range, 27–84 years; 68.9% male). Thirteen participants farmed grain, 120 farmed vegetables, 125 farmed fruits, 27 farmed livestock, and 8 engaged in other forms of farming. Only eight samples tested positive for SFTSV IgG, resulting in an overall prevalence rate of 2.4% (6/254 subjects). One subject showed positive results over the entire three year period.

2. Characteristics of SFTSV IgG seropositive subjects

Six patients and eight samples tested positive for SFTS IgG (**Table 1**), although all seropositive samples tested negative for the S segment of SFTSV in a reverse transcriptase polymerase chain reaction assay. The areas with the highest SFTSV IgG seropositivity rates were Seonheul-ri in Jocheon-eup, followed by Namwon-eup, which are also the regions in which SFTS was most common and had the highest number of reported SFTS-related deaths in 2013 and 2015. Fruit farmers were at a higher risk of exposure to SFTSV than were other farmers such as those who farmed grain, vegetable, and livestock, and those who engaged in other forms of farming (4.8% *vs* 0%; P <0.001). Farmers in Jocheon-eup also had a significantly higher exposure risk than those in other locations. The subjects who tested positive for

Table 1. Clinical characteristics of participants in the severe fever with thrombocytopenia syndrome virus specific immunoglobulin G-positive group

Sample No.	Sex	Age (yrs)	Location	IgG for SFTSV			Occupation	Duration of outdoor activity (h/day)
				2015	2016	2017		
10	F	77	Jocheon-eup	+ (1.19)	N/A	N/A	Fruit farmer	4
13	M	67	Jocheon-eup	+ (1.45)	N/A	N/A	Fruit farmer	12
17	M	78	Jocheon-eup	+ (1.51)	N/A	N/A	Fruit farmer	12
22	F	71	Jocheon-eup	+ (1.50)	N/A	N/A	Fruit farmer	12
311	M	65	Nawon-eup	N/A	+ (1.41)	N/A	Fruit farmer	10
368	M	56	Jocheon-eup	+ (1.46)	+ (1.50)	+ (1.27)	Fruit grower	12

Values declared in parentheses are OD_{450} values.
+ indicates positive results for SFTSV-specific IgG.
IgG, immunoglobulin G; SFTSV, severe fever with thrombocytopenia syndrome virus; F, female; M, male; N/A, not applicable.

SFTSV IgG were fruit farmers who cultivated mandarins. There was no significant difference in the proportion of participants who wore protective equipment between the seropositive and seronegative groups. Additionally, fruit farmers with vinyl greenhouses tended to have a lower seropositivity rate of SFTS IgG ($P = 0.09$). There were no significant differences in the other characteristics between the seropositive and seronegative groups. The subjects had no history of tick bites or contact with SFTS patients. The seropositive group included 4 men and 2 women, none of whom showed typical symptoms or other infectious diseases during the period of sample collection. The median age was 69 (range, 56 – 78) years.

DISCUSSION

In this study, we examined the prevalence of SFTSV IgG seropositivity among farmers in Korea. We found an SFTSV IgG prevalence rate of 2.4%. We evaluated information regarding occupation, outdoor activities, medical history, and contact history, focusing on the population of healthy farmers. In addition, we found one subject who tested SFTSV IgG positive for at least 3 years. In a follow-up study of anti-SFTSV antibodies conducted over a period of four years, all patients had protective antibody titer levels that declined yearly. The protection conferred by neutralizing antibodies against SFTSV could last as long as 9 years [18]. One subject in our study may also have experienced persistence of SFTS antibodies. The seropositive subjects had no history of tick bites and had not been in contact with SFTS patients. Compared with the urban population, these subjects had a higher probability of exposure to ticks or domestic animals with SFTSV, and the frequency of latent infection or asymptomatic patients with SFTS varied. Person-to-person transmission of SFTSV has been demonstrated in China and Korea. In these instances, the disease is typically fatal, with a high viral load in the blood observed following infection by contact with contaminants [8, 9]. However, this was not observed among our subjects. A previous study reported that the minimum infection rate of SFTSV from infected ticks was lower in Jeju Island than in other areas assessed (0.3% *vs* 1.9%) [4]. We presumed that all subjects were healthy and that farmers would be sporadically exposed to SFTSV via tick bites or contact with domestic animals with low viral loads of SFTSV.

Most studies regarding the SFTSV seroprevalence were conducted in China [19] and reported a seroprevalence of SFTS antibodies ranging from 0.2 – 9.1%. The pooled seroprevalence among farmers was 6.1%, and that among individuals older than 40 years was 4.9% [19]. In Japan, the SFTSV seroprevalence in the healthy population is low (0.3%) [15]. Recent studies estimated that the SFTSV seroprevalence in Korea ranged from 2.1 – 4.1% [16, 20]. However, these studies were not conducted in endemic areas of SFTS of Korea. Although these studies had some limitations, including their focus on urban areas and a lack of information regarding tick exposure, occupation, and outdoor activities, these findings might help explain the high seroprevalence observed in rural areas. Although the present study was performed in the most common endemic region for SFTSV in Korea, we detected a lower SFTSV IgG prevalence among farmers from Jeju Island than among those from the mainland (2.4% *vs.* 2.7 – 5.5%) [16, 20]. Based on the total population of agricultural workers on Jeju Island (88,385 people in 2017), 2,121 persons are predicted to be exposed to or infected with SFTSV.

Over 500 cases of SFTS have been reported in Korea since 2013 with Jeju Island being the most common location [7]. Seventy-three fatal cases of SFTS were reported in Korea before 2016, 6 of which were from Jeju Island. Fifty-one patients with SFTS were identified on Jeju

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Island and all lived in rural areas or were outdoor workers. Thirteen were grain farmers, 9 were fruit farmers, 7 were livestock farmers, 17 had other occupations, and 5 had unknown occupations. Approximately 67% of the patients were ≥65 years old, and most resided in the Northeastern region, followed by the Southeastern and South regions. In the present study, we only observed SFTSV IgG seropositivity among fruit farmers. Our findings were similar to those obtained in epidemiologic studies regarding SFTS prevalence among regions that assessed SFTSV IgG seropositive individuals and those with confirmed SFTS infection.

Our study had some limitations. First, SFTSV IgM was not evaluated in the serum samples, because the subjects were asymptomatic and we focused on healthy farmers. We cannot deny the fact that recent asymptomatic SFTS infections would not be detectable using IgG antibodies. Additionally, we could not differentiate a history of SFTS from those of common acute infectious diseases that can mimic SFTS. Second, it was difficult to evaluate regional differences in SFTS IgG seropositivity due to the uneven distribution of samples among locations. However, we obtained blood samples in regions where patients with SFTS had died and in areas where there were many patients with SFTS based on the assumption that these regions included many vector reservoirs. Third, it was difficult to confirm whether antibody levels had persisted for more than three years or if the patient had been repeatedly exposed to ticks and domestic animals because SFTSV infects humans with farming-related exposure as well as numerous domestic and wild animals and SFTSV may be circulating widely on Jeju Island [17]. However, the prevalence of SFTS was about 2 per 100,000 population in Korea [7], and the seroprevalence rate of SFTSV in the healthy population is less than 1%, suggesting that the chance of SFTSV reinfection is low [21]. Fourth, even though the results of ELISA were comparable to those of the IFA in our previous study, we did not know the exact sensitivity and specificity of our ELISA method.

This study assessed SFTSV circulation in the farmer population and evaluated the maintenance of antibody circulation within a 3 year period in Korea. Additionally, we found that a history of mild clinical symptoms or an asymptomatic presentation of SFTS could be possible. However, despite the high incidence of SFTS in the target area, the seroprevalence among farmers on Jeju Island was lower than that of the entire country. These results might help increase awareness regarding the occurrence of SFTS in Korea and provide useful public health information.

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