

# Evaluating the spatial and temporal patterns of the severe fever thrombocytopenia syndrome in Republic of Korea

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## Abstract

Severe fever with thrombocytopenia syndrome (SFTS) is a new infectious disease with a high mortality rate and increased incidence in Republic of Korea since the first case was reported in 2013. The average mortality rate varies by region and year but remains high in Asia. This study aimed to evaluate the spatial and temporal patterns of SFTS cases reported to the national Disease Control and Prevention Agency (KDCA). We analysed the spatial and temporal distribution of SFTS and observed changes in areas vulnerable to the disease. We analysed data concerning 1086 con-

firmed SFTS patients from 2013 to 2019 categorized according to the 247 district level administrative units. To better understand the epidemiology of SFTS, we carried out spatiotemporal analyses on a yearly basis and also calculated and mapped spatial clusters of domestic SFTS by global (regional) and local Moran's indices. To observe the annual changes in SFTS incidence rate, scan statistics for each city and district were calculated. The incidence rate showed significant clustering in specific regions, which reoccurred annually in some regions. In Republic of Korea, SFTS clusters have been expanding into the southern regions, with annual clusters concentrated between May and October. This pattern allows prediction of SFTS occurrences through spatiotemporal analysis, which makes it possible to guide measures of disease prevention.

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Ethical approval: this study used public data on severe febrile thrombocytopenia syndrome (SFTS) provided by the Korea Centers for Disease Control and Prevention (KDCA) and was conducted with the approval of the Chungnam National University Institutional Ethics Committee. As this was a retrospective study, the requirement for informed consent was waived as per Institutional Review Board approval (IRB no. 202012-SB-161-01).

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## Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne infectious disease first identified in rural areas of Hunan and Hubei in central China in 2009 (You *et al.*, 2020). During the initial epidemiological investigation in China, a group of patients with high fever, digestive symptoms and low platelet and white blood cell counts was observed. The causative agent for this disease was confirmed as the severe fever thrombocytopenia syndrome virus (SFTSV) belonging to the Bunyaviridae family (Yu *et al.*, 2011). The clinical signs of SFTS include fever, thrombocytopenia, and leukopenia, accompanied by coldness, headache, lymphoedema, anorexia, nausea, muscle pain, diarrhoea, vomiting, abdominal pain, bleeding gums, and conjunctival opacity (Yu *et al.*, 2011; Ding *et al.*, 2013). Although numbers of cases and deaths are increasing, effective treatment will be difficult to establish (Oh *et al.*, 2014).

Since its discovery, more than 13,000 SFTS cases have been reported worldwide, of which more than 8% have died (Miao *et al.*, 2020). More than 90% of SFTS cases have occurred in China, while the highest annual growth rate was recently observed in Republic of Korea (Miao *et al.*, 2020), where the disease is treated as a new notifiable infectious disease since 23 September 2013 (Seo *et al.*, 2017). In Republic of Korea, the first outbreak of SFTS was reported in May 2013, and the primary vector found to be the longhorned tick, *Haemaphysalis longicornis* (KDCA, 2016). Suspected cases are reported to the national Centers for Disease Control and Prevention (KDCA) within 24 hours, where the data on confirmed SFTS patients are recorded in a dedicated database and epidemiological investigations subsequently conducted.

In China, most hospitalized patients with SFTS are outdoor workers and the epidemic period of SFTS is from March to



November, with incidence rates peaking in June and July. So far, more than 50% of SFTS cases have occurred in Henan and Hubei provinces (Li *et al.*, 2017). In Japan, the first death due to SFTS was registered in the fall of 2012 (Takahashi *et al.*, 2014) and a case of infection with a virus related to SFTSV, the Heartland virus, was reported in the same year in the United States (McMullan *et al.*, 2012). Although the average mortality rate varies by region and year, it has remained relatively high in Japan (27%), Korea (23.3%) and China (5.3%-16.2%) (Yun *et al.*, 2020). According to China's national surveillance data covering 2011 to 2013, the number of patients with SFTS increased, while the number of deaths decreased (Liu *et al.*, 2015). In this country, the disease mostly affects the elderly and farmers (Liu *et al.*, 2015), while other epidemiologic characteristics, such as incidence, sex ratio, fatality rate, and seasonality vary considerably depending on the affected region, which could be due to local agricultural activities and the seasonal tick situation (Liu *et al.*, 2015). Severe outcome of SFTSV infection has been found to be related to climatic factors such as altitude, temperature, precipitation and relative humidity, with the probability of occurrence increasing under certain conditions (Sun *et al.*, 2020).

Since the initial symptoms are not distinguishable from other infectious diseases, the diagnosis is difficult. In addition, the clinical management is challenging due to the lack of effective preventive measures and clear means of treatment (Yoo & Heo, 2018). The fatality rate of SFTS differs across countries and regions, and there are regions with a fatality rate of 30% (Guo *et al.*, 2016; Liu *et al.*, 2015). On average, most patients died nine days after symptom onset, otherwise within 2 weeks (Yoo & Heo, 2018). Patients with complications can be difficult to manage secondary to their rapid clinical deterioration. Often, these patients die from unsequenced sepsis (Oh *et al.*, 2014; Yoo & Heo, 2018).

Infectious diseases such as SFTS appear repeatedly in a specific space and time; hence, areas with a high risk of occurrence should be identified to inform and initiate rapid prevention measures. The purpose of this study was to investigate the temporal and spatial characteristics of SFTS in Republic of Korea. Specifically, the study investigated the clustering and spatiotemporal propagation patterns of SFTS.

## Materials and methods

We analysed data of 1,086 SFTS patients, by administrative district, based on the data collected by the KDCA over the period 2013-2019. A cross table of the major characteristics of SFTS patients including deaths by season, region, sex and age was created, and statistical significance was evaluated using chi-square and fish exact tests. Global and local Moran's *I* and spatiotemporal scan statistics were used to evaluate the range of temporal and spatial clustering (clusters or hotspots) of domestic SFTS and the geographical risk patterns. Such a result can intuitively convey the spatial location of the disease cluster through geographic information systems (GIS). For spatial analysis, the cumulative incidence of SFTS per 100,000 people per year was calculated using the resident registered population for each of the 247 administrative districts as follows:

$$\text{Cumulative incidence} = \frac{\text{SFTS cases per year and district}}{\text{Resident population per year and district}} \times 100,000 \quad (1)$$

First, Moran's *I* was used to determine the spatial autocorrelation of SFTS occurrence in each city, county and district during the study period. Moran's *I* values range from -1 to 1 where 0 equal to normal distribution, positive values indicating clustered distributions or spatial autocorrelation and negative values indicating scattered distributions. Global Moran's *I* was used for the entire space and Local Moran's *I* regional distributions. The concept of local indicators of special assistance (LISA) analysis was developed by Anselin (1995). LISA calculates the value of Moran's *I* according to administrative district for the entire study area, thus identifying spatial autocorrelations by administrative district that can be calculated as follows:

$$I_i = \frac{(x_i - x^*) \sum_j w_{ij} (x_j - x^*)}{\sum_i (x_i - x^*)^2 / n} \quad (2)$$

where  $x_i$  is the value of  $x$  in spatial unit  $i$ ;  $x^*$  the mean of  $x$ ;  $n$  the number of spatial units; and  $w_{ij}$  the spatial weights matrix that measures the strength of the relationship between two spatial units. This formula generates values for local Moran's *I* that range from -1 (perfect negative spatial autocorrelation) to +1 (perfect positive spatial autocorrelation) (Andresen, 2011).

## Cluster classification

The SFTS clusters were divided into four groups: High-high (HH) clusters = high values in a high-value neighbourhood areas; low-low (LL) clusters = low values in a low-value neighbourhood areas; high low (HL) spatial outlier = a high value in a low-value neighbourhood; and low-high (LH) = a low value in a high-value neighbourhood

In this study, SaTScan™ software (Kulldorff, 2018) was used to evaluate the occurrence pattern of spatio-temporal clusters of SFTS, according to spatiotemporal factors. The spatio-temporal scan statistics using SaTScan were based on the Poisson model and were used to identify cluster areas with a statistically significant SFTS occurrence rate. Seasons were divided into spring (March-May), summer (June-August), autumn (September-November), and winter (December of the year and January and February of the following year).

Kulldorff's SaTScan gradually increases the size of each regional unit to create a hierarchical window that overlaps each other and calculates the log likelihood ratio (LLR) for all windows and the maximum test statistic. The scan statistics were tested for significance using the Monte Carlo approach, which randomly generates a large number of datasets under the null hypothesis (*i.e.* the risks of SFTS are the same in the units of space). Then, we calculated the test statistic for each data set to determine significance by checking the rank of the values of the test statistic calculated from the actual data. A simulation with 999 permutations was performed to ensure adequate power for defining the clusters (Kulldorff, 2018), which means that if the value of the test statistic calculated from the identified cluster falls within the top 10%, the cluster should be considered significant (Han & Lee, 2016).

The relative risk (RR) ratio, given by dividing the predicted risk value within the cluster by the predicted risk value outside the cluster, was calculated for each administrative district using the number of SFTS occurrences and population data during the study period. For example, an RR value of 10 for an administrative district means that the population in that area is 10 times more likely to be exposed to SFTS.

## Results

The number of confirmed SFTS patients reported to the KDCA from 2013 to 2019 was 1086, including 214 dead, which gives a fatality rate of 19.7% (Table 1). Although the number of male and female cases was equal ( $n=543$ ), there were more deaths among the women (54.7%) than the men (45.3%). However, the difference was not statistically significant ( $P=0.147$ ).

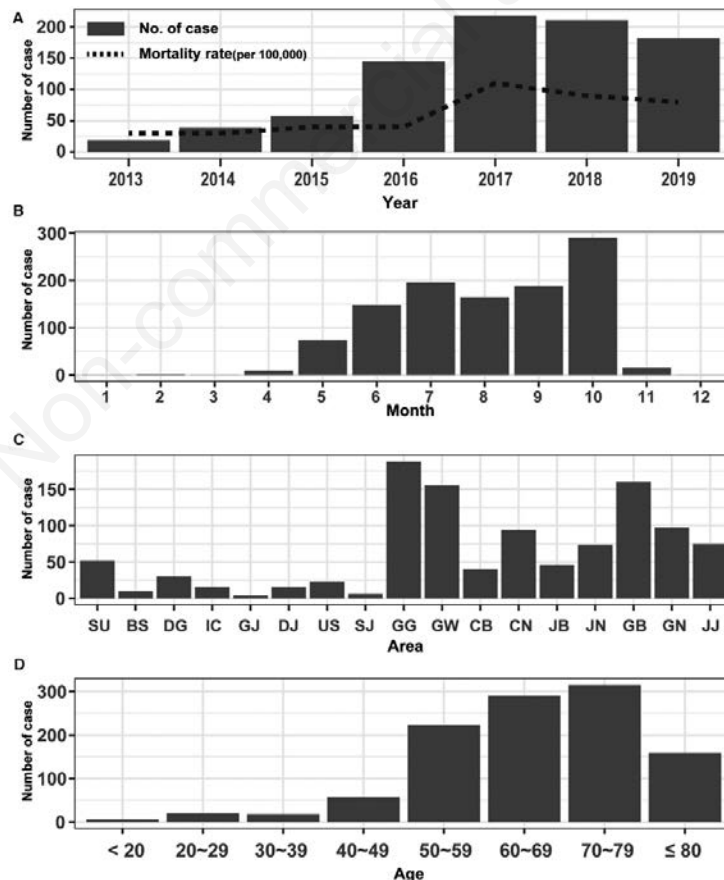
In terms of temporal occurrence there was a rising trend as seen in Figure 1. Out of the 36 cases of SFTS in the first year, 17 died. In 2019, that had changed to 223 cases and 41 deaths in 2019. Over the whole study period, most cases occurred between May and October ( $n=1061$ , 97.7%) and more frequent in summer ( $n=509$ , 47.0%) and fall ( $n=493$ , 45.3%), indicating a seasonal cycle. Indeed, the cumulative incidence of SFTS per 100,000 people per year in the 247 administrative districts showed an increasing trend and expansion into the eastern and southern region (Figure 2).

By age, 55.9% of all patients (607) were over 65 years, and the number of patients increased with age (Table 1 and Figure 1). The global spatial autocorrelation analysis of the annual incidences of SFTS through Global Moran's  $I$  significant clustering at the

**Table 1. Spatiotemporal overview of patients and outcomes with respect to the severe fever with thrombocytopenia syndrome.**

Characteristic	Non-fatal No. (%)	Fatal No. (%)	Total No. (%)	P
Season				<0.01
- Spring	59 (6.8)	24 (11.2)	83(7.6)	
- Summer	394 (45.2)	115 (53.7)	509(46.9)	
- Fall	418 (47.9)	75 (35.0)	493(45.4)	
- Winter	1 (0.1)	0 (0.0)	1(0.1)	
Region				0.181
- District	165 (18.9)	33 (15.4)	198 (18.2)	
- City	299 (34.3)	87 (40.7)	502 (46.2)	
- County	408 (46.8)	87 (40.7)	386 (35.5)	
Sex				0.147
- Male	446 (51.1)	97 (45.3)	543(50)	
- Female	426 (48.9)	117 (54.7)	543(50)	
Age				<0.01
- <65	429 (49.2)	50 (23.4)	479 (44.1)	
- ≥65	443 (50.8)	164 (76.6)	607 (55.9)	
Total	872 (100)	214 (100)	1086 (100)	

\*The fish exact test was used for the season variable; the chi-square test was used for all other variables.



**Figure 1. Distribution of patients with the severe fever with thrombocytopenia syndrome in Republic of Korea 2013-2019. A) year; B) month; C) area\*; D) age. \*SU=Seoul, BS=Busan, DG=Daegu, IC=Incheon, GJ=Gwangju, DJ=Daejeon, US=Ulsan, SJ=Sejong-si, GG=Gyeonggi-do, GW=Gangwon-do, CB=Chungcheongbuk-do, CN=Chungcheongnam-do, JB=Jeollabuk-do, JN=Jellanam-do, GB=Gyeonggangbuk-do, GN=Gyeonggangnam-do, JJ=Jeju-do.**

$P=0.01$  level had positive (+) values in all years. According to the spatial autocorrelation results, the early monitoring period (2013–2015) showed relatively low Moran's  $I$  values, while the more ones (2016–2019) had relatively higher Moran's  $I$  values (Table 2). In 2013, clusters of regions with a high SFTS occurrence rate (HH) appeared partially in the south-eastern region and on Jeju Island. Major HH clusters were observed in the eastern region of Gyeongbuk in 2014; the northern region of Gangwon-do in 2015 and 2016; the area of Gangwon and Gyeongbuk in 2017; the northern region of Gangwon in 2018; and Gangwon, Jeonbuk and Gyeongnam in 2019 (Figure 3).

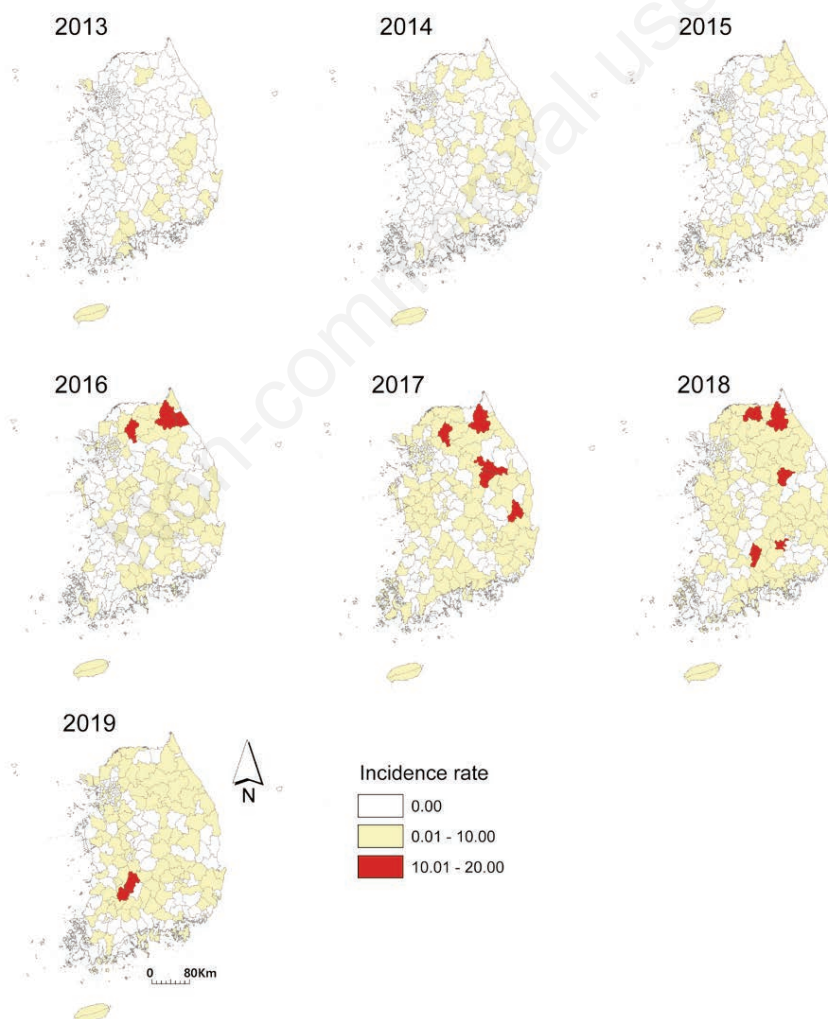
We also found that the disease returns repeatedly to certain areas at a certain times. Such multi-frequency areas included seven areas within a cluster range for six years. They included Inje-gun, Sokcho-si, Yangyang-gun, Yeongyang-gun, Cheongsong-gun, Yeongcheon-si, and Buk-gu of Pohang-si. In some cases, the area of occurrence could expand every year.

Table 3 shows the region range with a remarkably high incidence of SFTS and the region most likely to have spatiotemporal clusters. In 2013, statistically significant clusters were observed from 1 May to 31 July ( $RR=21.44$ ,  $P<0.001$ ). In 2014, 2017, 2018

and 2019, statistically significant clusters were observed from late May to early June to mid-October (2014:  $RR=19.00$ ,  $P<0.001$ ; 2017:  $RR=15.26$ ,  $P<0.001$ ; 2018:  $R=14.28$ ,  $P<0.00$ ; 2019:  $11.78$ ,  $P<0.001$ ). In 2016, a significant cluster was observed for the shortest time during the study period from September 4 to October 29 ( $RR=28.73$ ,  $P<0.001$ ).

**Table 2. Summary of Global Moran's  $I$  results.**

Year	Moran's $I$	Z score	P	Remark
2013	0.108	3.098	<0.01	Clustered
2014	0.106	3.021	<0.01	Clustered
2015	0.165	4.435	<0.01	Clustered
2016	0.339	9.134	<0.01	Clustered
2017	0.298	7.937	<0.01	Clustered
2018	0.263	6.940	<0.01	Clustered
2019	0.257	6.792	<0.01	Clustered



**Figure 2. Cumulative incidence of the severe fever with thrombocytopenia syndrome in Republic of Korea 2013-2019.**

## Discussion

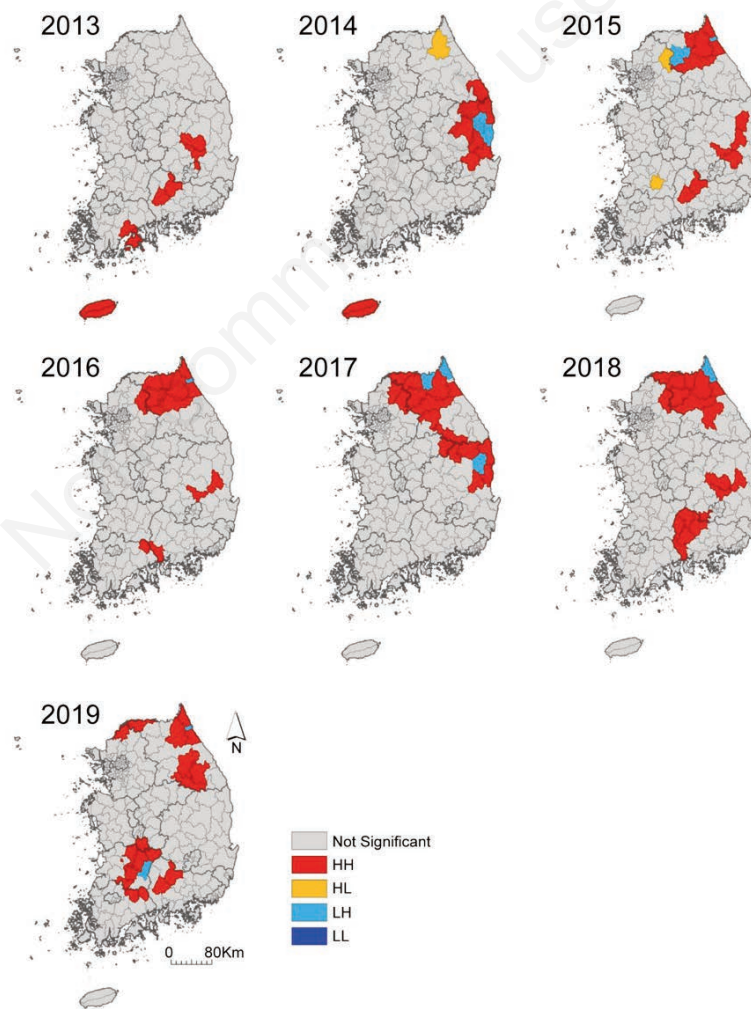
Spatial analysis of high incidence of disease can be performed through various methods such as density estimation and spatial interpolation; however, these methods are limited by difficulty in processing time variables by treating disease information as a two-dimensional and consequential factor without considering the time factors. Due to this limitation, a spatiotemporal cluster approach

and a technique to calculate the risk were used.

The method of expressing and analysing disease outbreak information on a map is a basic method to analyse regional variation in disease incidence across public health-related fields (Kandwal *et al.*, 2009). Understanding the geographic distribution of a disease can help identify high- or low-risk areas (Souza *et al.*, 2019). Our results show that, in Korea, SFTS exhibits spatial auto-correlation (*i.e.* the disease occurs repeatedly at a certain time and

**Table 3. SaTScan statistics for space-time clusters.**

Year	Cluster	Time frame	Zone (no.)	Cases obs. (no.)	Cases exp. (no.)	Relative risk	P
2013	Most likely	05/01-07/31	39	12	0.82	21.44	<0.0001
2014	Most likely	06/05-10/22	44	22	1.86	19.00	<0.0001
2015	Most likely	08/28-11/05	14	15	0.39	47.48	<0.0001
2016	Most likely	09/04-10/29	45	48	2.32	28.73	<0.0001
2017	Most likely	06/05-10/22	40	94	9.10	15.26	<0.0001
2018	Most likely	05/29-10/15	27	63	5.70	14.28	<0.0001
2019	Most likely	05/29-10/29	28	54	5.89	11.78	<0.0001



**Figure 3. LISA cluster maps for the severe fever with severe fever thrombocytopenia syndrome 2013-2019.**



in a certain area). For example, the county units (gun) in each city were selected for regional cluster (LISA) analysis and the findings showed some areas to be vulnerable to such spatial multi-frequency SFTS clustering.

Identification of regional clusters may provide valuable epidemiological insights into SFTS bolster its surveillance in Republic of Korea. Clusters in areas with a high RR ratio were found to occur every year, and this pattern should be evaluated for potential risk factors. The addition of spatial scan statistics analysis to rapid statistical analysis during monitoring would help in the management of potentially at-risk areas (Desjardins *et al.*, 2020). Thus, identifying areas with a high RR ratio for SFTS would help health authorities to monitor outbreaks in a timely manner and guide effective allocation of medical resources to manage disease outbreaks and prevent recurrence (Greenwood & Reid, 2020).

The monthly occurrence of SFTS in Republic of Korea during the initial monitoring period was found to be concentrated in July-August in the summer, while the time range expanded to early summer and autumn in recent years (2017-2018). This is in agreement with the finding by Miao *et al.* (2020) in China and several other Asian countries and supported by our SaTScan results of significant clusters with a high SFTS incidence between May and October in most years of observation. A study on SFTS in China suggests that the cause of the increasing incidence of SFTS could be due to a rise in infection opportunities and improved experience in the diagnosis of SFTS (Sun *et al.*, 2017). This could be the explanation for the similar increasing trend in Republic of Korea as well. However, it could also be due to a higher susceptibility in those above 50 years of age as they amount to 91% of all patients and constitute the main age group at risk in Republic of Korea (Figure 1). The real reason could be underlying diseases and decreased immune function. As there is currently no vaccine available to prevent SFTS, it is important to observe precautionary measures (Liu *et al.*, 2014). One should be aware of the time and region of the SFTS's temporal and spatial weakness.

A significant limitation of this study is that factors such as socioeconomic level, education level, occupation, geographic characteristics and weather characteristics, which can affect the occurrence pattern of SFTS patients, were not addressed. Further research that considers the effect of these factors on SFTS incidence is warranted.

## Conclusions

The importance of spatiotemporal, epidemiological analysis in identifying SFTS cluster areas requiring targeted public health prevention was demonstrated. Although the cumulative incidence of SFTS in Republic of Korea showed an increasing trend with a territorial expansion, and there was a constant seasonal pattern over the last 7 years (2013-2019). These results should help establish effective plans for controlling further spread of SFTS.

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