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Effects of climate factors on hemorrhagic fever with renal syndrome in Changchun, 2013 to 2017

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Abstract

Hemorrhagic fever with renal syndrome (HFRS) is a rodent-borne disease caused by hantaviruses (HVs). Climate factors have a significant impact on the transmission of HFRS. Here, we characterized the dynamic temporal trend of HFRS and identified the roles of climate factors in its transmission in Changchun, China.

Surveillance data of HFRS cases and data on related environmental variables from 2013 to 2017 were collected. A principal components regression (PCR) model was used to quantify the relationship between climate factors and transmission of HFRS.

During 2013 to 2017, a distinctly declining temporal trend of annual HFRS incidence was identified. Four principal components were extracted, with a cumulative contribution rate of 89.282%. The association between HFRS epidemics and climate factors was better explained by the PCR model ($F=10.050$, $P<.001$, adjusted $R^2=0.456$) than by the general multiple regression model ($F=2.748$, $P<.005$, adjusted $R^2=0.397$).

The monthly trends of HFRS were positively correlated with the mean wind velocity but negatively correlated with the mean temperature, relative humidity, sunshine duration, and accumulative precipitation of the different previous months. The study results may be useful for the development of HFRS preventive initiatives that are customized for Changchun regarding specific climate environments.

Abbreviations: AP = monthly accumulative precipitation, China CDC = Chinese Center for Disease Control and Prevention, HFRS = hemorrhagic fever with renal syndrome, HVs = Hantanviruses, MaxT = monthly mean maximum temperature, MinT = monthly mean minimum temperature, MT = monthly mean temperature, MWV = monthly mean wind velocity, PCR = principal components regression, RH = monthly mean relative humidity, SD = monthly sunshine duration, SEOV = Seoul virus.

Keywords: climate factors, hemorrhagic fever with renal syndrome, principal components regression model

1. Introduction

Hemorrhagic fever with renal syndrome (HFRS), a rodent-borne endemic disease, is caused by different species of Hantanviruses (HVs).[1–5] Hantaan virus (HTNV) and Seoul virus (SEOV) are the 2 main virulence factors of HFRS in China related to *Apodemus agrarius and* Rattus norvegicus, *respectively. The typical clinical symptoms of HFRS are fever, hemorrhage, headache, back pain, abdominal pain, acute renal dysfunction, and hypotension. Humans are usually get infected with HV by contact or inhalation of aerosols and secretions from infected rodent hosts.[6,7] The number of human HFRS cases in China accounts for almost 90% of the total cases worldwide.[8,9] At present, HFRS is endemic in 28 of 31 provinces, autonomous regions, and metropolitan areas of mainland China.[10] The number of cases of infections caused by HV varies both geographically and yearly.[11,12] In 2004, the National Notifiable Disease Surveillance System (NNDSS) was established online by Chinese Center for Disease Control and Prevention (China CDC), and HFRS cases in the whole country were reported daily through this system. Although environmental management, host surveillance, and HFRS vaccine implementation have played an important role in controlling HFRS, HFRS is still a serious public health problem in China, with about 20,000 to 50,000 human cases reported annually in mainland China.[13–15] As a seasonally distributed rodent-borne disease, external environmental factors including climate factors may play a significant role in its transmission. Indeed, studies in different areas of China and other countries have suggested that climate factors, such as temperature, precipitation, and relative humidity, may influence the incidence of HFRS.[16–20] Rodent population densities, virus prevalence in rodents, diversity of rodents, rodent community composition, and species distributions have important influences on HFRS transmission.[21–27] Since the first HFRS case in 1955, the Jilin Province, with all its 9 cities/autonomous prefectures, has*

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been susceptible to the disease.[28] The first HFRS case was reported in 1959 in Changchun of the Jilin Province,[29] where the incidence of HFRS has always been at the forefront in Jilin Province. A key research priority for effective HFRS prevention and control is improving the knowledge of epidemic characteristics and understanding the underlying risk factors for disease transmission. Here, we analyzed the surveillance data of both human cases and climate factors during the period (2013–2017) comprehended to characterize the epidemic trends of HFRS and explore the associations between climate factors and HFRS transmission in Changchun.

2. Materials and methods

2.1. Study area

The study area covers Changchun, the capital city of Jilin Province, located between latitude 43°26' to 45°03' north and longitude 124°50' to 127°2' east. Changchun consists of 10 counties distributed over 20,660 km^2 of land. The total population was 7.6 million. The annual mean temperature is about 5.8°C. The annual rainfall is typically 552.6 mm. The annual average sunshine time in the province is 2501.7 hours (the above meteorological data are the average for nearly 30 years.).

2.2. Ethical standards

This study was approved by the Ethics Committee of the Liaoning Center for Disease Control and Prevention (Liaoning CDC), and the requirement for ethical approval for this study was waived.

2.3. Data source

In 1950, HFRS was included on the list of Class B Notifiable Diseases in China. Clinical diagnostic criteria include: exposure history, that is, exposure to rodents and their excreta, saliva, and urine within 2 months before the onset of illness; acute illness with at least 2 of the following clinical symptoms: that is fever, chill, hemorrhage, headache, back pain, abdominal pain, acute renal dysfunction, and hypotension; experience or partial experience of the 5 phases of disease course, that is, fever, hypopiesis, oliguresis, hyperdiuresis, and recovery; and abnormality of blood and urine routine parameters. In this study, records from 2013 to 2017 on HFRS cases were obtained from the Jilin Notifiable Disease Surveillance System (JNDSS), an administrative database developed by China CDC. All HFRS cases were first diagnosed on the basis of clinical symptoms. Then, the patients' blood samples were collected in hospitals and sent to the laboratory of Jilin Provincial CDC for serological confirmation. Finally, the data were collected by case number according to the sampling results. Incidence rates were calculated per 100,000 individuals by using population estimates based on a census of China.

Meteorological data were collected from the Jilin Provincial Climate Center (http://www.jlqx.gov.cn/). The climate factors included monthly mean temperature (MT), monthly mean maximum temperature (MaxT), monthly mean minimum temperature (MinT), monthly mean relative humidity (RH), monthly accumulative precipitation (AP), monthly mean wind velocity (MWV), and monthly sunshine duration (SD). Measurements of these parameters were taken daily, and then monthly mean value was calculated.

2.4. Statistical analysis

The annual HFRS incidence from 2013 to 2017 was calculated and plotted to observe annual fluctuations in Changchun. Cumulative HFRS cases for each month from 2013 to 2017 were also calculated to observe seasonal fluctuations. Cross-correlation and autocorrelation analyses were performed to detect the lagged effect of climate factors on HFRS transmission and the autocorrelation of monthly HFRS cases. Cross-correlation could be observed if the absolute value of the cross-correlation coefficient (CCF) was 2 times higher than that of the standard error (SE).[30] Autocorrelation and partial correlation analyses were performed to explore whether the monthly HFRS cases were affected by the cases in the previous months using the Ljung-Box Q test, autocorrelation coefficient (AC) analysis, and partial autocorrelation coefficient (PAC) analysis.[30] If the Ljung-Box Q value is higher than a particular critical value, the autocorrelation of 1 or more delays may be significantly different from zero, indicating that the values are not independent and random during this period. Principal component analysis (PCA) was based on climate data from 2013 to 2017 to extract principal components. The extracted principal components and autocorrelation terms of monthly HFRS cases were added into a multiple regression model called principal components regression (PCR) model to quantify the relationship between climate factors, autocorrelation terms, and transmission of HFRS. All data were analyzed by using R 3.4.3 Software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Overview of the HFRS in Changchun

A total of 515 cases of HFRS was reported in Changchun from 2013 to 2017, and the cumulative number of cases annually year ranged from 76 to 121 cases. The incidence rate fluctuates between 0.98/100,000 and 1.81/100,000; the highest and lowest incidence years were 2013 and 2017, respectively. Annual incidence rates were 1.66, 1.54, and 1.11 per 100,000 in 2014, 2015, and 2016, respectively. The overall epidemic in Changchun showed a downward trend (Fig. 1). A large peak occurred in spring and summer (April to June) during which the number of cases reported accounted for 34.95% of total cases, and a small peak occurred in autumn and winter (October to December) during which the number of cases reported accounted for 22.72% of total cases (Fig. 2).

3.2. Cross-correlation between monthly number of HFRS cases and climate factors

As shown in Table 1, the RH_0 was negatively correlated with the monthly number of HFRS cases in Changchun. During the previous month, the monthly number of HFRS cases was negatively correlated with the RH_1 but positively correlated with the MWV_1. During the previous 2 months, the monthly HFRS cases were negatively correlated with the MT_2, $MinT_2$, $MaxT_2$, RH_2, and AP_2. During the previous 3 months, the monthly HFRS cases were negatively correlated with the MT_3, $MinT_3$, $MaxT_3$, AP_3, and SD_3. During the previous 4 months, the monthly numbers of HFRS cases were negatively correlated with the MT_4, $MinT_4$, $MaxT_4$, AP_4, and SD_4. During the previous 5 months, the monthly number of HFRS cases was negatively correlated with the MT_5, $MinT_5$, $MaxT_5$, and SD_5. During the previous

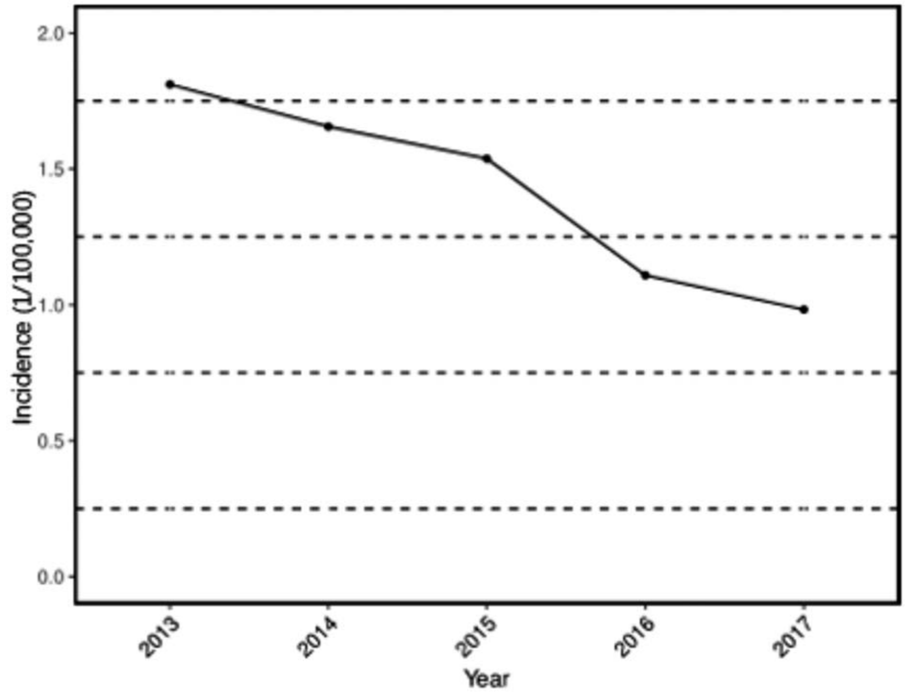

Figure 1. Annual trends of HFRS incidence in the study area. HFRS=Hemorrhagic fever with renal syndrome.

6 months, the monthly number of HFRS cases was negatively correlated with the SD_6.

3.3. Autocorrelation of monthly number of HFRS cases

The *P* value of the Ljung-Box Q statistic of each lagged month was <.05. The absolute value of AC and PAC during the first lagged months (Lag1) was greater than that of the other lagged months, which indicated that there was a strong autocorrelation of monthly HFRS cases during the first lagged month (Table 2).

3.4. Model evaluation

The PCA was performed by using the variables MT_2, MT_3, MT_4, MT_5, $MinT_2$, $MinT_3$, $MinT_4$, $MinT_5$, $MaxT_2$, $MaxT_3$, $MaxT_4$, $MaxT_5$, RH_0, RH_1, RH_2, MWV_1, AP_2, AP_3, AP_4, SD_3, SD_4, SD_5,

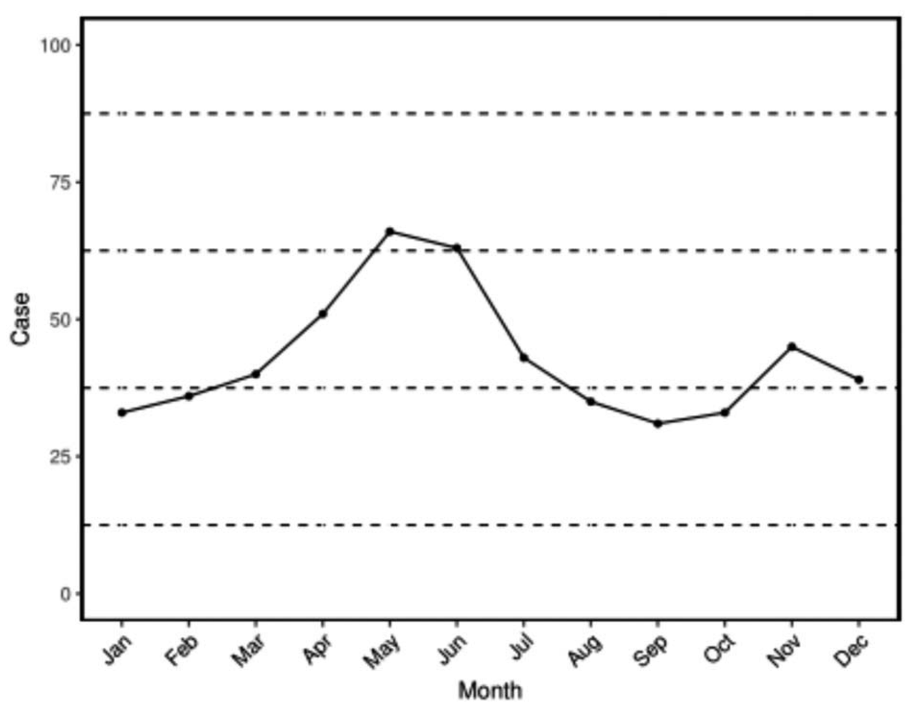

Figure 2. Monthly distribution of HFRS cases in Changchun, China. HFRS=Hemorrhagic fever with renal syndrome.

Table 1

Cross correlation between monthly HFRS cases and climate factors in Changchun, China.

Lag	MT		MinT		MaT		RH		AP		MWV		SD	
	CCF	SE	CCF	SE	CCF	SE	CCF	SE	CCF	SE	CCF	SE	CCF	SE
−6	−0.074	0.136	−0.063	0.136	−0.078	0.136	0.267	0.136	−0.033	0.136	−0.309	0.136	−0.325	0.136
−5	−0.402	0.135	−0.386	0.135	−0.407	0.135	0.286	0.135	−0.223	0.135	−0.427	0.135	−0.514	0.135
−4	−0.600	0.134	−0.599	0.134	−0.596	0.134	0.053	0.134	−0.465	0.134	−0.218	0.134	−0.454	0.134
−3	−0.609	0.132	−0.613	0.132	−0.605	0.132	−0.129	0.132	−0.528	0.132	0.061	0.132	−0.399	0.132
−2	−0.465	0.131	−0.478	0.131	−0.453	0.131	−0.431	0.131	−0.441	0.131	0.181	0.131	−0.153	0.131
−1	−0.233	0.130	−0.243	0.130	−0.230	0.130	−0.495	0.130	−0.174	0.130	0.411	0.130	−0.022	0.130
0	0.119	0.129	0.113	0.129	0.114	0.129	−0.310	0.129	0.161	0.129	0.220	0.129	0.251	0.129
1	0.401	0.130	0.402	0.130	0.394	0.130	−0.045	0.130	0.416	0.130	−0.057	0.130	0.410	0.130
2	0.567	0.131	0.57	0.131	0.562	0.131	0.077	0.131	0.491	0.131	−0.093	0.131	0.445	0.131
3	0.574	0.132	0.574	0.132	0.579	0.132	0.132	0.132	0.318	0.132	−0.279	0.132	0.405	0.132
4	0.409	0.134	0.408	0.134	0.412	0.134	0.156	0.134	0.210	0.134	−0.277	0.134	0.218	0.134
5	0.157	0.135	0.168	0.135	0.153	0.135	0.224	0.135	0.086	0.135	−0.272	0.135	−0.147	0.135
6	−0.134	0.136	−0.125	0.136	−0.133	0.136	0.242	0.136	−0.165	0.136	−0.268	0.136	−0.337	0.136

HFRS = hemorrhagic fever with renal syndrome.

and SD_6. Four principal components were extracted with a cumulative contribution rate of 89.282% (Table 3). The loadings of the 3 principal components of each variable were calculated (Table 4). Component 1 represented MT_2, MT_3, $MinT_2$, $MinT_3$, $MaxT_2$, $MaxT_3$, and SD_3; Component 2 represented MT_4, MT_5, $MinT_4$, $MinT_5$, $MaxT_4$, $MaxT_5$ and SD_6; Component 3 represented MWV_1, RH_1 and RH_2; and Component 4 represented RH_0. The PCR model was composed of 4 principal components and one autocorrelation term (Lag1). The following model gave the best results:

Y = 6.947–0.632 component 1 + 0.073 component 2–0.300 component 3–0.570 component 4 + 0.166 Lag1

The association between HFRS epidemics and climate factors was better explained in the PCR model ($F = 10.050$, $P < .001$, adjusted $R^2 = 0.456$) than in the general multiple regression model ($F = 2.748$, $P < .005$, adjusted $R^2 = 0.397$).

4. Discussion

To the best of our knowledge, this is the first comprehensive study to delineate the dynamic epidemic changes and investigated the relationships among HFRS occurrence and climate factors in Changchun. The results of this study confirmed that the incidence of HFRS decreased from 2013 to 2017, which may result from large-scale vaccination campaigns, and the promotion of urbanization, and the decrease of in agricultural and animal husbandry activities.[31,32] Changchun has a bimodal distribution of large peaks in spring and summer (April to June) and small peaks in autumn and winter (October–December). The seasonal distribution of HFRS is correlated with the dynamics of the main subtypes of HV. HFRS caused by HV occurs all year round but tends to peak in autumn and winter, while HFRS caused by SEOV usually peaks in spring. It is mainly transmitted by strains of *A agrarius* and *R norvegicus*.[33]

Table 2

Autocorrelation and partial correlation of monthly HFRS cases in Changchun, China.

Lag	AC	PAC	LB	*P*
1	0.446	0.446	12.517	<.001
2	0.257	0.073	16.758	<.001
3	0.130	−0.012	17.854	<.001
4	−0.116	−0.232	18.755	<.001
5	−0.197	−0.106	21.371	<.001
6	−0.253	−0.109	25.776	<.001
7	−0.178	0.046	27.996	<.001
8	−0.084	0.038	28.497	<.001
9	0.120	0.199	29.546	<.001
10	0.299	0.199	36.193	<.001
11	0.374	0.156	46.838	<.001
12	0.386	0.094	58.379	<.001
13	0.413	0.217	71.892	<.001
14	0.213	−0.013	75.571	<.001
15	−0.003	−0.078	75.572	<.001
16	−0.220	−0.211	79.669	<.001

HFRS = hemorrhagic fever with renal syndrome.

Previous studies have reported the association between HFRS epidemics and temperature in many areas of China.[34–37] These studies have indicated that temperature is an important factor for HFRS epidemics in China. On the one hand, temperature affects the incidence of HFRS by influencing rodent pregnancy rate, litter size, birth rate, and survival rate. On the other hand, temperature may affect the spread of HV among humans and the incidence of hemorrhagic fever in the population.[38,39] The results of the present study showed that MT_2, MT_3, MT_4, MT_5, $MinT_2$, $MinT_3$, $MinT_4$, $MinT_5$, $MaxT_2$, $MaxT_3$, $MaxT_4$, and $MaxT_5$ were negatively associated with the monthly HFRS cases in Changchun. Thus, effective surveillance of HFRS epidemics can be conducted by monitoring the fluctuations of these parameters in the area so that targeted countermeasures can be taken in advance. Liu et al have applied a case-crossover design and conditional logistic regression to analyze the relationship between the incidence rates of HFRS and meteorological variables in one national surveillance area for HFRS in Shandong Province.[40] They have found that the MWV was positively associated with HFRS incidence. We found that MWV_1 had positive effects on the monthly HFRS cases in a cross-correlation analysis, which was consistent with the previous studies in Shandong Province. However, no study has yet been published revealing the underlying mechanism. A possible explanation might be that high wind velocity is conducive to the spread of virus particles. Higher levels of humidity may affect the survival of rodent hosts but are also known to influence the infectivity and stability of the virus in the ex vivo environment.[41,42] Some studies also found that HV is limited in their spread to high humidity environments for extended ex vivo stability. The present study found that relative humidity factors, including RH_0, RH_1, and RH_2, affected HFRS negatively, which is

Table 3

Total variance of relative variables explained by PCA.

Component	Initial eigenvalues			Extraction sums of squared loadings		
	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
1	12.996	56.503	56.503	12.996	56.503	56.503
2	5.014	21.802	78.305	5.014	21.802	78.305
3	1.474	6.407	84.712	1.474	6.407	84.712
4	1.051	4.570	89.282	1.051	4.570	89.282
5	0.512	2.226	91.509	–	–	–
6	0.468	2.035	93.544	–	–	–
7	0.409	1.778	95.322	–	–	–
8	0.309	1.343	96.664	–	–	–
9	0.21	0.912	97.576	–	–	–
10	0.178	0.776	98.352	–	–	–
11	0.133	0.577	98.929	–	–	–
12	0.096	0.418	99.347	–	–	–
13	0.080	0.347	99.694	–	–	–
14	0.039	0.168	99.861	–	–	–
15	0.021	0.092	99.953	–	–	–
16	0.004	0.018	99.971	–	–	–
17	0.004	0.016	99.987	–	–	–
18	0.002	0.008	99.995	–	–	–
19	0.001	0.004	99.999	–	–	–
20	7.68E-05	0.000	99.999	–	–	–
21	6.23E-05	0.000	100.000	–	–	–
22	4.86E-05	0.000	100.000	–	–	–
23	2.02E-05	0.000	100.000	–	–	–

PCA = principal component analysis.

consistent with the findings of previous studies in China.[16,34] Appropriate precipitation not only stimulates plant growth but also improves the bioenergy and infection rate of the HV, which eventually increases HFRS incidence. However, excessive precipitation could have reduced the rodent population by destroying their habitats in Eastern China.[43,44] By reducing the possibility of human contact with rodents, the likelihood of transmission of the virus reduces as well. Our data indicate that AP_2, AP_3, and AP_4 were negatively associated with the incidence of HFRS, which is consistent with the findings of most of previous studies.[17,39,45,46] HV is easily inactivated by heat and ultraviolet radiation, which destroys the viral nucleic acid and reduces its infectivity.[47,48] A key finding of this study was that SD_3, SD_4, SD_5, and SD_6 were negatively associated with HFRS incidence, possibly because increased solar radiation may reduce virus survival outside the host and reduce the risk of disease in humans.[47] In the present study, multiple regression was applied to determine the relationship between HFRS epidemics and climate factors in Changchun, by incorporating climate factors of the previous months based on a PCA. This model was reliable and had a better fit (adjusted $R^2 = 0.456$) than that in the general multiple regression model (adjusted $R^2 = 0.397$).

Table 4

PCA matrix of component loadings.

Variable	Component			
	1	2	3	4
RH0	0.476	0.074	0.164	0.780
RH1	0.253	0.302	0.754	0.387
RH2	0.079	0.527	0.680	−0.354
MT2	0.981	−0.008	0.119	0.094
MT3	0.833	0.487	0.174	0.165
MT4	0.452	0.85	0.207	0.134
MT5	−0.036	0.982	0.140	0.011
MinT5	−0.046	0.982	0.114	0.005
MinT4	0.442	0.863	0.189	0.106
MinT3	0.823	0.506	0.189	0.134
MinT2	0.976	0.008	0.163	0.088
MaxT2	0.982	−0.011	0.080	0.092
MaxT3	0.835	0.479	0.152	0.191
MaxT4	0.450	0.842	0.215	0.163
MaxT5	−0.039	0.978	0.163	0.022
SD3	0.851	0.031	−0.075	0.127
SD4	0.695	0.384	0.108	0.301
SD5	0.334	0.720	0.202	0.304
SD6	−0.092	0.819	0.335	−0.039
MWV1	−0.166	−0.283	−0.771	−0.111
AP2	0.722	−0.086	0.544	−0.008
AP3	0.664	0.400	0.328	−0.254
AP4	0.405	0.745	−0.039	−0.180

AP = monthly accumulative precipitation, MinT = monthly mean minimum temperature, MWV = monthly mean wind velocity, PCA = principal component analysis, SD = monthly sunshine duration.

Despite the insights gained, the limitations of our study should also be acknowledged. First, this study examined only the effect of climate factors on HFRS epidemics. However, HV transmission results from a combination of rodent-related factors, land use, change in biotope, HV species, and social factors.[49,50] Unfortunately, data were unavailable on many of these factors. Second, the climate factors used in our models were the average value and the effects of extreme value on the survival and reproduction of rodents and transmission of HFRS require further investigation. These limitations may be overcome in better-designed future studies.

5. Conclusion

This study shows the temporal distribution of HFRS in Changchun throughout the years (2013–2017), with a distinctly declining trend. The month trends for HFRS were positively correlated with mean wind velocity of the different previous months but negatively correlated with the mean temperature, relative humidity, sunshine duration, and accumulative precipitation. Therefore, climate factors in the next years should be considered as early warning indicators for HFRS breaks in Changchun.

Author contributions

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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