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 < 0.001, adjusted $R^2 = 0.456$) than by the general multiple regression model (F = 2.748, P < 0.005, 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 = Hantaviruses, 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 Hantavirus (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 30,000 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...
been susceptible to the disease. The first HFRS case was reported in 1959 in Changchun of the Jilin Province, 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 km² 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: 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). 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. 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 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 but positively correlated with the MWV. During the previous 2 months, the monthly HFRS cases were negatively correlated with the MaxT, MinT, AP, and SD. During the previous 3 months, the monthly HFRS cases were negatively correlated with the MT, MinT, MaxT, AP, and SD. During the previous 4 months, the monthly numbers of HFRS cases were negatively correlated with the MT, MinT, MaxT, AP, and SD. During the previous 5 months, the monthly number of HFRS cases was negatively correlated with the MT, MinT, MaxT, and SD. During the previous...
6 months, the monthly number of HFRS cases was negatively correlated with the SD4.

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 MT2, MT3, MT4, MT5, MinT2, MinT3, MinT4, MinT5, MaxT2, MaxT3, MaxT4, MaxT5, RH0, RH1, RH2, MWV1, AP2, AP3, AP4, SD3, SD4, SD5.
and SD6. 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 MT2, MT3, MinT3, MinT4, MaxT2, MaxT3, and SD3; Component 2 represented MT4, MT5, MinT4, MaxT4, and SD4. Component 3 represented MWV1, RH1, and RH2; and Component 4 represented RH3. The PCR model was composed of 4 principal components and one autocorrelation term (Lag1). The following model gave the best results:

\[ Y = 6.947 - 0.632 \text{ component 1} + 0.073 \text{ component 2} - 0.300 \text{ component 3} - 0.570 \text{ component 4} + 0.166 \text{ Lag1} \]

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.

\[ \text{HFRS} = \text{hemorrhagic fever with renal syndrome}. \]

### Table 1

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

| Lag | CCF MT | SE | CCF MinT | SE | CCF MaT | SE | CCF RH | SE | CCF AP | SE | CCF MWV | SE | CCF SD | 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 | 0.571  | 0.131 | 0.562  | 0.131 | 0.077  | 0.131 | 0.491  | 0.131 | -0.093 | 0.131 | 0.446  | 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.

### 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.
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 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 \(R^2 = 0.397\)).

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.

### Table 3

| Component | Initial eigenvalues | Extraction sums of squared loadings |
|-----------|---------------------|----------------------------------|
|           | Total % of variance | Cumulative %                     | Total % of variance | Cumulative %                     |
| 1         | 12.996              | 56.503                           | 56.503              | 56.503                           |
| 2         | 5.014               | 21.802                           | 78.305              | 78.305                           |
| 3         | 1.474               | 6.407                            | 84.712              | 84.712                           |
| 4         | 1.051               | 4.570                            | 89.282              | 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                            | 99.999              |                                |
| 19        | 0.001               | 0.004                            | 100.000             |                                |
| 20        | 7.68E-05            | 0.000                            | 100.000             |                                |
| 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.

### Table 4

**Table 4**

| 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    | 0.635     | 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     |
| 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.

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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