Climate and socio-economic factors drive the spatio-temporal dynamics of HFRS in Northeastern China

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\begin{abstract}
Background: Hemorrhagic fever with renal syndrome (HFRS) occurs widely in Northeastern China, but the mechanism and interactions of meteorological and socio-economic factors on the transmission of HFRS are still largely unknown.

Objective: We explored the effects of socioeconomic-environmental factors on the spatio-temporal variation of HFRS incidence from 2001 to 2019 in Northeastern China. Specifically, the relative importance and contribution rates (CR) of determinants of HFRS were identified by boosted regression tree and variance partitioning analysis, respectively. Structural equation models (SEMs) were used to explain the roles of climatic and socio-economic factors in the transmission of HFRS. And a negative binomial regression was used to identify the risk effect between monthly meteorological variables and HFRS with 0–6 months lags in Northeastern China.

Results: Over the past decades, the high-risk areas of HFRS were mainly concentrated in the northern and eastern areas of Northeastern China. Additionally, HFRS mainly presented a decreasing trend from 2001 to 2019 in most areas of Northeastern China, but slightly increased in the cities of Daqing, Songyuan, Baicheng, and Tonghua. The temporal dynamics of the incidence of HFRS were primarily explained by the variations in population density (CR = 27.30%), climate (CR = 13.30%), and economic condition (CR = 9.45%). The spatial variations of HFRS were medicated by the climate (CR = 16.95%) and population density (CR = 16.95%) and medical health care (CR = 2.25%). The SEM models indicated that humid and warm climates were conducive to the incidence and increase of HFRS, but the improvement in education and an increase in population density reduced the transmission of HFRS.

Conclusion: Climate and population density appeared to mediate the spatio-temporal variation of HFRS in Northeastern China. These findings may provide valuable empirical evidence for the management of HFRS in endemic areas.
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1. Introduction

Changes in climate and socio-economic development concerning human health have been fiercely debated over the past decades [1–4]. Moreover, the outbreak and incidence of zoonotic diseases are changing dramatically in response to ecological and socio-economic effects [5–7], exhibiting obvious seasonal and interannual variations. As a climate-sensitive infectious disease controlled by various social elements, hemorrhagic fever with renal syndrome (HFRS) is caused by hantavirus and carried by rodent hosts [8–10]. Although HFRS is spreading in several countries worldwide, 90% of the globally reported cases occurred in China with 576,361 HFRS cases from 1995 to 2020 [8,11]. In China, HFRS has been identified as a category B infectious disease and hospital physicians must report the HFRS case to the health authority through the national infectious disease system. In the past 50 years, although the government has made progress in the control and prevention of HFRS, HFRS remains a long-term epidemic in northeastern China and is at high risk nationwide [12,13], posing a threat to the health of the local residents and causing a heavy disease burden.

HFRS is driven by multiple factors, including ecological, animal hosts and social environments; therefore, analyzing and predicting where and when a sustained HFRS transmission might be occurring is a significant public health challenge [14,15]. Some previous studies have explored the mechanisms of HFRS in response to socio-environmental factors [16,17]. For example, a study found that the urbanization process and the degree of social civilization in the region reduce the risk of exposure to numerous animal parasites and improve overall health in general [18]. The research highlights the delicate interaction between zoonotic disease spread and urbanization, which pointed to hantavirus epidemics in cities being exacerbated by urbanization [18].

Meanwhile, temperature, precipitation, humidity, normalized difference vegetation index (NDVI) and land use can also impact the spatial and temporal variation of HFRS incidence in China [19,20]. Precipitation and humidity have been incorporated as critical risk factors for infectious diseases in several regions worldwide [9]. Relative humidity not only reflects regional rainfall and temperature levels but also influences the infectivity and stability of hantavirus in the environment, for example, mountain areas with humid climates in China are the regions with the highest incidence of HFRS [21–23]. Moreover, the aridity index (AI) is also a critical determinant in driving plague outbreaks of pre-industrial Europe [24]. Human activity patterns are also governed by weather conditions and seasonal changes, which affect the opportunities for contact between humans and rodents.

A better understanding of the environmental and social drivers of HFRS is needed to unravel the puzzle that has led to the widespread epidemic in northeastern China since the last century. However, the underlying mechanisms of climate and socio-economic factors in the spatial-temporal dynamics of HFRS in Northeastern China remain poorly validated. To establish early warning systems for zoonotic diseases and preventive interventions, it is imperative to quantify the impact of climatic and socio-economic factors on the pattern of HFRS and analyze the underlying mechanisms of HFRS transmission. Hence, this study aimed to determine how climate and socio-economic development affect the spatial-temporal variation of HFRS from 2001 to 2019 in Northeastern China and report the potential mechanisms of HFRS transmission so that effective zoonotic disease control programs can be developed.

2. Materials and methods

2.1. Study area

Northeastern China included a total of 36 prefecture-level cities from the provinces of Heilongjiang, Jilin and Liaoning (38°43′N ~ 53°33′N, 118°53′E ~ 135°05′E), covering a total area of 787,300 km² (Fig. 1).

According to the 7th demographic census of China in 2020, the total population of Northeastern China accounted for about 6.98% of the national population (141.78 million). Northeastern China has a temperate monsoon climate, with warm and rainy summers and cold and dry winters. The landscape of the three northeastern provinces is a mixture of plains and mountains, with a forested land area of 38.75 million hectares, accounting for 14.7% of the total land area of China.

2.2. HFRS data

Data on monthly HFRS cases from January 2001 to December 2019 were collected from the Chinese Center for Disease Control and Prevention. In this study, all HFRS cases were confirmed according to the unified diagnostic criteria issued by the Ministry of Health of the People’s Republic of China [8,25].

2.3. Climatic data

The monthly climate data including monthly mean precipitation, monthly sunshine duration, monthly relative humidity and monthly mean temperature were collected from the China Meteorological Administration and then were transformed to mean precipitation (AMP), annual sunshine duration(SSD), relative humidity (RHU) and mean temperature (AMT) values in Northeastern China during the study period. Additionally, the spatial interpolation of AMP and AMT was performed using the software of Anusplin 4.2 (Centre for Resource and Environmental Studies, Australian National University, Canberra). Finally, the climatic information of prefecture-level cities in Northeastern China was extracted by ArcGIS 10.2 (ESRI, Inc., Redlands, CA, USA).

2.4. Socio-economic data

The socio-economic indicators in this study mainly concern the level of economic, population density, medical and educational indicators of prefecture-level cities in Northeastern China. The data were obtained from the China Statistical Yearbook of the National Bureau of Statistics and the China Statistical Yearbook of prefecture-level cities. Specifically, this study included demographic variables of population density (PD), the economic group included variables of gross domestic product (GDP) and gross domestic product per capita (PGDP). The educational group included variables of the number of students enrolled in secondary vocational and technical schools (NS), the number of full-time teachers in secondary vocational education schools (NT), and the total number of books in public libraries (NL). The medical group included the variables of the number of doctors (practicing physicians & practicing assistant physicians, ND), number of beds in hospitals (NBH), and number of hospitals (NH).

2.5. Data analyses

Firstly, we calculate the average value of the aridity index (AI) by Eq1:

$$ AI = \frac{AMP}{AMT + 10} $$

The AI is a key parameter in the exploration and prediction of multifactorial mechanisms in this study, which is a means to reflect the cause, extent and scope of drought, and is an indicator to characterize the degree of dryness or wetness of a region [24,26].

Secondly, we calculated the annual change rate for HFRS and all independent factors by the least square method, as Eq2:

$$ \beta = \frac{n \sum XY - \sum X \sum Y}{n \sum X^2 - (\sum X)^2} $$

where n is the number of years from 2001 to 2019, X is the year, and Y is
the incidence of HFRS.

Thirdly, to determine the relative importance of climatic and socio-economic factors on the temporal and spatial variation of HFRS, boosted regression tree analysis was conducted in R 4.1.1 with the "gbm" package (R Core Development Team, R Foundation for Statistical Computing, Vienna, Austria).

Then, the total 14 variables (environmental and socio-economic factors) were categorized into specific classifications of controlling groups. The variation partitioning analysis (VPA) technique could be used to quantify the contribution rate when two or more factors are analyzed to explain variation in the independent variables [27]. The contribution rate of the top four controlling groups on HFRS was quantified by VPA in "vegan" package in R 4.1.1. And a negative binomial regression model was formulated for monthly HFRS counts to reveal the risk effect between the climate factors and the HFRS epidemic.

Furthermore, the structural equation models (SEMs) were employed to evaluate the standard total effects of various social and climatic factors on HFRS. SEMs are a statistical technique for testing and estimating potential causal relationships between different variables. It has obvious advantages when some indirectly observable variables, i.e., latent variables, were considered [28].

Principal component analysis (PCA) is a statistical method that converts multiple quantitative indicators into a few composite indicators by linear dimensionality reduction [29,30]. Notably, PCA was conducted using R 4.1.1 (with packages of "FactoMineR", "factoextra" and "corplot") to extract the PC1 of each group (86.10%-94.60% of these groups were explained by the PC1), and the PC1 of each group was introduced as a new variable into the SEMs. And the selected key factors in each group from regression tree analysis were also used in SEMs when the interpretation rate of PC1 is <80%. Finally, generalized additive models and smooth curve fittings ("mgcv" in R) were conducted to predict HFRS response to the determinants selected from SEMs.

3. Results

3.1. Spatial distribution and dynamic of HFRS from 2001 to 2019

A total of 98,472 cases were reported in 36 prefecture-level cities from 2001 to 2019 in Northeastern China. The average annual incidence rate of HFRS varied from 0.02/10,000 to 2.30/10,000 in 36 prefecture-level cities. Jiamusi, Shuangyashan, Heihe and Panjin were the prefecture-level cities with the highest HFRS incidence rate (Fig. 2a). The incidence rate was generally higher in the eastern region than in the western and tended to decrease toward the west. HFRS exhibited a decreasing trend from 2001 to 2019 in most areas of Northeastern China, but slightly increased in the prefecture-level cities of Daqing, Songyuan, Baicheng and Tonghua (Fig. 2b).

3.2. Linking environmental and socio-economic factors to HFRS

Our results indicated that AMT, RHU and AI (see Table 1) were the top three key factors (combined relative importance >55%) that explained the incidence rate of HFRS, accounting for 22.07%, 21.97%, and 11.25% of HFRS, respectively (Fig. 3a). However, the annual change rate of HFRS was primarily associated with socio-economic factors of PD, NH and NBH with the relative importance of 27.41%, 14.28%, and 13.94%, respectively (Fig. 3b).

Variation partitioning analysis further indicated that the incidence rate of HFRS was mainly explained by climate (13.30%), followed by population density (27.30%), and economics (1.90%) (Fig. 4a). Similarly, climate explained a much greater portion of the annual change rate of HFRS (16.95%) than population density (9.45%), medical (2.25%) (Fig. 4b).

3.3. Meteorological risk in the HFRS epidemic

A negative binomial regression was used to identify the relationship between monthly meteorological variables and HFRS with 0–6 months...
Each increase in average temperature was associated with a 2% (IRR = 1.02, 95% CI: 1.01–1.03, P < 0.01) increase in the HFRS cases, and a 1% rise in monthly average relative humidity corresponded to a 2% (IRR = 1.02, 95% CI: 1.01–1.02, P < 0.01) increase in the HFRS in the lag four months. The results showed that HFRS was associated with lagged climatic factors, which also illustrated the vital role of climatic factors. We have put this result into the support information to explain the lagged effect of meteorological factors in HFRS.

3.4. Mechanisms of HFRS transmission

According to the results of SEMs, 38% of the HFRS incidence (Fig. 5a) and 52% (Fig. 5b) of the slope of HFRS incidence in Northeastern China were explained by environmental and social-economic factors, respectively. Aridity index (AI; scored at 0.40) and population density (PD; scored at −0.26) were two critical factors that regulated the incidence rate of HFRS (Fig. 5a). In contrast, Education conditions (scored at −0.92) and medical condition (scored at 0.73) were the key factors that mediated the dynamic of HFRS (Fig. 5b). Taken together, the SEMs results showed that socio-environmental factors such as AI, PD, education and medical condition were the critical factors regulating the temporal and spatial variation of HFRS from 2001 to 2019 in Northeastern China.

4. Discussion

Several studies have investigated the association between HFRS and meteorological factors or urbanization [18,31,32], but few studies have explored the mechanisms of infectious disease pathogenesis from the perspective of multiple factors (e.g., climate, economic factors, and medical resources). To the best of our knowledge, this study is the first attempt to jointly explore the underlying mechanisms of climate and socio-economic factors influencing the incidence and rate of change of HFRS in Northeastern China. We found the spatial-temporal dynamics of HFRS incidence were mainly affected by climate and education, which contributes to explaining the drivers of zoonotic disease variation and control in Northeastern China.

4.1. Spatial distribution and dynamic of HFRS

This study reveals that the eastern and coastal prefecture-level cities in Northeastern China had the highest incidence of HFRS (Fig. 2a). Similar to previous studies, Northeastern China has been a high-risk area for HFRS in China for many years, and the High-High cluster is mainly concentrated in the eastern and coastal prefecture-level cities of Heilongjiang, Liaoning and Jilin provinces [33,34]. Nevertheless, HFRS mainly exhibited a decreasing trend from 2001 to 2019 in the eastern prefecture-level cities, but slightly increased in the western prefecture-level cities such as Daqing, Songyuan, Baicheng and Tonghua (Fig. 2b). These findings suggest that HFRS in the eastern region was effectively controlled while it is not so in the western region.

These different spatial-temporal dynamic patterns of HFRS were due mainly to a combination of climatic and socio-economic factors, with the spatial distributions of meteorology, land use, and GDP contributing to regional variations in incidence rates of HFRS [16,35]. The hilly areas in the eastern part of Liaoning Province were at higher risk of HFRS, which is similar to the finding that zoonosis is related to its topographical features [34,36]. In Liaoning Province, it can be roughly divided into highlands in the west, plains in the center and hills in the east [36,37]. The eastern part of Liaoning Province forms the Liaodong Peninsula, a region dominated by East Asian monsoons with high levels of ocean water vapor, which could indicate there has a higher AI value.
The relative importance of climatic and socio-economic factors on (a) the incidence rate of HFRS and (b) the annual change rate of HFRS. The abbreviations are defined in Table 1.

The increase in AI index means that this area is in a relatively more wet climate, which could relate to a rise in the incidence of HFRS, which is further consistent with the positive role of humidity and rainfall as drivers of HFRS. Meanwhile, the humid climate and more rivers in the Ussuri, Songhua, and Mudan River regions of Northeastern China’s eastern and southeastern coastal regions (Fig. 2b) are linked to a higher incidence of HFRS [33]. While, from the perspective of climate factors, Baicheng city of the western region in Northeastern China contributes to the lower incidence of HFRS, because it is located in the middle temperate semi-arid monsoon climate zone, with the dry and cold climate(Low AI Value, Fig. 2a and Fig. 5a). Moreover, the eastern and southeastern parts of Heilongjiang Province are mainly mixed land types with forests(Mosaic forest or shrub-land or grassland), favorable for the survival and reproduction of rodents of hantavirus transmission [19,38]. As China’s economy improves, the coastal areas are urbanizing more rapidly compared to inland prefecture-level cities, thus improving financial expenditures and medical resources in the eastern regions. This has a positive effect on infectious disease prevention and control, therefore contributing to the decrease of HFRS [33,39].

4.2. Mechanisms of HFRS transmission

Our findings highlight that the climatic factors were the dominant drivers of HFRS variation in Northeastern China (Fig. 4a), implying that climatic factors had a more significant impact on the incidence of HFRS than economic, educational and demographic factors, with the AMT, RHU and AI are the top three variables in terms of the climate and socio-economic factors.

The finding that weather variability plays an arcrical role in the transmission of HFRS in China, which is consistent with a previous study that explored the influence of meteorological factors on HFRS [40]. There are two types of HFRS epidemic areas in China: one is the wild rodent epidemic area caused by Hantaan virus (HTNV) and dominated by wild rodent species such as the Apodemus agrarius; the other is the domestic rodent epidemic area caused by Seoul virus (SEOV) and mainly dominated by Rattus norvegicus [41]. According to the surveillance data, Heilongjiang, Jilin, and Liaoning provinces in Northeastern China mainly belonged to the mixed epidemic areas where HFRS was mainly caused by wild rats correspondingly, and the seasonal distribution of HFRS in this region showed bimodal characteristics, with autumn and winter being higher than spring and summer. Therefore, the seasonal distribution of HFRS highly coincided with the cycle of agricultural activities in spring and autumn in China, and it was inferred that seasonality could influence the activities and reproductive cycles of local rodents, such as the climatic and environmental factors in different seasons.

![Fig. 3](image_url)
As a measure of the wetness and dryness of an area, the AI in our study is jointly influenced by rainfall and temperature, which usually play a vital role in the transmission of zoonotic diseases such as HFRS (Fig. 5a). According to our analysis, AI had a more prominent effect on HFRS and disclosed a nonlinear characteristic, i.e., an inverted U-shaped curve in the association between AI and HFRS. This is similar to the study, which showed an "inverted U-shaped" relationship between temperature and HFRS in Qingdao City of China, with a 2.56% increase in excess risk for every 1 °C increase in temperature when the average temperature was below 17 °C [40]. The spatial distribution of HFRS is closely linked to the natural characteristics of the region, such as the eastern regions of the three provinces of Northeastern China having more abundant precipitation and a wetter climate, leading to the high prevalence of HFRS [42, 43]. Climatic conditions, such as temperature, relative humidity, sunshine duration and rainfall [44], could affect the transmission of HFRS primarily by altering the lifecycles and habitat of rodents. For example, it has been found that temperature, humidity and precipitation affect both the growth of plants necessary for the development of juvenile rodents and the stability and infectivity of hantaviruses in isolated environments [45].

Additionally, our study indicates that population density is the most important factor affecting the annual rate of change of HFRS in Northeastern China (Fig. 4a and b), which is negatively correlated with the HFRS pattern (Fig. 5a and b). The population density is an indicator of the economic development of a city, and a higher economic level is conducive to reducing the likelihood of the HFRS epidemic [46], because the developed regions have more economic, educational and medical resources, thus providing superior conditions for the prevention and control of zoonotic diseases. This may explain the negative correlation between population density and the occurrence of HFRS (Fig. 5a and b). Economic development could also lead to the improvement of medical services and hygiene conditions, providing people with enhanced access to healthcare and nutrition and case management [47]. In terms of medical resources, excellent medical resources may lead to a positive association between medical conditions and HFRS, as good medical facilities are more likely to diagnose HFRS and HFRS patients may seek specialized treatment in cities with good medical conditions [47]. On the other hand, the investment in educational resources helps to improve literacy and promote awareness and prevention of diseases, thus guiding the public to take appropriate protective measures against diseases, which helps to reduce and prevent the transmission of HFRS [48].

4.3. Implications for HFRS management

As a zoonotic infectious disease, the incidence of HFRS is determined by a complex interplay of multiple-dimensional factors. This study helps to better understand the impacts of climate and socio-economic factors, and how they interact with HFRS. This can further help the medical profession to develop effective HFRS prevention strategies. We formulate the following recommendations to improve HFRS control and prevention programs in China:

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![Fig. 4. Relative contributions of environmental factors to the incidence rate of HFRS (a) and the annual change rate of HFRS (b).](image-url)

![Fig. 5. The standard total effects of meteorological and socio-economic factors on (a) the incidence rate (IR) of HFRS and (b) the annual change rate (slope) of HFRS. The thickness of the solid arrows represents the magnitude of effects; black and red arrows indicate positive and negative effects, respectively; grey arrows indicate the effects were < 0.05. Notably, the meanings of abbreviations are shown in Table 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image-url)
(a) The incidence of HFRS is higher in the cold northern, eastern, and coastal areas of the three northeastern provinces of China (Fig. 2a), and it is necessary to focus on these areas to strengthen the disease control and risk management efforts. Some prefecture-level cities such as Daqing and Song Yuan showed an increasing trend of HFRS in the past 19 years, which suggests that special attention should be paid and more public health resources must be mobilized toward this region.

(b) The wetter region, have a higher incidence of HFRS (Fig. 5a), so the relevant government departments should strengthen the monitoring of climate changes and pay attention to the changes in rainfall and temperature in summer and autumn to limit the emergence of HFRS transmission in wet areas.

(c) Improving education can substantially reduce the interannual change rate of HFRS (Fig. 5b). Therefore, strengthening investment in health education can both improve the scientific and cultural literacy of citizens and also has positive effects on the prevention and control of infectious diseases.

(d) The population density is a key factor affecting the incidence of HFRS (Fig. 4) and responding to the level of modern socio-economic development, which suggests it is necessary for densely populated regions to manage the risk of rodent density to reduce virus transmission and adjust the local human resources development plans.

In summary, the current work systematically exposes the specific mechanisms underlying the influence of different dimensional factors on the HFRS and quantifies the differences between socio-economic and climatic factors on the changes in HFRS. It provides first-hand evidence for the health department to identify the dominant role of climate and the significant effect of education in China, which demonstrates the progress China has made in the prevention and control of zoonotic diseases.

Meanwhile, we should acknowledge that our study has some limitations. First, the data on HFRS cases were obtained from a passive infectious disease surveillance system in China, and thus there may be unavoidable data errors. For example, some patients with mild symptoms may not seek medical care and thus, the data may miss some mild cases, which may lead to underreporting bias. Second, there is a lack of a database of rodent density and population immunity rate, which is also relevant to the HFRS epidemic, in addition to the climatic and socio-economic factors mentioned in this paper. Due to the complexity of the environment and the large geographical extent of Northeastern China, monitoring rodents requires the mobilization of a large number of people and considerable funding support, and we collected some seasonal rodent monitoring data in the Supporting information(S1). The variables in this study have measured the cause of the changes in the rodent densities and vegetation so we have, in a way, already captured some related information in our model, and we will try to improve this work in the future.

5. Conclusion

Environmental and socio-economic changes are affecting and will be increasingly impacting the spread and control of zoonotic infectious diseases, which is one of the most important challenges facing humanity in the twenty-first century. By constructing a dataset of HFRS and influencing factors in high-risk regions of China, the findings of this study provide new evidence for assessing the interactions of climate and socio-economic factors on HFRS dynamics and exploring the mechanisms of HFRS transmission in Northeastern China. In addition, our study provides more quantitative insights to explore the direct or indirect link between climate and socio-economic factors in the variability of zoonotic diseases. The findings of this study may help public health departments and related government agencies work together more closely to improve zoonotic disease prevention and control strategies, allocate health resources effectively and develop HFRS early warning systems in a timely manner.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not Applicable.

Availability of data and materials

Data and codes are accessible to researchers upon request for data sharing to the corresponding author.

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Author’s contribution

Yong Wang, Wenyi Zhang and Yuming Guo: conceptualization, review and editing paper, supervision. Yanding Wang: collected data, conducted the experiments, analyzed and interpreted the data, and drafted the manuscript. Xianyu Wei: collected data and analyzed. Meitao Yang, Wenwu Yin, Xuyang Xiao, Zhiqiang Li: collected data. Junyu He, Zhoupeng Ren, Shilu Tong: review and editing paper.

Declaration of Competing Interest

None declared.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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