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Review

Haemorrhagic fever with renal syndrome: literature review and distribution analysis in China

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SUMMARY

Hantaviruses infect their reservoir hosts and humans, but the infection only causes disease in humans. In Asia and Europe (the Old World), the hantaviruses usually cause haemorrhagic fever with renal syndrome (HFRS). This article summarizes the current understanding of hantavirus epidemiology, as well as the clinical manifestations, pathogenesis, renal pathology, diagnosis, treatment, and prevention of HFRS. Moreover, the spatiotemporal distribution of HFRS was analysed based on the latest data obtained from the Chinese Centre for Disease Control and Prevention, for the period January 2004 to April 2015, to provide valuable information for the practical application of more effective HFRS control and prevention strategies in China.

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1. Introduction

Haemorrhagic fever with renal syndrome (HFRS), a rodent-borne infectious disease caused by hantaviruses, is clinically characterized in humans by fever, haemorrhage, headache, abdominal pain, and acute kidney damage. HFRS occurs primarily in the Old World and is endemic all over China, with the exception of the Taiwan region.[1,2] China has the highest incidence of HFRS, accounting for approximately 90% of HFRS cases globally in the last few decades. During recent decades, the incidence of HFRS has fluctuated, but it has remained one of the top nine communicable diseases in mainland China. This study was performed to review what is known about HFRS and to identify its epidemiological distribution in China.

2. HFRS-associated hantavirus infection

Hantaviruses are single-stranded, enveloped RNA viruses of the *Bunyaviridae* family. They cause two human syndromes, hantavirus cardiopulmonary syndrome (HCPS) in the Americas and HFRS in Europe and Asia.[3] Seven sero/genotypes of HFRS-associated hantaviruses have been identified (Hantaan, Dobrava, Saaremaa, Seoul, Amur, Puumala, and Far East), and two of these, Hantaan virus (HTNV) and Seoul virus (SEOV), are the major causative agents of HFRS in China.[4]

Hantaviruses are unexpectedly stable in air and can survive >10 days at room temperature and >18 days at 4 °C and −20 °C.[5,6] Hantaviruses are mainly carried by rodents, insectivores, and bats. They are transmitted to humans via inhalation of virus-contaminated aerosols of excreta and secreta, via contaminated food, and rarely, via rodent bites.[7] Hantavirus infection has also been reported in several species of domestic animals, such as cats, dogs, pigs, and rabbits.[8] The survival of hantaviruses depends on the maintenance of persistent infection within their reservoir hosts.[9] Thus, hantavirus emergence in humans depends on the following factors: (1) the external environmental factors including temperature, rainfall, relative humidity, land use, the normalized difference vegetation index (NDVI), the temperature vegetation dryness index (TVDI), and elevation, which play significant roles in reservoir host density and the level of exposure to infectious viruses;[1,10,11] (2) the frequency of contact between the human and rodent populations, which is associated with human activities, living conditions, working conditions, and urbanization;[12] and (3) the proportion of infections resulting in HFRS, which may be due to the susceptibility of humans to hantaviruses and may be influenced by population immunity and vaccination.[3,13]

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3. Clinical manifestation of HFRS

The clinical picture of HFRS is characterized by acute renal failure, accompanied by haemorrhage and flu-like symptoms, such as fever, headache, and abdominal/back/orbit pain.[14] Kidney manifestations are characterized predominantly by massive proteinuria, haematuria, and a rapid decline in glomerular filtration rate (GFR), resulting in oedema, disorder of electrolytes and acid–base balance, and the need for dialysis.[15] Severe complications may involve multiple systems. In the neurological system, meningoencephalitis, acute disseminated encephalomyelitis, generalized seizures, Guillain–Barré syndrome, urinary bladder paralysis, and seizures have been reported. In the cardiopulmonary system, shock, perimyocarditis, and pulmonary oedema may develop. Disseminated intravascular coagulopathy, multiple bleedings, pancreatitis, and multiorgan failure have also been observed, all of which may lead to a lethal outcome.[16]

Classic clinical HFRS occurs in five phases: febrile phase (3–7 days), hypotensive phase (hours to 2 days), oliguric phase (3–7 days), diuretic phase (polyuria) (days to weeks), and convalescent phase (2–3 months). Long-term outcomes after HFRS show a much higher prevalence of renal tubular dysfunction, glomerular hyperfiltration, chronic glomerulonephritis, hypertension, acute myocardial infarction, and stroke compared with the general population.[16–18]

4. Pathogenesis of HFRS

Humans are not a natural reservoir and, therefore, become infected when they come into contact with the excreta of reservoir hosts, such as rodents. Infections can result in serial diseases, and the pathogenesis and outcomes vary with the different species of hantavirus. The hallmarks of HFRS are increased vascular permeability, thrombocytopenia, coagulopathy, and haemorrhagic manifestations. The molecular mechanisms of HFRS are not well understood. A complex interplay between hantaviruses, host immune responses, and endothelial cells has emerged as a common theme. Hantavirus infection directly or indirectly leads to the activation of signalling pathways and the dysregulation of immune cells, such as CD4+ T-cells and CD8+ T-cells. The inflammatory response leads to the activation of the complement system, the formation of circulating immune complexes, and the secretion of multiple proinflammatory cytokines. These cytokines promote endothelial cell dysfunction and capillary leakage.[14,19] Haemorrhage is common in HFRS. The coagulopathy appears to be a thrombosis–fibrinolysis imbalance combined with platelet deposition and dysfunction. Severe thrombocytopenia is associated with a more severe course of the disease in HFRS.[20,21]

5. Renal pathology of HFRS

Increased vascular permeability in HFRS is indicated by widespread capillary engorgement, focal haemorrhage, and interstitial oedema in the renal medulla. Hantavirus nephropathy is an uncommon aetiology of acute renal failure due to hantavirus infection. Light microscopy of renal biopsies from hantavirus nephropathy patients shows interstitial haemorrhage and oedema, acute tubular necrosis, inflammation of the renal microvessels, cortical peritubular capillaritis, and medullary vasa recta inflammation, with minor changes in the glomeruli. Immunohistochemical studies have shown the deposition of circulating immune complexes and activation of the complement system. Furthermore, anti-CD3, anti-CD68, and anti-CD34 antibodies have positively highlighted the involvement of T-cells and macrophages in renal microvascular inflammation.[22] Electron microscopy has revealed podocyte foot process effacement, which indicates that hantavirus infection might perturb podocyte integrity, resulting in glomerular proteinuria. These alterations of acute tubular necrosis and podocytes may be reversible and transient and may resolve within weeks to months.[23]

6. Diagnosis and biomarkers of HFRS

The diagnosis of hantavirus infections in humans is based on clinical and epidemiological information as well as laboratory tests. Laboratory testing should be performed for patients with fever of unknown origin, thrombocytopenia, renal failure, or respiratory distress, who live in hantavirus disease-endemic regions. The laboratory diagnosis of hantavirus infection is based mainly on three primary categories of test: serology, molecular methods, and immunochemistry (Table 1).[24–38] The most practical approach is a serological test to detect IgM/IgG antibodies of the three structural hantavirus proteins (Gn, Gc, and N) using ELISAs. Real-time RT-PCR is a sensitive tool for the early detection of hantavirus RNA that can detect hantavirus RNA prior to the appearance of IgM antibodies. Therefore, the combination of IgM/IgG ELISAs and RT-PCR is a sensitive and desirable approach for the laboratory diagnosis of hantavirus infection. Immunohistochemistry is of great utility for identifying viral antigens in tissues, particularly in fatal cases without other types of sample. Virus isolation from human samples is rare, and it is not an option in the diagnosis of human hantavirus infection.

Many new biomarkers have been reported to be associated with a severe course of hantavirus infection. Several examples that have been reported recently are listed here. CD163 is expressed by monocytes/macrophages in response to inflammatory stimuli. The level of plasma soluble CD163 in HFRS patients has been found to increase at fever onset and to peak in the oliguric phase, positively correlating with the severity and progression of disease.[39,40] The level of high mobility group box protein 1 (HMGB-1) has been found to correlate positively with the white blood cell count and blood urea nitrogen (BUN) and to correlate negatively with the platelet count, albumin, and uric acid (UA). The HMGB-1 level has been found to be predictive of the prognosis in HFRS patients.[41] The serum decoy receptor 3 (DcR3) level has been shown to be positively correlated with tumour necrosis factor alpha (TNF-α) and to peak during the oliguric phase, reflecting the severity of kidney damage, characterized by elevated BUN, creatinine, and proteinuria.[42] Interleukin 21 (IL-21) has been shown to stimulate T-cell and B-cell responses in the pathogenesis of HFRS. IL-21 begins to increase in the fever phase, peaks in the oliguric phase, and is associated with the disease severity of HFRS.[43] As one of the vascular permeability cytokines, the serum level of vascular endothelial growth factor (VEGF) has been reported to be persistently elevated throughout the various stages and types of HFRS and to be closely correlated with the progression of HFRS as well as the severity of kidney damage.[44]

7. Treatment and prevention of HFRS

The treatment of HFRS is based on the clinical symptoms of the disease and occasionally includes haemodialysis, oxygenation, and shock therapy. There is no specific therapy available. The use of ribavirin, an antiviral agent, has resulted in a reduction in morbidity and a decrease in fatalities in HFRS patients in China.[45] Other promising new ideas, including the use of a bradykinin receptor antagonist (bradykinin is involved in vasodilatation and increases vascular permeability) and passive immune therapy with human plasma, have mainly been based on similar findings in the hamster model, and have not been used widely in humans.[46,47] Steroid-based anti-inflammatory treatment options have been described in several case reports, particularly in patients with

Table 1
Laboratory methods used for hantavirus diagnostics in clinical practice

Methods	Advantages	Disadvantages	Recommendation	Ref.
Serological methods				
ELISAs (IgM, IgG)	Sensitive and specific Cross-reactivity allows the detection of unexpected hantaviruses Low cost Can be used during entire clinical course	Do not allow serotyping	Most commonly used Positive later than RT-PCR	24–27
ICG test	Rapid, sensitive, and specific Low cost Easy to perform (no need for special equipment or trained staff)	Does not allow serotyping	Commonly used Cost-effective	28–30
IFA	More specific than ELISAs	Low sensitivity Laborious	Uncommonly used	26,31,32
WB	More sensitive and specific than ELISAs	Expensive and laborious	Uncommonly used	24–26,33
SIA	More specific than WB	Low sensitivity Expensive and laborious	Uncommonly used	24–26
Neutralization test	Allows serotyping	Expensive and laborious Needs a BSL-3 lab	Uncommonly used	25,26,34
Molecular methods				
Real-time RT-PCR	Rapid, high sensitivity and specificity Quantitative assay	Expensive Does not detect hantavirus after viremic phase	Commonly used Positive earlier than ELISAs	33,35
NGS	Useful for virus discovery and genotyping	Too expensive and complex	Rarely used	36,37
Microarray	Rapid, sensitive, and specific	Too expensive and complex	Rarely used	37
Others				
IHC	Detects hantavirus antigens in tissues	Laborious	Mostly used in biopsy or post-mortem	38
Virus culture	Allows further virological studies	Low sensitivity Expensive and laborious Needs BSL-3 lab and trained staff	Rarely used	37,38

ELISA, enzyme-linked immunosorbent assay; RT-PCR, reverse transcription-polymerase chain reaction; ICG, immunochromatographic; IFA, immunofluorescence assay; WB, Western blot; SIA, strip immunoblot assay; BSL-3 lab, biological safety level 3 laboratory; NGS, next generation sequencing; IHC, immunohistochemistry.

prolonged and non-resolving renal failure.[48] However, there has been no clinical trial to confirm the benefit of glucocorticoid treatment.[37]

There are three types of vaccine for HFRS: killed vaccines, DNA vaccines, and attenuated live vaccines. The latter two are still in phase I and II clinical studies or pre-clinical studies.[49,50] In different countries and regions, the species of pathogenic hantaviruses may be different, and specific vaccines may be required for the different species. Several killed vaccines have been generated by inactivation of hantavirus in the rodent brain and from cell culture-derived hantaviruses, and a few of them are commercially produced and licensed for use in humans, such as Hantavax in Korea and the monovalent HTNV and SEOV vaccines, as well as the bivalent HTNV/SEOV vaccines, in China.[27,51–53] Large-scale human trials have been reported in China that have demonstrated a protective efficacy of 93.77–97.61% for the inactivated monovalent vaccines[54] and nearly 100% for the inactivated bivalent vaccines.[52] Hantavirus vaccines have been used in China and Korea for years, while there are no licensed vaccines available in any other regions,[2] because there have been no similar efforts for HFRS vaccine development in other regions. One reason for this is that the incidence of HFRS in the regions outside of China and Korea might be much lower. From a health economics perspective, the vaccination is only provided to adults in China in the areas where the incidence of HFRS is higher than 50/100 000 persons.[55] Another reason might be that it is difficult to produce effective HFRS vaccines against local pathogenic species of hantaviruses.[56,57] Exposure prophylaxis is still the most important approach to prevent hantavirus infections.[37] Improving general awareness and knowledge of pathogen sources, transmission routes (how to avoid contact with hantavirus), housing conditions, good hygiene, and human migration from rural areas to cities might contribute to the decline in HFRS.[2]

8. Spatiotemporal distribution of HFRS in China

Data on the reported HFRS cases and the monthly and annual HFRS incidence in China from January 2004 to April 2015 were obtained from the Chinese Centre for Disease Control and Prevention (CDC). HFRS cases were first diagnosed according to clinical symptoms, then blood samples were collected in the hospital and serological identification was performed in the laboratory of each provincial CDC to confirm the clinical diagnosis. The serologically confirmed cases were collected. This study was reviewed by the research institutional review board of the Xuzhou Central Hospital and the China CDC. The review board concluded that utilization of disease surveillance data did not require oversight by an ethics committee.

9. Temporal distribution analyses

The numbers of monthly HFRS cases in China from January 2004 to April 2015, including the numbers of deaths, were calculated and plotted to observe seasonal fluctuations. The results showed that the numbers of HFRS cases decreased sharply from 2004 to 2009, then increased markedly from 2010 to 2012, and have decreased again since 2013. The numbers of HFRS cases were found to vary seasonally; most cases occurred in the winter (November to January) and early summer (May to July), and they usually peaked in June and November. The numbers of deaths revealed a similar trend (Figure 1).

10. Geographical information system (GIS) mapping for the incidence of HFRS

To conduct a GIS-based analysis of the spatial distribution of HFRS, a province-level map of China was obtained. The province-level point

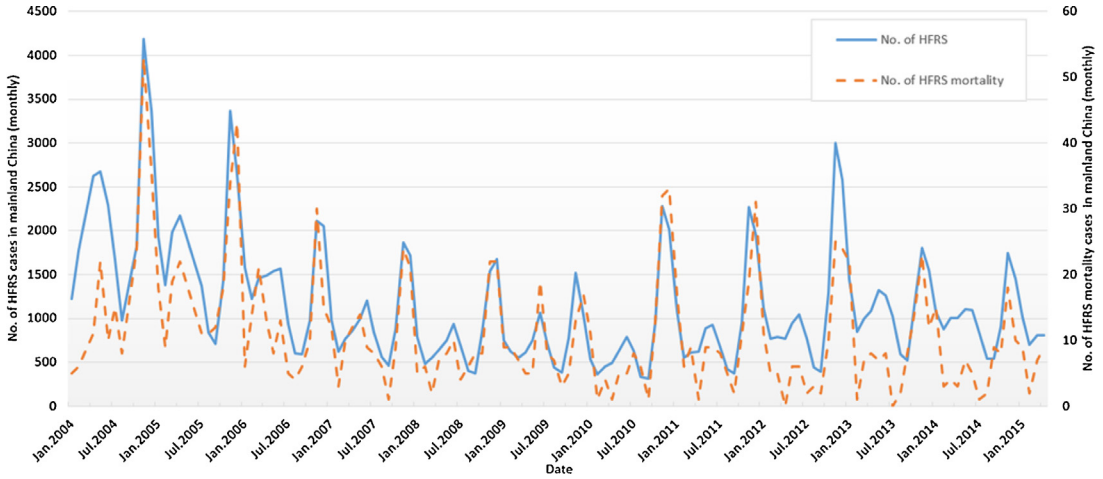

Figure 1. Temporal distribution of HFRS in China from January 2004 to April 2015. The solid blue line represents the number of HFRS cases; the dashed orange line indicates the number of HFRS mortality cases. Most cases occurred in the winter and early summer, usually in June and November.

layer that contained information regarding latitudes and longitudes of central points of each province was created. To lessen variations, the annual incidence of HFRS per 100 000 persons for each province was calculated. The annual incidence of HFRS for each province was mapped using a GIS technique and Mapinfo software (Professional Version 12.0.2). Based on the average annual incidence, the provinces were grouped into five categories: no data areas; low endemic areas with an average annual incidence between 0 and

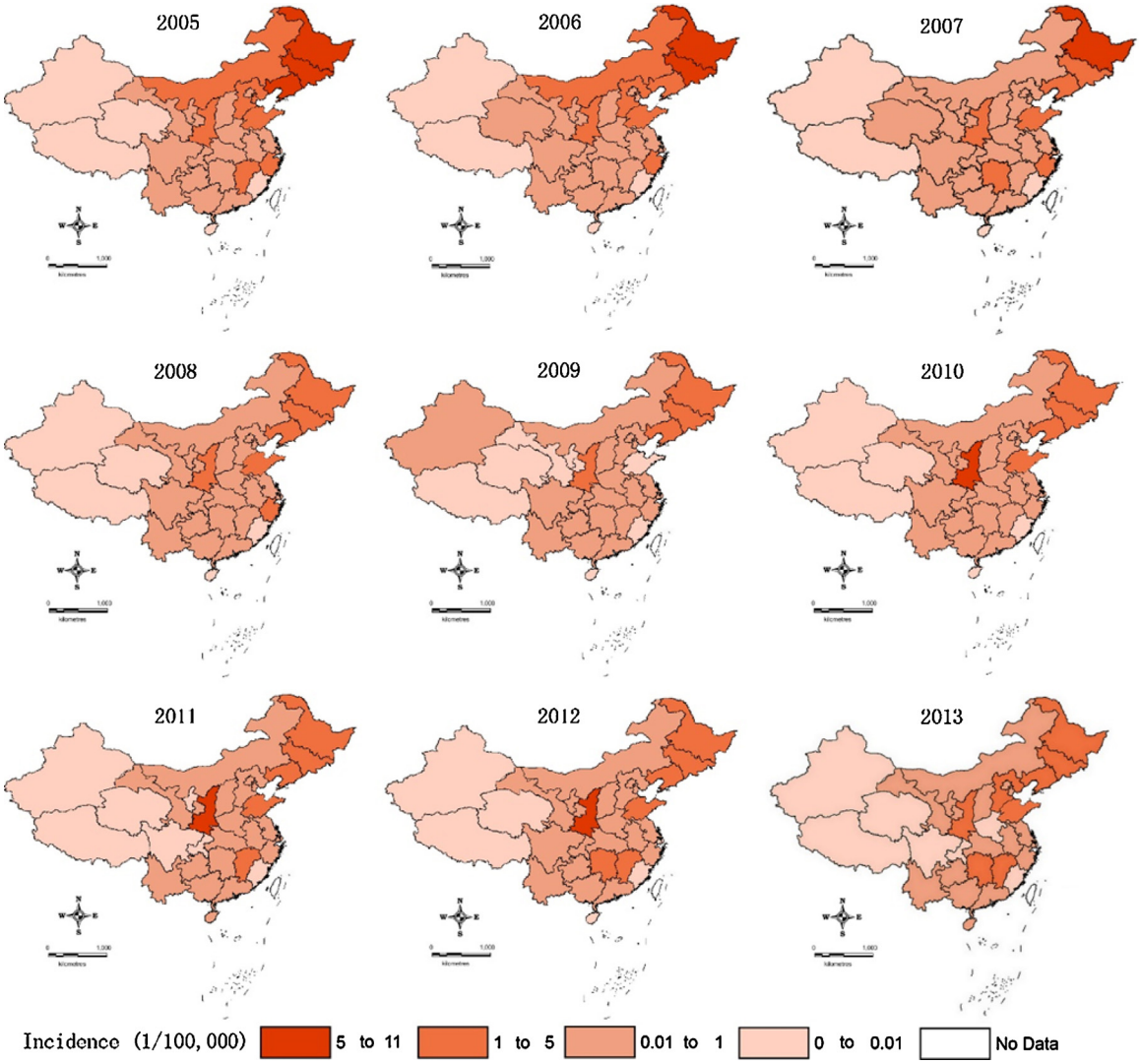

Figure 2. Yearly distribution of HFRS incidence in China, 2005–2013.

0.01/100 000 persons; medium endemic areas with an average annual incidence between 0.01 and 1/100 000; higher endemic areas with an average annual incidence between 1 and 5/100 000; and highest endemic areas with an average annual incidence >5/100 000. The five categories were colour-coded on the maps.

The HFRS incidence varied between the provinces (Figure 2). In 2005, Heilongjiang, Jilin, and Liaoning exhibited the highest incidences, and Inner Mongolia, Hebei, Shandong, Shaanxi, Zhejiang, and Jiangxi exhibited the second highest incidences. The HFRS incidences in these provinces have tended to decline since 2005, with the exception of the HFRS incidence in Shaanxi. From 2010 to 2012, Shaanxi surpassed Heilongjiang and became the province with the highest HFRS incidence.

Previous studies have revealed that climatic factors can influence HFRS incidence through their effects on the reservoir host and environmental conditions. However, climatic changes are mainly associated with global climate patterns, usually indicated by the multivariate El Niño Southern Oscillation (ENSO) index (MEI), and are difficult to control by government measures.[58] Thus, the HFRS incidence in northeast China (a traditional epidemic area) has declined since 2005, mainly due to rodent control measures, improvements in the environment, and effective vaccination programmes.

11. Conclusions

Hantavirus infection and HFRS should be suspected in patients with symptoms of acute renal failure, fever, haemorrhage, headache, and abdominal/back/orbit pain, who live in rural areas or who have had possible rodent exposure within the last 7 weeks. A timely diagnosis requires serological tests to detect the IgM/IgG antibodies of hantaviruses, combined with RT-PCR and new biomarkers. These biomarkers may be correlated with the disease severity of HFRS. Increasing our knowledge of the pathogenesis and renal pathology will contribute to our understanding of the mechanisms of vascular leakage and kidney damage, which will help in the proper treatment of the severe forms of HFRS. No specific therapy is in use in China, and well-planned randomized controlled trials are needed to develop new treatment measures. There is an urgent need to generate vaccines with a higher degree of cross-reactivity for the diversity of hantavirus species.

Epidemiological surveillance of communicable diseases is one of the most traditional health-related activities. This article provides the latest data on the geographical distribution, yearly trends, and seasonal trends in HFRS in mainland China, which will help to increase our understanding of the factors influencing hantavirus infection and provide valuable information for the hygiene authorities to design and implement effective measures for the control and prevention of HFRS in China.

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