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An epidemiological analysis of human bocavirus infection in Wuhan, China

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Abstract

Introduction: Human bocavirus (HBoV) is a critical pathogen responsible for acute respiratory infections in young children. However, there is a relative paucity of relevant epidemiological data related to the HBoV infection, which constrains a comprehensive understanding of the infection and transmission patterns of the virus.

Objective: This study aimed to address the knowledge gaps and to provide a scientific basis for public health strategies and clinical management programs for HBoV through epidemiological analyses.

Methods: This study analyzed 416 HBoV-positive respiratory cases in Wuhan, China, from July 2021 to December 2024, focusing on demographic characteristics, clinical manifestations, and co-infection patterns.

Results: The results indicated that 86.3% of infections occurred in children under 3 years of age, with a male-to-female ratio of 1.5:1. Seasonal peaks were observed in autumn, accounting for 54.81%, and winter, accounting for 26.68%. The AutoRegressive Integrated Moving Average+Seasonal-Trend decomposition using the Loess model predicted that HBoV infections would continue to be concentrated in autumn and winter in 2025. The most common co-infections were with human rhinovirus (HRV), *Mycoplasma pneumoniae*, and other pathogens. The HRV co-infection rate was 22.84%. Elevated levels of interleukins (IL)-6, IL-8, and IL-2R, as well as altered lymphocyte subsets, such as reduced natural killer cells, suggested compromised immune responses during infection.

Conclusion: HBoV infections are highly prevalent in young children, particularly during autumn and winter. Frequent co-infections and immune dysregulation underscore the need for improved diagnostics and surveillance. Public health interventions should focus on high-incidence seasons to reduce the burden of HBoV-associated respiratory infections.

Keywords: Human bocavirus; Epidemiology; Respiratory infections; Co-infection; Pediatric population

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1. Introduction

Human bocavirus (HBoV) is a non-enveloped, single-stranded linear DNA virus belonging to the Parvoviridae family.[1,2] The genome length of HBoV ranges from 5.2 to 5.5 kb and encodes four key proteins: NS1, a non-structural protein that regulates viral replication; VP1/VP2, which form the capsid; and NP1, a nucleoprotein involved in nucleic acid metabolism.[3,4] Four distinct genotypes have been identified: HBoV1, HBoV2, HBoV3, and HBoV4.[5,6] HBoV infection typically presents with common upper respiratory tract symptoms such as cough, fever, respite,[7] and diarrhea.[8] However, it has also been linked to a range of serious complications, including pneumonia, asthma, and bronchitis.[9,10]

The epidemiological profile of HBoV infection exhibits a global epidemiological trend. The global prevalence of HBoV infection is approximately 6%.[3] The prevalence of HBoV infection is also notably high in Asia, especially in densely populated countries such as China and India. There are geographical differences in HBoV infections in different regions. For example, in China, the infection rates were relatively low in Kunming,[11] as compared to the higher infection rates reported in Qingdao.[12] This suggests that environmental factors, including climatic conditions and population mobility, may contribute to these differences by influencing viral transmission dynamics.

The infection of HBoV exhibits seasonal fluctuations, with typical peaks occurring in autumn and winter.[13-15] These peaks often coincide with epidemics of other respiratory viruses. Consequently, HBoV is frequently co-infected with various pathogens, particularly respiratory viruses such as human rhinovirus (HRV), human adenovirus (HAdV),[16] respiratory syncytial virus (RSV), human metapneumovirus (HMPV),[17] severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[18] *Mycoplasma pneumoniae* (Mp), and *Chlamydia pneumonia*.[19] Clinical manifestations of infection tend to be more severe in cases of co-infection compared to single infections.[20]

The detection and diagnosis of HBoV infection can be challenging due to its frequent co-infection with other respiratory pathogens and its potential to persist for extended periods in asymptomatic children, which may lead to an underestimation of HBoV prevalence. Laboratory diagnosis primarily relies on molecular biology and immunological techniques. Polymerase chain reaction (PCR) has become the clinically preferred method due to its high sensitivity in amplifying the conserved region of the *VP1/NP1* genes.[1,21] Southern blotting can distinguish between active and latent viral replication through hybridization with specific probes.[22] Enzyme-linked immunosorbent assay is valuable for seroepidemiological studies because of its ability to detect specific immunoglobulin (Ig)G/IgM antibodies or viral capsid proteins.[23]

Previous studies highlight the global prevalence of HBoV and its association with co-infections;[24] however, regional epidemiological data, particularly from China, remain limited.[12,25] Wuhan, as a megacity with over 10 million people in central China and a national transportation hub, has a super-high population density with a large-scale migrant population and a complex social structure, all of which have shaped a unique environment for virus transmission dynamics. This study is based on a continuous and systematic HBoV laboratory-confirmed dataset from a large general hospital in Wuhan. This dataset features a long time span (July 2021–December 2024), a large sample size, comprehensive clinical information (age stratification, clinical manifestations, co-infections), and high pathogen reliability. Therefore, we selected "key cases" from this high-intensity transmission environment in Wuhan as the study subjects, aiming to deepen national understanding of HBoV while also providing empirical evidence for precise prevention and control measures in similar large cities. This study investigates the age-specific susceptibility, seasonal trends, clinical outcomes, and pathogen interactions of HBoV in Wuhan from 2021 to 2024. Our findings indicate that HBoV primarily affects children under the age of three, with a peak incidence occurring in the fall. Most patients with HBoV present with bronchopneumonia and co-infection with HRV. In addition, we predicted the prevalence of HBoV in Wuhan for 2025 by constructing an AutoRegressive Integrated Moving Average (ARIMA) + Seasonal-Trend decomposition using the Loess (STL) model using case data from previous years. Mathematical models can be used not only to study and reveal potential transmission patterns, but also to predict future numbers of virus infections, thereby reflecting the future transmission trends of the virus to a certain extent. This work aims to inform region-specific public health strategies and clinical management protocols by addressing the gaps in localized data.

2. Materials and methods

2.1. Study population

This study analyzed the medical records of 416 patients admitted to Tongji Hospital in Wuhan, China, between July 2021 and December 2024, who were suspected of having HBoV infection (Figure 1).

2.2. Laboratory investigations

Upon admission, all patients underwent a comprehensive series of standardized laboratory tests, including routine

blood counts, biochemical parameters, coagulation tests, and infection-related biomarkers, such as the erythrocyte sedimentation rate (ESR) and serum ferritin levels.

2.3. Imaging studies

A subset of patients underwent chest imaging to evaluate pulmonary involvement and identify any additional lesions. Both chest computed tomography (CT) scans and X-ray examinations were conducted to provide detailed visualization of lung parenchyma and airway pathology.

2.4. Pathogenetic testing

Nasopharyngeal swab samples were preserved in test tubes containing 3 mL of virus preservation solution. The tubes were then shaken and mixed thoroughly. Subsequently, 200 μL was extracted for viral nucleic acid analysis, which was performed using the PANA9600S fully automatic nucleic acid workstation (Xi'an Tianlong Science and Technology Co., Ltd., China). Nucleic acids were amplified using the Multiplex Detection Kit for 13 Respiratory Pathogens (PCR-Capillary Electrophoresis Fragment Analysis Method) from Ningbo HEALTH Gene Technologies Co., Ltd. (China). The amplified products were analyzed using the ABI 3500Dx Genetic Sequencer (Applied Biosystems, USA).

2.5. TBNK Lymphocyte counting

Cell subpopulation analysis was conducted using a TruCOUNT tube in conjunction with the BD Multitest 6-color TBNK Reagent Kit (BD Biosciences, USA). Briefly, 50 μL of whole blood was aliquoted and stained with the 6-color TBNK antibody cocktail, followed by a 15-min incubation at room temperature. After incubation, 450 μL of FACS lysing solution was added to lyse the red blood cells. The samples were then analyzed using a FACSCanto flow cytometer (BD Biosciences) along with the FACSCanto clinical software to quantify both the percentage and absolute counts of lymphocytes.

2.6. Cytokine profile analysis

To evaluate the concentrations of various cytokines in the serum of patients, levels of interleukin-1β (IL-1β), interleukin-2 receptor (IL-2R), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) were quantified using a solid-phase, two-site chemiluminescent immunometric assay with the IMMULITE 1000 Analyzer (Siemens, USA). In addition, interleukin-6 (IL-6) concentrations were measured using the electrochemiluminescence method (Roche Diagnostics, USA).

2.7. STL-based forecasting for HBoV cases

In this study, we employed the STL approach[26,27] to forecast HBoV cases. To enhance forecasting accuracy, we integrated STL with an ARIMA model[28] for trend prediction and utilized a seasonal pattern replication technique, while addressing residual errors through a stochastic method.

2.7.1. Data decomposition using STL

The original dataset contains 416 records of bocavirus cases reported in Wuhan from July 2021 to December 2024. Considering data sparsity and the need for model forecasting, the total number of cases per month was aggregated as the model input. After processing, the dataset consists of 42 data points. The model uses data from the first 30 months as the training set and the past 12 months as the test set. Root mean squared error (RMSE) was used as the evaluation metric. The optimal model was selected through parameter search based on performance on the test set. We decomposed the data into three components: (i) Trend (Tt): Captures the underlying long-term movement in the data. (ii) Seasonal (St): Represents recurring seasonal patterns within a defined period. (iii) Residual (Rt): Accounts for irregular fluctuations and noise.

2.7.2. STL additive structure assumption

It is assumed that the time series can be decomposed as yt = Tt (trend) + St (seasonal) + Rt (residual). STL assumes that the seasonal component repeats within the same period, *i.e.*, St ≈ S(t + k*P), where P is the seasonal period length, and k is an integer.

2.7.3. The parameters of the model

The STL parameters include the period length (period) and the seasonal window length (seasonal). A grid search was conducted over period ∈ [10, 14] and seasonal ∈ [5, 12], yielding optimal values of period = 12 and seasonal = 10. The ARIMA parameters include p (autoregressive [AR] order), d (differencing [I] order), and q (moving average [MA] order), which mainly influence the prediction of the trend component in STL. A grid search was conducted over p ∈ [3, 9], d ∈ [1, 5], and q ∈ [1, 4], resulting in optimal parameters of p = 6, d = 1, and q = 2.

2.7.4. Forecasting three components

(i) To predict future values of the trend component, we applied an ARIMA model. ARIMA is a robust statistical method for time series forecasting that combines AR, I, and MA components. Based on model selection, we set the ARIMA order to (6,2,3), where AR = 6 accounts for dependencies on the past six observations, I = 2 ensures stationarity through two levels of I, and MA = 3 smooths noise using the past three residuals

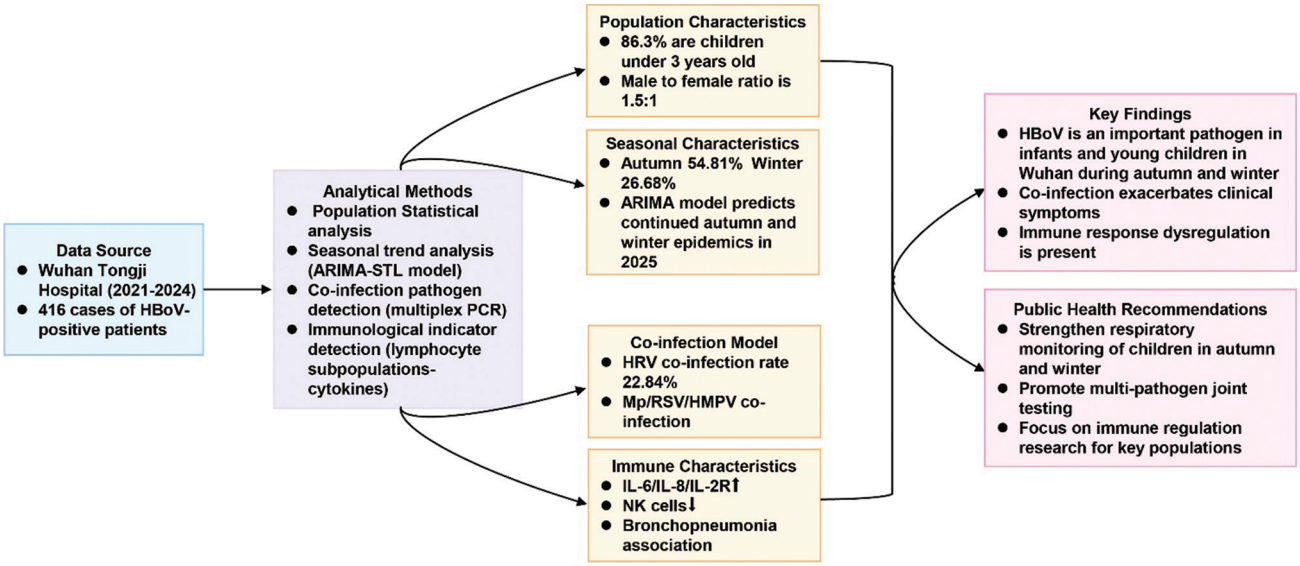


Figure 1. Comprehensive research design integrating demographic characteristics, seasonal trend predictions, co-infection patterns, and immune marker analysis

Abbreviations: HBoV: Human bocavirus; HMPV: Human metapneumovirus; HRV: Human rhinovirus; IL: Interleukin; Mp: *Mycoplasma pneumoniae*; PCR: Polymerase chain reaction; NK cells: Natural killer cells; RSV: Respiratory syncytial virus.

(ii) The seasonal component exhibits recurring patterns over a fixed period (e.g., 12 months). We extracted the most recent seasonal cycle and replicated it over the forecast period to maintain periodicity. This assumption is valid when the disease demonstrates stable seasonality, such as annual infection waves

(iii) Residual errors often contain unpredictable noise. Instead of modeling them explicitly, we assume that the residuals follow a normal distribution and generate synthetic values using a Gaussian noise model. The standard deviation of historical residuals was utilized to ensure realistic variability.

2.7.5. Forecast synthesis

The final forecast was obtained by summing the predicted trend, the replicated seasonal pattern, and the generated residuals. This method ensures that both systematic patterns and random variations are incorporated into the predictions.

2.8. Statistical analysis

Data on demographic, symptomatic, and laboratory parameters were analyzed using Excel (Microsoft Corporation, Redmond, USA) and Tableau (Tableau Software, Seattle, USA) software to explore the epidemiological characteristics of HBoV infection. The Chi-square test was employed to compare the distribution of age and sex. Seasonal trends were evaluated through time series analysis. Descriptive statistics and correlation analysis were utilized to assess co-infection rates and cytokine levels.

3. Results

3.1. HBoV primarily affects children aged 0–3 years, with peak incidence occurring in the autumn and winter

Respiratory diseases caused by viral infections are relatively common. To assess the epidemiological characteristics, we calculated the infection rates of 13 common respiratory viruses in over 20,000 patients at Tongji Hospital, Wuhan, from July 2021 to December 2024. Our study found that HRV and Mp had the highest infection rates, at 17.11% and 14.72%, respectively. In addition, RSV, HAdV, and HMPV exhibited infection rates exceeding 5%. The positive detection rate of HBoV was 1.51%. To further elucidate the epidemiological characteristics of HBoV infection, we systematically analyzed 416 cases of HBoV infection from a total of 27,608 patients (Figure 2A and Table S1).

HBoV infections are more prevalent in infants and young children. Our study found that HBoV infections can affect individuals aged from 0 to 65 years, and that the group of young children aged 0–3 years represented the majority of infected cases, accounting for 86.3% of the total. Analysis of gender distribution revealed a significantly higher infection rate among males (59.62%) compared to females (40.38%), resulting in a male-to-female ratio of 1.5:1 (Figure 2B).

Common respiratory viral infections display distinct seasonal patterns. For example, winter and early spring are peak periods for viruses such as influenza and RSV.[29,30] The findings of this study revealed a significant presence of

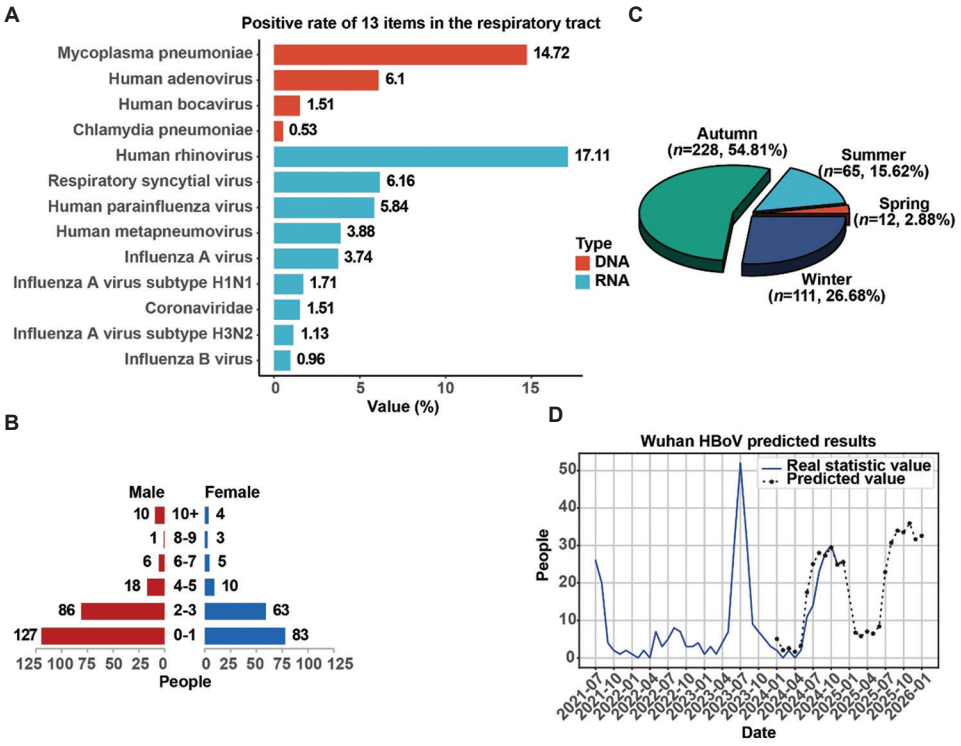


Figure 2. Epidemiological characteristics of HBoV Infection. (A) Positive test rates for respiratory pathogens. This graph presents test data for 13 common respiratory viruses from July 2021 to December 2024, illustrating the distribution of positive rates for each virus. (B) Demographic characteristics of HBoV infections. This chart displays the distribution of infections stratified by sex (red: male, blue: female) and age (y-axis: age group, x-axis: number of infections). (C) Seasonal characteristics of HBoV infection. The pie chart presents the composition ratio of positive cases in spring, summer, autumn, and winter. (D) ARIMA+STL model, offering a prediction of the HBoV prevalence in Wuhan for the year 2025.
Abbreviation: HBoV: Human bocavirus.

seasonal fluctuations in HBoV infection. Out of 416 cases of HBoV infection, 228 (54.81%) occurred in autumn and 111 (26.68%) in winter, together accounting for 81.49% of annual cases, which is markedly higher than in other seasons (Figure 2C).

To formulate more accurate prevention and control strategies, this study inputs the collected HBoV case data into the ARIMA+STL model to predict the epidemiological trend of HBoV in Wuhan through 2025. The results indicated that the ARIMA+STL model fit this dataset well (RMSE = 12.3085), demonstrating high reliability. The analysis revealed that the peak period of HBoV infection remains concentrated in the autumn and winter. Further analyses showed that the number of HBoV infection cases in 2022 was significantly lower than in previous years, which may be related to the outbreak of COVID-19 (Figure 2D).

3.2. HBoV infection is associated with bronchopneumonia and compromised immune responses in numerous children

Understanding the distribution and characteristics of clinical symptoms following viral infections is crucial for the epidemiological diagnosis, treatment, and prevention of HBoV. Therefore, we analyzed the clinical symptoms and complications in patients who tested positive for HBoV. These patients typically present with a variety of respiratory symptoms, including fever, diarrhea, cough, vomiting, rhinorrhea, and respite. Cough (356 cases), fever (339 cases), and respite (87 cases) were the most common symptoms (Figure 3A). In addition, patients may develop complications such as bronchitis, pneumonia, cardiac arrhythmia, elevated lactate dehydrogenase, coagulation abnormalities, consolidation of the lung, and sepsis. Among these, pneumonia (326 cases) was the most prevalent serious complication (Figure 3B). Notably, almost all HBoV-positive patients exhibit varying degrees of pneumonia symptoms. To illustrate the different types and severities of pulmonary lesions that infection may cause, we selected two representative lung CT slices from over 400 HBoV infection cases (Figure 3C and D). Figure 3C shows early or relatively mild infection signs: a faint, patchy, ground-glass-like shadow with slightly increased density is visible in the posterior segment of the right upper lobe, with blurred borders, consistent with an infectious lesion. Figure 3D

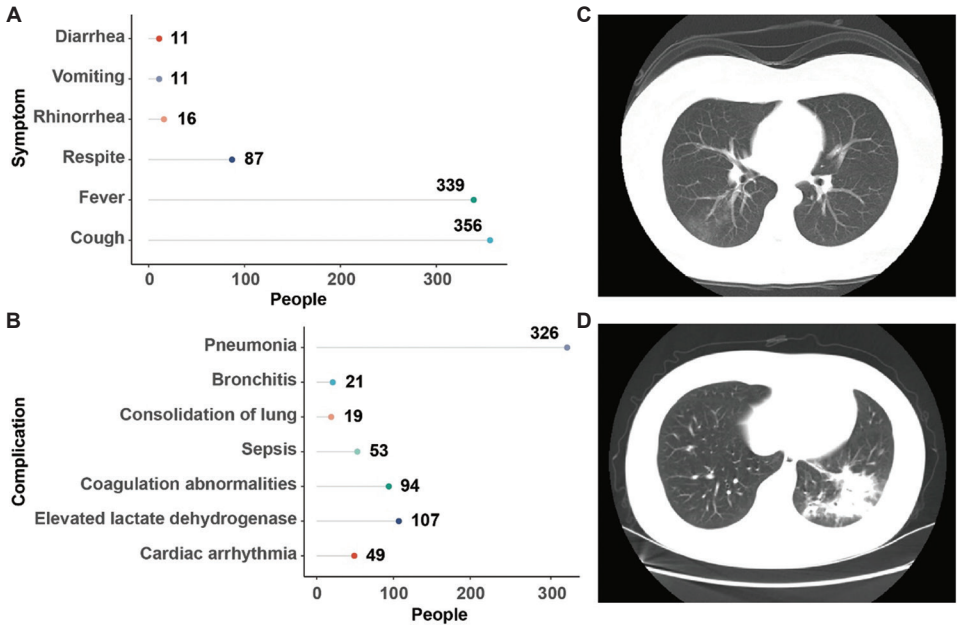


Figure 3. Analysis of clinical symptoms in patients with HBoV. (A) Distribution of patients exhibiting various clinical symptoms. (B) Distribution of patients with different complications. (C and D) Chest computed tomography images of a patient diagnosed with HBoV.
Abbreviation: HBoV: Human bocavirus.

shows advanced or more severe infection signs: extensive patchy and nodular consolidation shadows are observed in the posterior and lateral basal segments of the left lower lobe, accompanied by a faint halo sign. Adjacent areas showed long spicules and pleural thickening, with uneven density within the consolidation area, and suspected bronchial signs. These findings are consistent with progressive pneumonia.

Lymphocyte subpopulations reflect the balance between cellular and humoral immunity in the body and serve as biomarkers for disease progression. Since the majority of infected cases were in children, lymphocyte subpopulations in patients with HBoV aged 0–12 years were specifically analyzed. The reference ranges for lymphocyte subsets in children are as follows: natural killer (NK) cells, 90–900/μL; total B cells, 200–1600/μL; total T cells, 700–4200/μL; suppressor T cells (Ts), 300–1800/μL; and helper T cells (Th), 300–2000/μL. Most patients in this study fell within the normal range. However, the number of helper T cells (Th cells) was elevated in 34.21% of the patients, while NK cell counts were decreased in 21.05% of the patients (Figure 4A). Patients suffering from viral infections often exhibit elevated levels of both pro-inflammatory and anti-inflammatory factors. In our study, we observed increased levels of various interleukins, notably IL-6, IL-8, and IL-2R, in many patients (Figure 4B). Regarding blood indices, approximately 40% of patients exhibited elevated ESR and decreased hemoglobin levels. However, ferritin levels were mostly within normal parameters (Figure 4C-E). Elevated ESR was typically associated with an inflammatory response, which aligns with the increased levels of interleukins.

3.3. Co-infections of HBoV with other respiratory pathogens

HBoV can cause standalone infections but is also frequently detected in co-infections with other respiratory pathogens. In this study, co-infections involving HRV, Mp, RSV, and HMPV were identified in HBoV-positive patients (Figure 5A and Table S2). Among these, co-infection with HRV was the most prevalent; however, there was no significant gender difference in this co-infection, which primarily affected children aged 0–3 years (Figure 5B). The proportion of patients presenting with symptoms such as fever, cough, and pneumonia increased following HBoV-HRV co-infection (Figure 5C). Notably, some co-infections of HBoV and Epstein–Barr virus (EBV) were detected in this study through PCR and antibody detection (Figure 5D and E). EBV early antigen IgG and EBV capsid antigen IgM are typically present during the early stages of EBV infection. The presence of EBV capsid antigen IgG and EBV nuclear antigen IgG is generally associated with the persistence of EBV infection. A high number of positive test results for EBV capsid antigen IgG and EBV nuclear antigen IgG may indicate that these patients have been infected with EBV for an extended period; however,

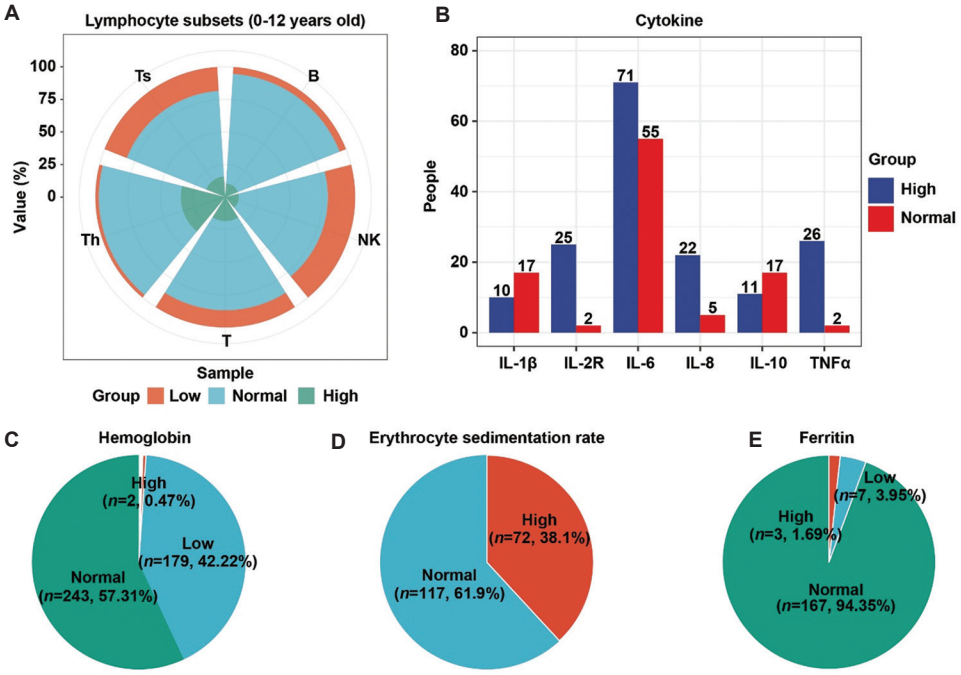


Figure 4. Analysis of laboratory testing data in patients with HBoV. (A) Changes in lymphocyte subsets in children aged 0–12 years. (B) Variations in cytokine levels among patients. (C-E) Blood parameters of patients: hemoglobin (C), erythrocyte sedimentation rate (D), and ferritin (E).
Abbreviation: HBoV: Human bocavirus.

the virus may currently be inactive, or the patient may have developed a prolonged immune response.

4. Discussion

Our analysis of clinical HBoV infection patterns in Wuhan from 2021 to 2024 revealed a significant susceptibility among children under 3 years of age, and the proportion of male children infected with HBoV was slightly higher than that of female children, consistent with global epidemiological reports.[31] In addition, our data show that HBoV infections in Wuhan are primarily concentrated in the autumn and winter months. This seasonal trend may be attributed to factors such as the increased stability of the virus in low-temperature environments and a rise in indoor activities among the population. In this study, the ARIMA+STL model was utilized to predict and analyze the epidemiological trends of HBoV in Wuhan throughout 2025. The results indicated that HBoV infections peak during the autumn and winter months. The analysis revealed a significant decline in HBoV infection cases in 2022 compared to previous years. The non-pharmacological interventions implemented during the COVID-19 pandemic had a substantial impact on the transmission of other respiratory pathogens. For instance, the incidence of other respiratory pathogens, including influenza viruses, Mp, and ADV, experienced a significant decline between 2020 and 2021.[32] This finding underscores the effectiveness of non-pharmacological interventions in mitigating respiratory infectious diseases.

Our study demonstrated that HBoV infection is associated with a range of clinical symptoms, including, but not limited to, cough, fever, respite, and diarrhea.[33,34] Further analysis revealed that patients with HBoV infection may develop additional complications, such as bronchitis, pneumonia, cardiac arrhythmia, elevated lactate dehydrogenase, coagulation abnormalities, consolidation of the lung, and sepsis. Notably, symptoms of bronchopneumonia were observed to varying degrees in almost all patients infected with HBoV in our study. This may be attributed to HBoV's ability to directly invade bronchial epithelial cells, triggering an inflammatory response that can lead to the development of bronchopneumonia. The immune cells, including NK cells, B cells, T cells, suppressor T cells (Ts cells), and Th cells, did not exhibit typical changes. This atypical response of immune cells may be associated with the immune escape mechanisms of HBoV.[35] However, inflammatory cytokines such as IL-6, IL-10, and IL-1β were elevated to varying degrees in many cases. These cytokines play a crucial role in promoting the inflammatory response, regulating immune cell activation and proliferation, and controlling the extent of inflammation.[36] This suggests that while the cellular immune responses are not effectively activated

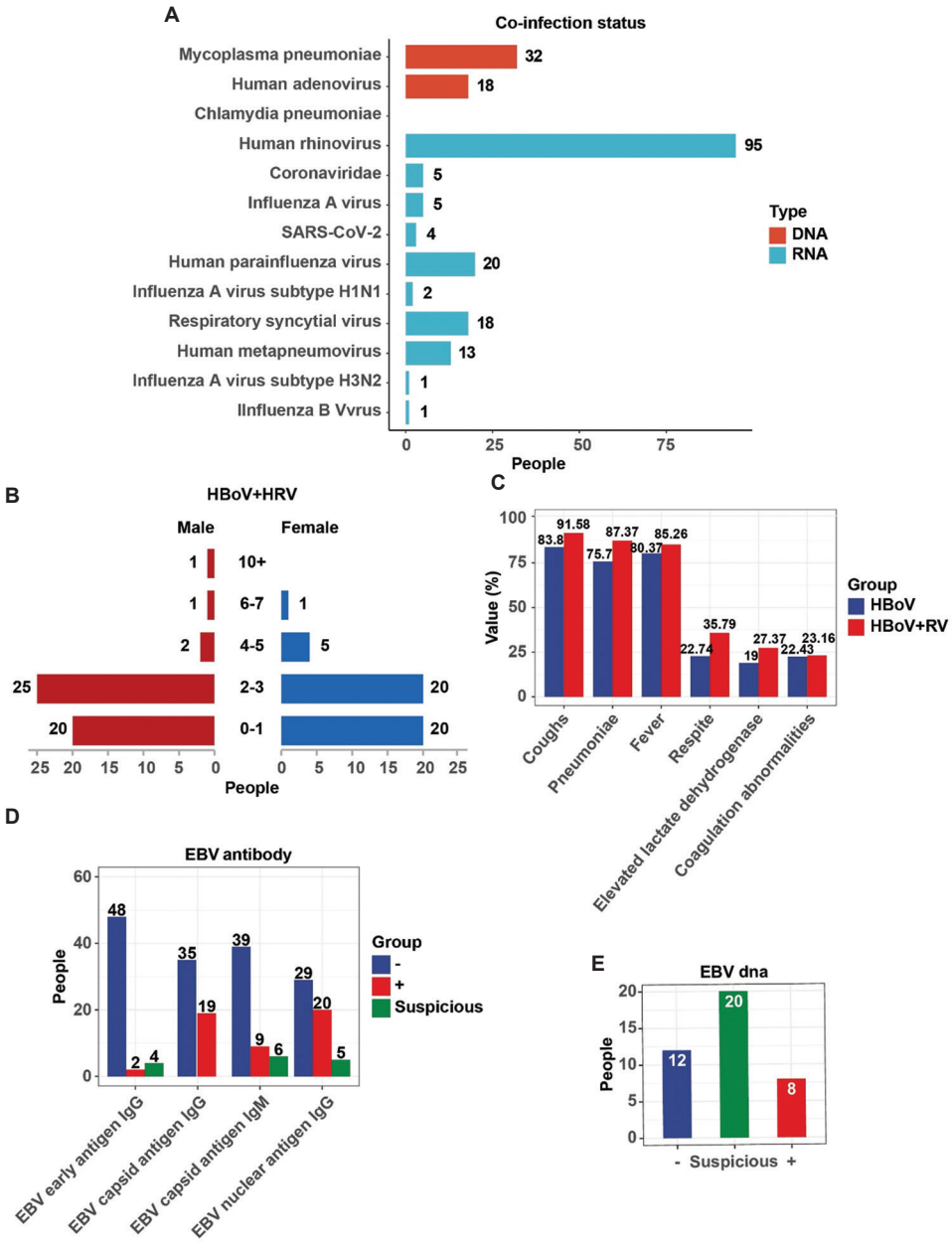


Figure 5. Co-infection of HBoV with other pathogens. (A) Number of patients co-infected with HBoV and other common respiratory pathogens. (B) Gender and age distribution of patients co-infected with HBoV and HRV. (C) The proportion of patients infected with HBoV alone compared to those co-infected with HRV, categorized by different clinical symptoms. (D and E) Results of IgG and IgM tests (D) and EBV DNA tests (E) in patients with HBoV.

Abbreviation: EBV: Epstein–Barr virus; HBoV: Human bocavirus; HRV: Human rhinovirus.

by HBoV infection, the cytokine-mediated inflammatory response could be considered a significant feature of the infection, potentially contributing to disease pathogenesis.

HBoV is frequently co-infected with other respiratory viruses. Our study demonstrated that HBoV frequently co-infects with HRV, Mp, human parainfluenza virus, RSV, and HMPV. The most prevalent type of co-infection observed in this study was with HRV. Co-infection with HRV and HBoV increases the likelihood of symptoms such as fever, cough, and bronchopneumonia.[37-39] Co-infection with other viruses alongside HBoV should be thoroughly considered in both diagnosis and treatment. Healthcare professionals are advised to employ a combination of

tests to identify all potential pathogens when addressing respiratory infections in children.[40]

Although our study revealed the epidemiological characteristics of HBoV infection, the sample was limited to a specific time frame and geographic region, which may affect the generalizability of the results. To obtain more comprehensive epidemiological insights, future studies should increase the sample size and expand the geographic scope to gather more extensive data.

5. Conclusion

Epidemiological investigations of HBoV play a critical role in elucidating viral transmission patterns, informing clinical decision-making, shaping health policy frameworks, and accelerating the development of vaccines and antiviral treatments. Such research has enhanced our understanding of HBoV infection dynamics and disease presentations, contributing to improved diagnostic accuracy and optimized therapeutic strategies. Our findings indicate that children under 3 years of age are particularly vulnerable to HBoV, which is most prevalent in the autumn season. Clinical symptoms associated with HBoV infection include cough, fever, and pneumonia. Therefore, it is essential to strengthen temperature and symptom monitoring during the HBoV epidemic season. Prompt medical attention for respiratory symptoms, such as cough and fever, can facilitate the timely identification and isolation of infected individuals, thereby reducing the spread of the virus.

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Conflict of interest

All authors have declared that they have no conflicts of interest.

Author contributions

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Formal analysis: Fuyu Luo
Methodology: Peiyu Wang, Jingyuan Wang
Writing–original draft: Fuyu Luo, Haibin Liu
Writing–review & editing: Jiangpeng Feng, Haojie Hao, Wuxiang Guan

Ethics approval and consent to participate

Written consent was obtained prior to participation in the study, in accordance with the protocol approved by the institutional ethics review board. Ethics ID: TJ-IRB202508106. Samples were collected only after obtaining written consent from the participants or their legal guardians.

Consent for publication

Verbal informed consent was obtained from all patients during the collection of patient samples and data, permitting the publication of their data and/or images in this paper.

Availability of data

Data is available from the corresponding author upon reasonable request.

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