The Journal of Infectious Diseases

MAJOR ARTICLE

Rhinovirus-Associated Lower Respiratory Tract Infection in Hospitalized Adult Patients: A Retrospective Cohort Study

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Background. The role of human rhinovirus (HRV) in adult lower respiratory tract infections (LRTIs) remains controversial due to limited direct evidence of alveolar tropism and age-specific clinical characterization.

Objectives. To determine HRV's clinical impact, validate its capacity to infect lower respiratory tract cells, and identify predictors for HRV-associated pneumonia in adults.

Methods. In this retrospective study (January 2020–December 2023), all hospitalized adults screened for HRV via RT-PCR were enrolled for analysis. In bronchoalveolar lavage fluid (BALF)-HRV-RNA-positive patients with available transbronchial lung biopsy (TBLB) or transbronchial cryobiopsy (TBCB) specimens, immunofluorescence (IF) staining was used to assess infection of LRT cells. Multivariable logistic regression analyzed demographics, comorbidities, and symptoms.

Results. HRV was detected in 4.6% (437/9544) of patients, with bimodal seasonal peaks (February–April and September–November). Co-infection occurred in 49.0% (214/437), predominantly bacteria (34.1%) and viruses (25.7%). Among the 437 HRV-positive patients, 224 cases complicated with pneumonia, but only 34 (7.8%) met the diagnostic criteria for simple viral pneumonia. Multivariate analysis identified male (OR 2.69, 95% CI 1.04–6.99, $P = .042$), fever (OR 3.79, 95% CI 1.52–9.44, $P = .004$), and cough (OR 7.33, 95% CI 1.64–32.83, $P = .009$) as independent predictors of simple rhinovirus pneumonia. IF staining confirmed HRV VP3 protein in TBLB/TBCB specimens in 61.5% (8/13) of cases, resolving debates about HRV's LRT cells tropism.

Conclusions. This study provides the first histological evidence of HRV's LRT cells infection in immunocompetent adults. Despite high co-infection rates, HRV independently drives pneumonia, particularly in males and those with fever or cough.

Keywords. rhinovirus; lower respiratory infection; immunofluorescence staining; risk factors.

Human rhinoviruses (HRVs), members of the *picornaviridae* family, were first isolated in 1956 [1]. These non-enveloped, positive-sense single-stranded RNA viruses are classified into three species—HRV-A, HRV-B, and HRV-C—which include at least 165 recognized serotypes. Most rhinoviruses exhibit better growth in cell culture in the cooler temperature found inside the nose than at core body temperature [2, 3]. This temperature preference has suggested that rhinoviruses may not typically infect the lower airways. Notably, nasal organoids are more susceptible to HRV-C infection than airway organoids [4].

It is widely accepted that rhinoviruses are a major cause of upper respiratory infections. However, their role in lower respiratory disorders is attracting increasing attention recently. In children, they are associated with asthma exacerbations [5]. Additionally, rhinoviruses appear to contribute to exacerbations of cystic fibrosis in children. Rhinoviruses are linked to nearly five hospitalizations per 1000 children under 5 years of age [6]. Among the different species, HRV-A and HRV-C are more strongly associated with severe illness and wheezing, while HRV-B is more commonly associated with mild or asymptomatic infections. However, research on the impact of rhinovirus in adults remains relatively limited.

Though recent studies strongly suggest the importance of HRVs in the pathogenesis of severe respiratory illness [7–9], the potential role of rhinovirus infections as a cause of pneumonia remains controversial. The role of rhinovirus in lower

Received 23 July 2025; accepted 20 December 2025; published online 26 December 2025

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The Journal of Infectious Diseases®

https://doi.org/10.1093/infdis/jiaf651

respiratory tract (LRT) infections is primarily supported by its nucleic acid detection through polymerase chain reaction (PCR) [10]. Recent studies have established that, under experimental conditions, rhinovirus can replicate in the LRT cells [4], but the ability of rhinoviruses to infect LRT cells during natural infection remains an area of ongoing research. Previous studies have shown that HRV can replicate at 37°C and infect bronchial epithelial cells through ICAM-1 and CDHR3 receptors, which are expressed in both the upper and lower respiratory tracts [11, 12]. In experimental infection tests, viral RNA has been detected in bronchoalveolar lavage fluid (BALF) of infected healthy adults, suggesting a potential involvement of the LRT [13]. In some studies, HRV has even been observed to cause interstitial involvement and acute inflammation in the alveoli [14, 15]. However, particularly in immunocompetent adults, histological evidence directly demonstrating HRV replication within the alveolar epithelium remains very limited. Bridging this knowledge gap is essential for elucidating the pathogenic role of HRV in LRT infections.

In this study, we retrospectively analyzed adult patients with HRV infection from 1 January 2020 to 31 December 2023 and assessed their clinical and laboratory characteristics. We also used lung biopsy samples to confirm, via immunofluorescence (IF) staining, that rhinoviruses are capable of causing LRT infections in immunocompetent adults.

METHODS

Study Design and Data Collection

This study employed a retrospective design. Between 1 January 2020 and 31 December 2023, we enrolled and analyzed hospitalized patients at the China-Japan Friendship Hospital who underwent HRV screening via real-time polymerase chain reaction (RT-PCR) as clinically indicated. Exclusion criteria included non-hospitalized status, incomplete core variable data, or age under 18 years (Supplementary Figure 1). Demographic characteristics, clinical symptoms, comorbidities, laboratory test results, pathogen detection data, and radiological imaging findings were extracted from electronic medical records for all included patients. Laboratory parameters were derived from the test result closest in time to the initial positive rhinovirus detection date.

The study protocol received ethical approval from the Institutional Review Board of China-Japan Friendship Hospital (approval number: 2025-KY-136). As a retrospective analysis utilizing anonymized residual clinical specimens obtained during routine diagnostic procedures, this research posed no additional risks to study participants. The Ethics Committee granted a waiver of informed consent in accordance with national regulations and institutional guidelines governing the use of de-identified biological samples for biomedical research.

Case Definition

Pneumonia is defined as new lung infiltrates on imaging, accompanied by respiratory symptoms, after excluding other pulmonary pathologies (eg, pulmonary edema, malignancy). Simple rhinovirus pneumonia met standardized clinical criteria with HRV identified as the sole pathogen. Exclusion of other respiratory pathogens was confirmed through comprehensive microbiological testing, including multiplex PCR, targeted PCR assays, and conventional bacterial and fungal cultures. Only patients who tested positive for HRV and negative for all other pathogens across these modalities were classified as having simple rhinovirus pneumonia. Complicated rhinovirus pneumonia was characterized by co-detection of HRV with ≥1 additional bacterial or viral pathogen in respiratory specimens, regardless of clinical severity. Bacterial co-infection was defined by either a positive respiratory tract bacterial culture or a serum procalcitonin (PCT) level exceeding 0.5 ng/mL [16]. Virus co-infection was defined as the detection of HRV along with other respiratory viruses. Patients underwent in-hospital multiplex testing for a range of pathogens, enabling the identification of co-infections such as rhinovirus with SARS-CoV-2 or influenza viruses.

Immunodeficiency was defined as patients receiving systemic corticosteroids (oral or intravenous), immunosuppressive therapy, individuals with lung transplantation, patients receiving maintenance therapy for hematological malignancies, or those undergoing active chemotherapy for solid malignancies [17]. Hematologic malignancies were defined as a confirmed diagnosis of leukemia, lymphoma, multiple myeloma (MM), or myelodysplastic syndromes (MDS) in the medical record.

Pathogen Testing

Rhinovirus detection was performed using a commercial 13-plex multiplex PCR kit (Hai'er Shi Gene Technology, 1060071) capable of simultaneous identification of respiratory pathogens including: influenza A virus (FluA, covering H1N1, H3N2, H5N1, and H7N9), pandemic H1N1, seasonal H3N2, influenza B virus (FluB, covering *Victoria* and *Yamagata*), respiratory syncytial virus (RSV, covering groups A and B), human parainfluenza virus (HPIV, covering types 1–4), human coronaviruses (OC43, HKU1, NL63, and 229E), human metapneumovirus, bocavirus, adenovirus (Groups B, C, and E), as well as atypical bacterial pathogens Chlamydia pneumoniae and Mycoplasma pneumoniae. Detailed information is provided in the Supplementary Information.

In addition to the 13-plex testing, conventional pathogen detection methods were routinely performed as clinically indicated, including conventional bacterial, fungal, and mycobacterial cultures, GeneXpert MTB/RIF detection for *Mycobacterium tuberculosis* [18], RT-PCR for SARS-CoV-2, cytomegalovirus (CMV), and *Pneumocystis jirovecii* [19]. More detailed pathogen detection methods have been published in other study [20].

Cell Line, Virus, and IF Staining

H1-HeLa cells were obtained from ATCC. The positive control was the HRV-B3 strain, isolated from a clinical sample.

To identify rhinovirus in lung tissue, IF staining was performed on 10 μm-thick paraffin-embedded lung tissue sections. Briefly, rhinovirus was detected using a mouse anti-VP3 antibody (Invitrogen, MA5-18249), followed by an HRP-conjugated goat anti-mouse secondary antibody (ZSBIO, PV-6002) and IF488-Tyramide (Servicebio, G1231) for signal amplification. Subsequently, a second round of antigen retrieval was performed to remove the first set of antibodies. Sections were then co-stained for alveolar type 1 (AT1) cells with rabbit anti-AQP5 (Abcam, ab92320) and alveolar type 2 (AT2) cells with rabbit anti-SFTPC (Proteintech, 10774-1-AP), using an HRP-conjugated goat anti-rabbit secondary antibody (ZSBIO, PV-6001) and IF555-Tyramide. Nuclei were counterstained with DAPI, and slides were mounted in 50% glycerol. Images were acquired using a Leica confocal microscope. Detailed information is provided in the Supplementary information.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, and comparisons were made using Pearson's chi-square test or Fisher's exact test. Continuous variables were evaluated for normality through the Shapiro-Wilk test and reported as mean ± standard deviation (for normally distributed data) or median with interquartile range (IQR; for non-normally distributed data), analyzed using Student's *t*-test or Mann-Whitney U test, respectively. To identify risk factors associated with simple rhinovirus pneumonia, both univariable and multivariable logistic regression models were employed. Given that the laboratory tests included in this study did not represent baseline measurements, only demographic characteristics, clinical symptoms, and comorbidities were incorporated into the analysis. Individual comorbidities as well as a composite comorbidity variable underwent evaluation in univariable analysis. Variables with $P < .05$ in the univariate analyses were entered into a multivariable logistic regression model, using stepwise forward selection. A two-sided $\alpha < 0.05$ was deemed statistically significant. Statistical analyses were performed using R version 4.4.2.

RESULTS

Epidemiological Characteristics of HRV Detection in Hospitalized Adult Patients

During the study period, 15 350 clinical specimens from hospitalized patients were screened for HRV infection. After excluding pediatric cases, 12 937 samples from 9544 adult patients were analyzed, including nasopharyngeal swabs (n = 2663), oropharyngeal swabs (n = 2434), BALF (n = 5228), and sputum (n = 2612) (Supplementary Figure 1).

HRV was detected in 501 samples collected from 437 individuals, corresponding to an overall patient-level infection rate of 4.6% (437/9544) and a specimen-level detection rate of 3.9% (501/12 937) (Figure 1*A*). Specimen-specific positivity rates varied significantly: sputum exhibited the highest detection rate (6.3%, 165/2612), followed by nasopharyngeal swabs (3.2%, 84/2663), oropharyngeal swabs (3.7%, 91/2434), and BALF (3.1%, 161/5228) (Figure 1*B*).

HRV infections displayed a distinct seasonal pattern, with bimodal peaks occurring annually during February–April and September–November (Figure 1*C*). Notably, while the absolute number of Rhinovirus-positive cases rose sharply in 2023, the positivity rate remained stable across the study period. Furthermore, no age-dependent increase in HRV detection was observed, with elderly patients (≥65 years) showing comparable infection rates to younger adults.

Pathogen co-detection Patterns and Clearance Dynamics in Hospitalized Patients With HRV Infection

Among the 437 HRV-positive patients, 49.0% (214/437) exhibited pathogen co-infection (Figure 2*A*). Co-infection of with bacterial pathogens alone constituted the predominant pattern (34.1%, 73/214), followed by rhinovirus co-infection with another viral pathogens alone (25.7%, 55/214). Mixed bacterial-fungal co-infections were observed in 7.5% (16/214) of cases. Viral co-pathogen profiling revealed CMV (17.3%, 37/214) as the most prevalent, followed by SARS-CoV-2 (10.7%, 23/214), FluA (6.1%, 13/214), and HPIV (4.7%, 10/214) (Figure 2*B*).

To investigate rhinovirus clearance dynamics, we analyzed 67 hospitalized patients with serial pathogen test results, including 44 with pneumonia and 23 without pneumonia. Among them, 26 patients (38.8%) had persistent rhinovirus positivity (≥2 consecutive positive tests) (Figure 2*C, D*). This subgroup had a median age of 63 years (IQR 55–72), with male predominance (73.1%, 19/26). Comorbidities were prevalent (92.3%, 24/26), including immunocompromised status (38.5%, 10/26) and hematologic malignancies (7.7%, 2/26) (Supplementary Table 1).

Due to the retrospective study design, viral clearance was not systematically monitored. Thus, we compared the interval between the first and last rhinovirus-positive tests as a surrogate for viral persistence. The maximum observed interval reached 24 days. Among pneumonia patients, the median persistence interval was 5 days (IQR 1–9 days), which did not significantly differ from that of non-pneumonia patients (median: 6 days, IQR 5–8 days) (Figure 2*D*).

HRV Can be Detected in LRT Cells via IF Staining

The capacity of HRV to infect the LRT cells in adults remains contentious, largely due to historical limitations in detecting rhinovirus in lower airway samples. Previous studies employing BALF for rhinovirus nucleic acid detection faced criticism over potential contamination from upper respiratory tract specimens or methodological constraints [10]. To address this

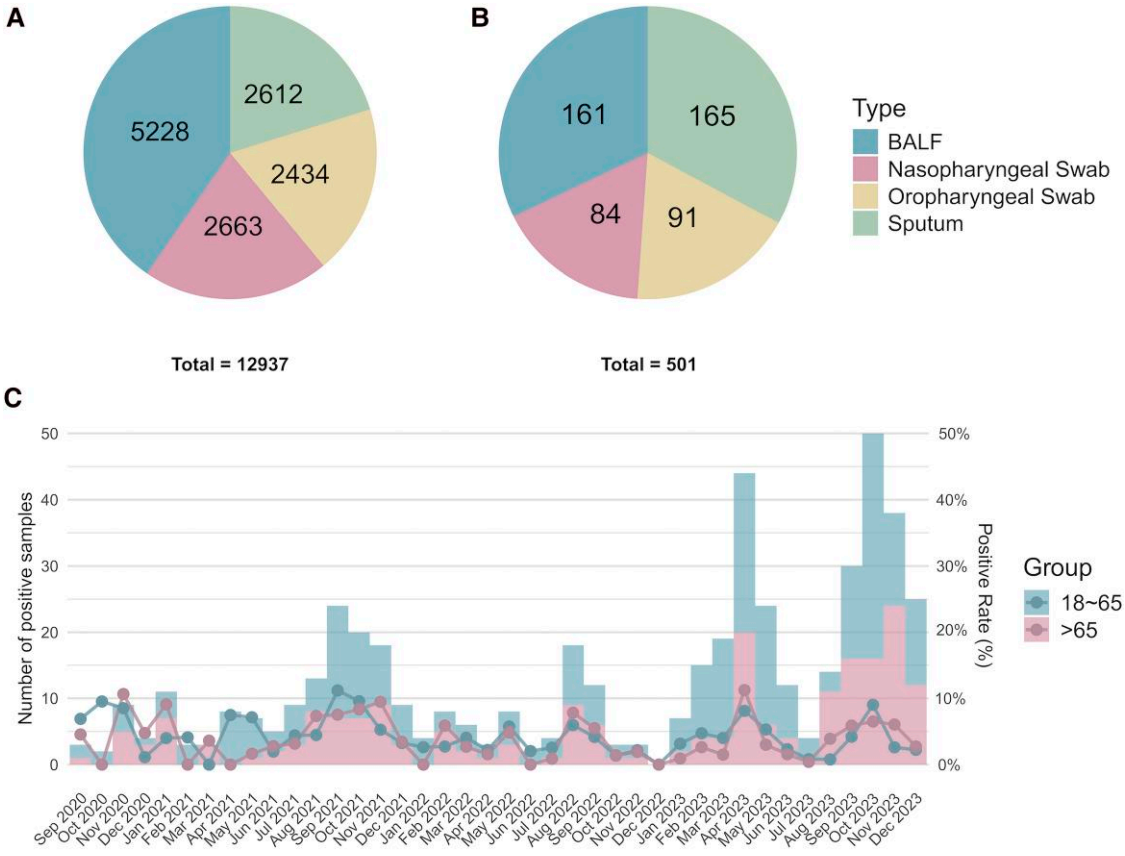

Figure 1. HRV detection in hospitalized adult patients with respiratory symptoms. (*A*) Samples from hospitalized adult patients screened for rhinovirus infection. (*B*) Rhinovirus was detected in 501 samples. (*C*) Monthly distribution of positive tests for (bars) and detection rate of (lines) rhinovirus among patients with acute respiratory tract infection during 2020–2023 by age group.

critical gap, we conducted a paired analysis of BALF and transbronchial lung biopsy (TBLB)/transbronchial cryobiopsy (TBCB) specimens from 13 adults with confirmed rhinovirus RNA detection in BALF. These 13 patients underwent bronchoscopic lung biopsy primarily to characterize the nature of pulmonary nodules or radiographic opacities, or due to clinical suspicion of interstitial lung disease (ILD) (Supplementary Table 2).

IF staining revealed that 61.5% (8/13) of cases displayed intracellular rhinoviral positivity within LRT cells (Figure 3*A*, *B*). Strikingly, viral antigens were additionally detected in both AT1 and AT2 cells (Figure 3*C*, *D*), thereby confirming that HRV can indeed infect tissue cells of the LRT. Positive and negative controls for the IF assay is provided in Supplementary Figure 2.

Clinical Characteristics of Hospitalized Patients With Simple HRV Pneumonia

Among the 437 HRV-positive patients, 224 cases complicated with pneumonia, but only 34 (7.8%) met the diagnostic criteria for simple viral pneumonia (Table 1). We compared the characteristics of the 34 simple rhinovirus pneumonia patients with the 190 non-pneumonia patients. There were no significant differences in age between the groups. However, female patients accounted for a significantly higher proportion in the non-pneumonia group (46.8% vs 20.6%, $P = .008$). Clinical symptoms such as fever (67.6% vs 38.9%, $P = .003$) and cough (88.2% vs 65.2%, $P = .014$) were more frequently reported among pneumonia patients. Though the overall prevalence of comorbidities did not differ significantly between the two groups, diabetes (41.2% vs 20.0%, $P = .013$) was more common in the pneumonia group. Other conditions such as COPD, ILD, bronchiectasis, and immunodeficiency showed no significant differences. Overall, apart from a significantly elevated hsCRP level in the pneumonia group (36.5 vs 6.0 mg/L, $P < .001$), most laboratory parameters were comparable between the two groups.

Risk Factors Associated With Simple HRV-Associated Viral Pneumonia Compared to Non-pneumonia Patients

Multivariate analysis revealed that male was associated with higher odds of pneumonia (OR 2.69, 95% CI 1.04–6.99, $P = .042$), while fever (OR 3.79, 95% CI 1.52–9.44, $P = .004$) and cough (OR 7.33, 95% CI 1.64–32.83, $P = .009$) were significantly associated with increased pneumonia risk (Table 2).

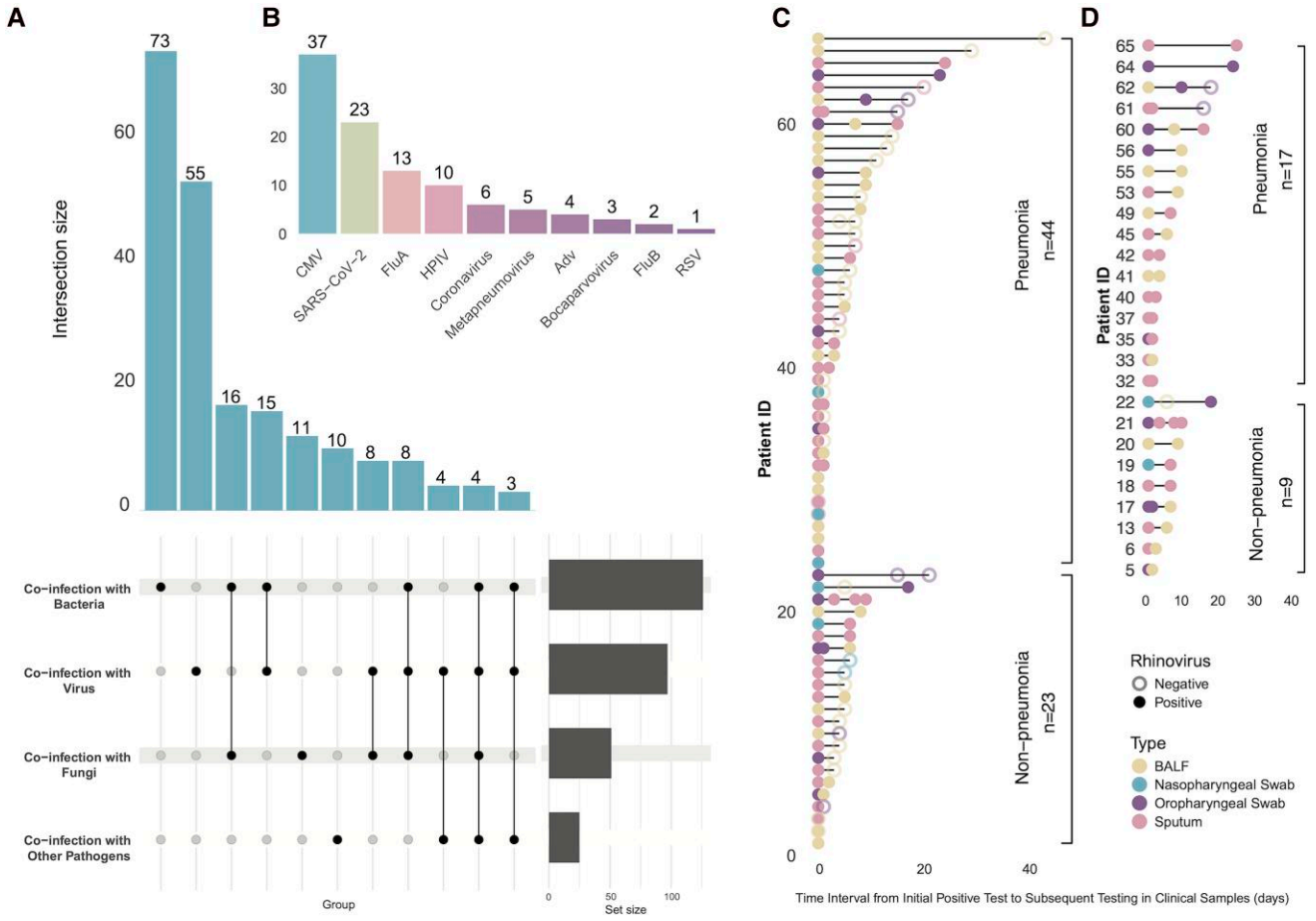

Figure 2. Pathogen co-detection patterns and clearance dynamics in hospitalized patients with *rhinovirus* infection. (*A*) Pathogen co-detection patterns. Only intersections involving at least three patients (min size ≥ 3) are displayed. (*B*) Viral co-pathogen profiling. (*C*) Rhinovirus clearance dynamics among 67 patients with serial pathogen test results. (*D*) Rhinovirus clearance dynamics among 26 patients (38.8%) with ≥2 consecutive positive tests. FluA, influenza A virus; HPIV, human parainfluenza virus; FluB, influenza B virus; CMV, cytomegalovirus; RSV, respiratory syncytial virus.

DISCUSSION

This study provides novel insights into the clinical impact of HRV infections in hospitalized adults, challenging traditional paradigms through direct evidence of LRT involvement. Our findings demonstrate that HRV is not merely an upper respiratory pathogen but plays a significant role in adult lower airway disease.

The significant role of HRV in severe LRT infections is increasingly recognized. In pediatric populations, HRV is one of the frequently identified pathogen in cases of community-acquired pneumonia (CAP) [21]. HRV infection is also strongly associated with acute bronchiolitis and respiratory failure, highlighting its potential to cause substantial morbidity [22]. In our study, approximately 3.9% of hospitalized adult patients tested positive for HRV, consistent with earlier reports [23]. Our IF data provide the first definitive evidence of rhinovirus infecting alveolar epithelium in immunocompetent adults (Figure 3). The co-localization of VP3 protein with both AT1 ($AQP5^+$) and AT2 (SPC^+) cells demonstrates dual alveolar tropism [24], potentially explaining the 7.8% incidence of rhinovirus-attributable pneumonia. This resolves longstanding controversies about PCR detection in BALF, confirming that positive results reflect true infection rather than upper airway contamination.

The observed bimodal seasonal peaks (February–April and September–November) in northern China, while seemingly paradoxical given the virus's renowned stability in cooler temperatures, can be explained by the influence of population immunity and contact patterns [25, 26]. The autumn peak coincides with the reopening of schools, which concentrates susceptible children and facilitates transmission. The spring peak follows the decline of major winter viruses (eg, influenza), reducing competition and allowing HRV to resurge. Thus, HRV seasonality is primarily a consequence of social dynamics and immune cycling, with temperature acting as a contributing factor rather than the sole determinant.

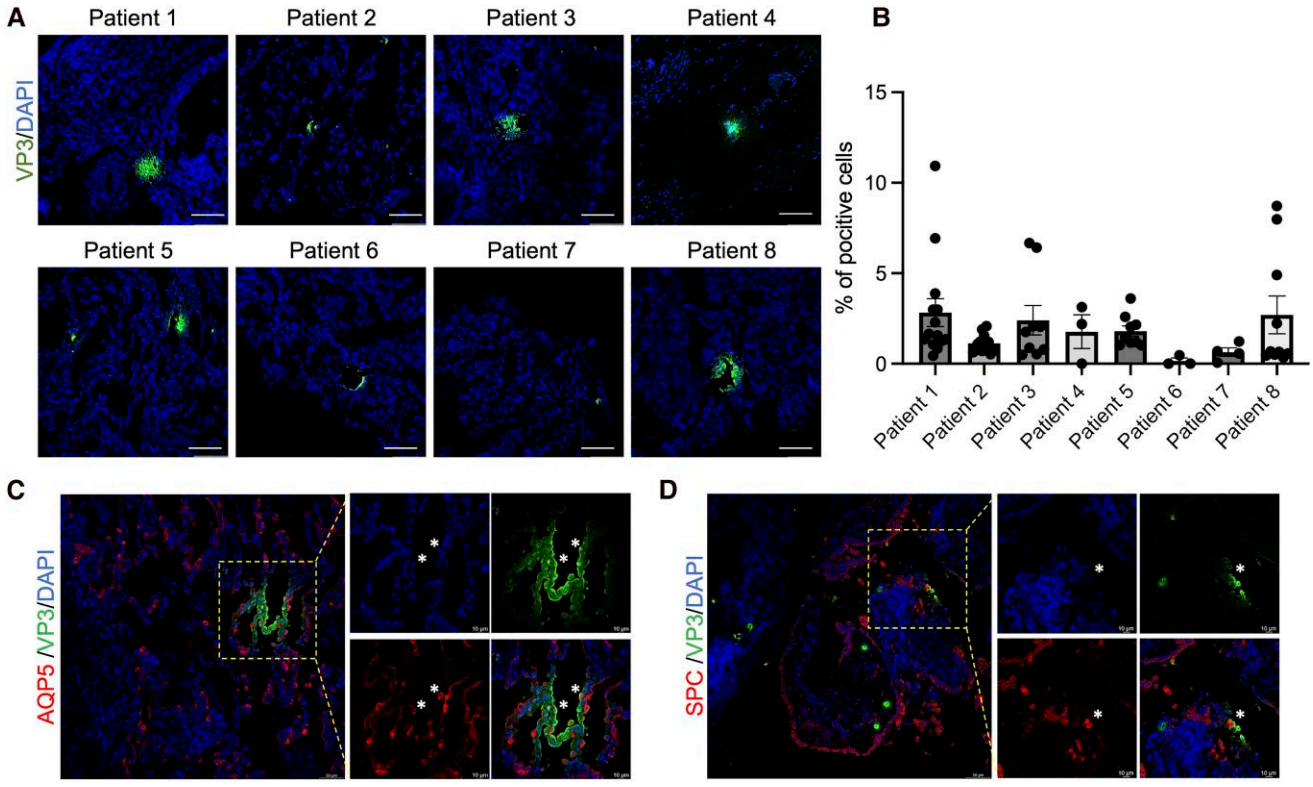

Figure 3. Rhinovirus can be detected in the lower respiratory tract cells. (*A*) Representative confocal images show the VP3 expression in human lung samples. Biopsy samples were obtained from individuals who tested positive for rhinovirus in BALF samples. VP3 protein was detected in 8 out of 13 patients. VP3, rhinovirus (green); DAPI, nuclear (blue). Scale bar, 100 μm. (*B*) To quantify the percentage of VP3 positive cells, the total cell count was determined by identifying DAPI positive cells using Image J. The percentage was then calculated as the ratio of VP3 positive cells to the total DAPI positive cells, with each patient sample analyzed individually. (*C, D*) HRV VP3 protein is co-localized with human AT1 and AT2 cells. The asterisks indicated the co-localization of VP3 with SPC or AQP5. VP3, rhinovirus (green); SPC, AT2 cells (red); AQP5, AT1 cells (red); DAPI, nuclear (blue). Scale bar, 50 μm (left) and 10 μm (right).

The high co-infection rate (49.0%) underscores rhinovirus's role as both a primary pathogen and a facilitator of secondary infections [27]. The study identified the most common co-infecting pathogens were bacteria, likely reflecting rhinovirus-induced epithelial damage that enhances bacterial adherence [23, 28]. A recent study revealed that asymptomatic HRV infection in adults that could increase the risk of subsequent *pneumococcus* infection [29]. The unexpected prevalence of CMV co-infection in our cohort may relate to the high proportion of immunocompromised patients (38.5% in persistent infection subgroup), suggesting synergistic viral interactions in immunosuppressed hosts. These findings emphasize the need for comprehensive pathogen screening in severe cases.

The presence of viral antigen in both AT1 and AT2 pneumocytes suggests a potential for dual alveolar tropism. Although receptors primarily utilized by HRV such as ICAM-1 (for HRV-A and -B) and CDHR3 (for HRV-C), are predominantly expressed in the upper airways and are present at low levels in the alveoli under physiological conditions, their expression on alveolar epithelial cells may be upregulated in the context of respiratory inflammation. Inflammatory cytokines released during infection can enhance the surface expression of ICAM-1, potentially facilitating viral entry into alveolar cells [30]. Nevertheless, whether individuals with compromised epithelial barriers are indeed more susceptible to HRV-associated pneumonia remains a subject for further large cohort investigation.

The association between simple rhinovirus pneumonia development and male sex, fever, and cough suggests sex-specific immune responses and symptom-driven diagnostic biases. It should be noted that in univariate analysis, diabetes and CKD appeared to be potential risk factors for simple rhinovirus pneumonia. However, they did not remain significant independent predictors after multivariate adjustment. This finding likely reflects the complex interplay between diabetes, CKD, and other host factors. Metabolic disturbances associated with these conditions may impair immune defenses and increase overall susceptibility to infection. Moreover, the relatively small sample size of the simple rhinovirus pneumonia group may have limited the statistical power. Future studies with larger cohorts are needed to further elucidate the roles of diabetes and CKD in the pathogenesis of simple rhinovirus pneumonia.

The prolonged rhinovirus detection (up to 24 days) in serially tested patients raises critical questions about viral-host dynamics. Notably, rhinovirus RNA persistence exceeding one

Table 1. Characteristics of People With Rhinovirus

	All N = 437	Single rhinovirus infection		P
		Non-pneumonia N = 190	Pneumonia N = 34	
Age, year	63.0 (54.0–70.0)	59.5 (52.0–68.0)	59.5 (46.8–67.8)	.651
Female sex	171 (39.1%)	89 (46.8%)	7 (20.6%)	.008
Fever	225 (51.5%)	74 (38.9%)	23 (67.6%)	.003
Sore throat	33 (7.6%)	17 (8.9%)	5 (14.7%)	.344
Cough	304 69.3%)	124 (65.2%)	30 (88.2%)	.014
Sputum	277 (63.4%)	106 (55.8%)	25 (73.5%)	.081
Diarrhea	15 (3.4%)	6 (3.2%)	4 (11.8%)	.048
Comorbidities	379 (86.7%)	168 (88.4%)	27 (79.4%)	.166
COPD	59 (13.7%)	26 (13.7%)	1 (2.9%)	.089
Asthma	22 (5.1%)	13 (6.8%)	0 (0.0%)	.226
ILD	127 (29.5%)	58 (30.5%)	10 (29.4%)	1.000
Bronchiectasis	11 (2.6%)	5 (2.7%)	1 (3.0%)	1.000
Immunodeficiency	130 (30.2%)	54 (28.4%)	9 (26.5%)	.979
Lung cancer	36 (8.4%)	18 (9.5%)	3 (8.8%)	1.000
CHD	73 (16.9%)	31 (15.8%)	6 (17.6%)	1.000
Hypertension	138 (31.8%)	58 (30.5%)	10 (29.4%)	1.000
Diabetes	107 (24.9%)	38 (20.0%)	14 (41.2%)	.013
HBV	15 (3.5%)	8 (4.2%)	3 (8.8%)	.223
Hematologic malignancy	29 (6.8%)	14 (7.4%)	0 (0.0%)	.136
CKD	37 (8.6%)	12 (6.3%)	6 (17.6%)	.037
Laboratory characteristics	…	…	…	…
WBC ($\times 10^9$/L)	7.3 (5.3–9.8)	6.8 (5.4–8.9)	7.6 (5.4–9.7)	.236
Neutrophils ($\times 10^9$/L)	4.9 (3.4–7.6)	4.4 (3.2–6.1)	5.3 (3.8–8.3)	.058
Lymphocytes ($\times 10^9$/L)	1.3 (0.8–1.8)	1.4 (0.9–1.9)	1.3 (0.9–1.7)	.225
Platelets ($\times 10^9$/L)	212.0 (156.0–268.0)	221.0 (168.0–260.0)	212.0 (173.2–266.2)	.785
hsCRP (mg/L)	14.5 (3.0–62.4)	6.0 (2.5–28.5)	36.5 (6.5–75.4)	< .001
PCT (ng/mL)	0.2 (0.1–0.2)	0.2 (0.1–0.2)	0.2 (0.2–0.2)	.176
ALT (U/L)	21.0 (13.0–35.0)	21.0 (15.0–32.0)	25.0 (15.0–52.0)	.239
AST (U/L)	21.0 (17.0–31.0)	20.0 (17.0–28.0)	26.0 (16.0–36.0)	.210
BUN (mmol/L)	5.7 (4.1–7.6)	5.4 (4.1–6.8)	4.3 (3.6–7.8)	.483
PT(s)	13.5 (13.1–14.4)	13.4 (13.0–14.1)	13.9 (13.1–14.6)	.091
APTT (s)	37.6 (33.9–42.5)	36.8 (33.0–40.3)	37.8 (35.0–47.3)	.029
D-Dimer (mg/L)	0.7 (0.3–1.7)	0.4 (0.2–1.2)	0.8 (0.3–1.3)	.310

Laboratory results were obtained from the test performed closest to the time of rhinovirus-positive detection.

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CHD, coronary heart disease; HBV, hepatitis B virus infection; CKD, chronic kidney disease; APTT, activated partial thromboplastin time; FDP, fibrin degradation products.

month (34 days) has been documented even in immunocompetent adults [31], challenging the paradigm of transient upper respiratory tract infection. Viral clearance dynamics directly reflect host immune competence, as demonstrated by the striking disparity in mean shedding duration between hypogammaglobulinemia patients (31.5 days) and immunocompetent controls (10.9 days) [32]. However, in line with Peltola's finding [32], immunodeficiency was not an independent predictor for acquiring simple rhinovirus pneumonia. This suggests that the progression to pneumonia likely depends on additional host and viral factors beyond shedding duration alone.

This study has several limitations. First, the retrospective design precludes definitive causal attribution of pneumonia to rhinovirus alone. Second, we are unable to quantify the viral load or determine the specific HRV subspecies. Given the well-documented association between different HRV species and varying clinical outcomes, the absence of this genotyping data prevents us from establishing whether specific viral subtypes are disproportionately associated with the development of severe pneumonia. Future studies incorporating quantitative viral load measurements and precise viral genotyping will be essential to validate our pathological findings and to better elucidate the virological and host factors driving severe HRV-associated pulmonary complications. Third, potential blood-borne dissemination and extrapulmonary impacts remain unexplored. Emerging evidence challenges the traditional view of rhinovirus as a locally restricted pathogen, with studies detecting rhinoviral RNA in plasma—particularly among pediatric populations [33]. Prospective cohorts with serial virologic/immunologic profiling are needed to clarify pathogenesis.

Table 2. Risk Factors Associated With Simple HRV Pneumonia Compared to Non-pneumonia Patients

	Univariate		Multivariate	
Variables	OR (95%CI)	*P*	OR (95%CI)	*P*
Age	0.99 (0.97–1.01)	.399	…	
Male	3.40 (1.41–8.18)	.006	2.69 (1.04–6.99)	.042
Fever	3.42 (1.54–7.60)	.003	3.79 (1.52–9.44)	.004
Sore throat	1.75 (0.60–5.14)	.229	…	…
Cough	4.84 (1.42–16.49)	.012	7.33 (1.64–32.83)	.009
Sputum	2.30 (0.98–5.37)	.054	…	…
Diarrhea	4.37 (1.16–16.50)	.030	1.70 (0.29–9.95)	.556
Comorbidities	0.51 (0.20–1.30)	.156	…	…
COPD	0.19 (0.03–1.49)	.115	…	…
Asthma	0.00 (0.00-Inf)	.988	…	…
ILD	0.97 (0.43–2.16)	.935	…	…
Bronchiectasis	1.14 (0.13–10.06)	.908	…	…
Immunodeficiency	0.93 (0.41–2.13)	.865	…	…
Lung cancer	0.94 (.26–3.39)	.923	…	…
CHD	1.13 (.43–2.95)	.810	…	…
Hypertension	.93 (.42–2.08)	.867	…	…
Diabetes	2.74 (1.27–5.93)	.010	2.26 (0.86–5.96)	.099
HBV	2.24 (.56–8.91)	.253	…	…
Hematologic malignancy	.00 (.00-Inf)	.988	…	…
CKD	3.24 (1.12–9.36)	.030	1.29 (0.32–5.20)	.716

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CHD, coronary heart disease; HBV, hepatitis B virus infection; CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval.

Fourth, while the cohort of patients with available lung tissue biopsies is small (n = 13), it is critical to acknowledge that our study is uniquely positioned to provide direct histological evidence of LRT HRV infection.

In conclusion, our findings redefine rhinovirus as a dual respiratory tract pathogen capable of causing lower airway disease in adults. The detection of viral antigens in LRT cells, combined with distinct clinical risk profiles, mandates a paradigm shift in managing rhinovirus infections—from dismissive symptomatic treatment to targeted surveillance in high-risk populations. Future research should prioritize antiviral development and investigate mechanisms underlying sex differences in disease severity.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Financial support. This work was supported by the funds of Beijing Nova Program under grant NO.20220484049, National Natural Science Foundation of China (NSFC, NO.82030002/H0104), the National High Level Hospital Clinical Research, the Elite Medical Professionals Project of China-Japan Friendship Hospital (No. ZRJY2021-QM09) and New Cornerstone Science Foundation.

Author Contributions. Rongling Zhang, Xiao Shang, and Chunlei Wang contributed equally to this work as co-first authors.

Bin Cao and Hui Li conceptualized the study, acquired funding, and served as guarantors responsible for the overall content. Rongling Zhang, Xiao Shang, and Chunlei Wang drafted the initial manuscript and performed formal data analysis. Nana Liu, Xiaochen Shen, Zeyi Wang, Fei Zhou, and Jiuyang Xu contributed to clinical data curation and validation. Xiao Shang, Xiaochen Shen, and Dingrong Zhong designed and executed immunofluorescence staining experiments. Hong Zhou contributed to this study by performing the isolation of HRV from clinical samples.

All authors critically revised the manuscript for intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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