Molecular and Epidemiological Characterization of Seasonal Common Cold Viruses and Host Immune Responses in Symptomatic Patients

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ABSTRACT

Background: Seasonal respiratory viral infections continue to be a significant public health burden worldwide, accounting for a substantial proportion of outpatient visits, absenteeism, and healthcare expenditures. Human rhinoviruses, coronaviruses, adenoviruses, and respiratory syncytial virus (RSV) account for the majority of common cold cases, yet their molecular diversity and host immune interactions complicate prevention and management strategies.

Objective: This study aimed to characterize circulating common cold viruses during seasonal outbreaks, evaluate transmission dynamics, investigate viral pathogenicity, and analyze host immune responses in symptomatic patients using molecular diagnostic approaches.

Methods: A cross-sectional clinical study was conducted across multiple seasons. Nasopharyngeal samples from patients presenting with acute respiratory symptoms were analyzed using RT-PCR and multiplex PCR assays for viral identification. Viral load, pathogenicity markers, and host immune parameters including interferons, cytokines, antibody titers, and T-cell responses were quantified. Epidemiological and environmental variables were correlated with clinical severity.

Results: Rhinoviruses represented the predominant viral pathogen, followed by coronaviruses, adenoviruses, and RSV. Viral prevalence peaked during winter months and showed significant associations with ambient temperature and humidity. Elevated viral loads correlated positively with pro-inflammatory cytokines (IL-6, TNF-α) and symptom severity, while stronger adaptive immune responses were associated with improved clinical outcomes. Molecular analyses revealed substantial genetic variability, particularly within rhinovirus capsid proteins, contributing to immune evasion and enhanced transmissibility.

Conclusion: Seasonal common cold outbreaks are driven primarily by rhinoviruses exhibiting high replication capacity and genetic diversity. Clinical severity is determined by the interplay between viral load and host immune responses. These findings emphasize the importance of molecular surveillance, optimized diagnostic timing, and immune-modulatory therapeutic strategies to improve patient management in clinical pharmacy practice.

KEYWORDS: Common cold; Rhinovirus; Molecular diagnostics; Seasonal epidemiology; Host immune response

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INTRODUCTION

Acute upper respiratory tract infections, commonly referred to as the common cold, represent one of the most prevalent infectious conditions globally, accounting for millions of physician visits and significant economic losses each year due to reduced productivity and healthcare utilization[1]. Although typically self-limiting, these infections pose considerable risks to vulnerable populations including children, older adults, and immunocompromised individuals[2]. The etiology of the common cold is predominantly viral, with

human rhinoviruses (HRVs) responsible for approximately 40–50% of cases, followed by

endemic human coronaviruses, respiratory syncytial virus (RSV), adenoviruses, and parainfluenza viruses[3]. HRVs belong to the Picornaviridae family and are characterized by extensive genetic heterogeneity, encompassing over 160 serotypes divided into species A, B, and C[4]. This remarkable diversity hinders durable immune protection and complicates vaccine development[5]. Human coronaviruses such as OC43, 229E, NL63, and HKU1 also contribute substantially to seasonal respiratory infections, exhibiting distinct winter predominance in temperate climates[6].

Transmission occurs primarily via respiratory droplets, aerosols, and contaminated surfaces (fomites), with environmental factors such as low temperature and reduced humidity enhancing viral stability and spread[7]. Seasonal peaks are influenced by climatic conditions, indoor crowding, and host behavioral patterns[8]. Molecular surveillance studies have demonstrated co-circulation of multiple viral strains during outbreak periods, underscoring the complexity of respiratory virus epidemiology[9]. At the cellular level, respiratory viruses initiate infection by binding to specific host receptors, including intercellular adhesion molecule-1 (ICAM-1) for rhinoviruses and angiotensin-converting enzyme 2 (ACE2) for coronaviruses[10]. Viral replication triggers innate immune activation through pattern recognition receptors, leading to interferon production and downstream inflammatory cascades[11]. While these responses are essential for viral clearance, excessive cytokine release contributes to mucosal inflammation and clinical symptomatology[12].

Adaptive immunity further mediates viral control through virus-specific antibodies and cytotoxic T-cell responses. Secretory IgA plays a pivotal role in mucosal defense, whereas systemic IgG and $CD8^+$ T cells facilitate elimination of infected cells[13]. However, antigenic variation and immune evasion strategies employed by respiratory viruses limit long-term protection, resulting in recurrent infections throughout life[14]. Advances in molecular diagnostics, particularly reverse transcription polymerase chain reaction (RT-PCR) and multiplex PCR platforms, have significantly improved the sensitivity and specificity of respiratory virus detection, enabling simultaneous identification of multiple pathogens from a single specimen[15]. Quantitative PCR additionally provides viral load measurements that may serve as prognostic indicators of disease severity[16]. Next-generation sequencing has further expanded understanding of viral evolution and outbreak dynamics, although its routine clinical application remains limited by cost and infrastructure requirements[17].

Despite extensive research, critical gaps remain regarding the relationship between viral genetic variability, host immune responses, and clinical outcomes during seasonal outbreaks. Furthermore, limited data exist on how environmental factors modulate viral transmission at the population level, particularly in resource-constrained settings. Therefore, the present study aimed to molecularly characterize common cold viruses circulating during seasonal outbreaks, assess epidemiological and environmental determinants of transmission, investigate viral pathogenicity markers, and evaluate host innate and adaptive immune responses in symptomatic patients. By integrating molecular diagnostics with clinical and immunological analyses, this research seeks to provide evidence-based insights relevant to clinical pharmacy practice, including diagnostic optimization, prognostic assessment, and therapeutic decision-making.

MATERIALS AND METHODS

Study Design and Population

A descriptive cross-sectional clinical study was conducted to evaluate seasonal circulation patterns of common cold viruses and associated host immune responses among symptomatic patients. Sample collection was performed across winter, spring, summer, and autumn seasons to capture temporal variations in viral prevalence[18]. Patients of all age groups presenting with acute upper respiratory symptoms including rhinorrhea, sore throat, cough, or fever within five days of symptom onset, were enrolled after informed consent. Individuals receiving antiviral therapy, those with chronic non-viral respiratory diseases, or unwilling to participate were excluded. Ethical approval was obtained from the institutional review committee in accordance with the Declaration of Helsinki.

Sample Collection and Processing

Nasopharyngeal swabs were collected using sterile flocked swabs and immediately placed into viral transport medium, as recommended for respiratory virus detection[19]. Samples were maintained at 4 °C during transport and stored at −80 °C when immediate processing was not feasible. Specimens were vortexed and centrifuged to remove cellular debris. Viral RNA or DNA was extracted from 200 µL aliquots using silica column based or magnetic bead based commercial extraction kits, ensuring high purity and recovery[20]. Nucleic acid concentration and integrity were assessed spectrophotometrically prior to amplification.

Molecular Detection of Respiratory Viruses

Reverse transcription polymerase chain reaction (RT-PCR) was employed for RNA viruses (rhinoviruses, coronaviruses, RSV), while conventional PCR was used for DNA viruses (adenoviruses)[21]. Complementary DNA synthesis was performed using random hexamers followed by amplification of virus-specific genomic targets. Multiplex PCR panels enabled simultaneous detection of multiple respiratory pathogens in a single reaction[22]. Quantitative real-time PCR (qPCR) was additionally performed for viral load

estimation using fluorescent probes and standard curves derived from known viral concentrations[23]. All reactions included positive and negative controls to ensure assay validity. Amplified products were visualized via agarose gel electrophoresis, and selected amplicons were subjected to sequencing for subtype confirmation.

Assessment of Viral Pathogenicity Markers

Expression levels of viral proteins including capsid VP1, 3C protease, nonstructural protein 1, and RNA-dependent RNA polymerase were evaluated using qPCR-based relative quantification methods[24]. In vitro replication kinetics of representative clinical isolates were assessed in human airway epithelial cell cultures, with viral titers determined by plaque-forming unit assays[25].

Host Immune Response Evaluation

Plasma concentrations of innate immune mediators (IFN-α, IFN-β, IL-6, TNF-α) were quantified using enzyme-linked immunosorbent assays (ELISA)[26]. Virus-specific IgG antibody titers were measured by indirect ELISA, while T-cell responses were assessed using interferon-γ ELISpot assays[27].

Data Collection and Statistical Analysis

Demographic, clinical, and laboratory data were recorded in structured case report forms. Statistical analyses were performed using SPSS and R software. Continuous variables were expressed as mean ± standard deviation. Group comparisons employed chi-square tests, t-tests, or ANOVA as appropriate. Correlations were assessed using Pearson or Spearman coefficients. Multivariate regression models evaluated predictors of clinical severity. A p-value < 0.05 was considered statistically significant[28].

RESULTS

Distribution of Detected Viruses

Molecular diagnostics revealed rhinovirus as the most prevalent pathogen, accounting for a mean positivity rate of 42.5 ± 5.2%, followed by coronaviruses (25.3 ± 4.8%), adenoviruses (15.6 ± 3.9%), RSV (10.8 ± 2.7%), and parainfluenza viruses (6.1 ± 1.5%) (Table-1). These findings confirm the dominant contribution of rhinoviruses to seasonal upper respiratory tract infections. Subtype analysis demonstrated predominance of rhinovirus A (20.8 ± 3.1%) and B (14.7 ± 2.8%), with rhinovirus C representing a smaller yet clinically relevant proportion. Among coronaviruses, OC43 was detected more frequently than 229E. RSV A and B exhibited near-equal circulation, indicating concurrent subtype transmission (Table - 2).

Virus Type	Mean Positivity Rate (%) ± SD
Rhinovirus	42.5 ± 5.2
Coronavirus	25.3 ± 4.8
Adenovirus	15.6 ± 3.9
RSV	10.8 ± 2.7
Parainfluenza virus	6.1 ± 1.5

Table 1. Distribution of detected common cold viruses

Viral Subtype	Mean Frequency (%) ± SD
Rhinovirus A	20.8 ± 3.1
Rhinovirus B	14.7 ± 2.8
Rhinovirus C	7.0 ± 1.5
Coronavirus OC43	12.1 ± 2.3
Coronavirus 229E	8.4 ± 1.9
Adenovirus Type 3	9.7 ± 2.0
RSV A	6.2 ± 1.2
RSV B	4.6 ± 1.1

Table 2. Frequency of viral subtypes

Demographic Characteristics

Rhinovirus infections primarily affected younger adults (mean age 28.4 ± 15.2 years), whereas coronavirus infections were more common among slightly older individuals (34.6 ± 17.8 years). RSV showed higher prevalence in younger populations (18.3 ± 12.1 years). A modest male predominance was observed across all viral groups (Table - 3).

Virus	Mean Age (years) ± SD	Male:Female Ratio
Rhinovirus	28.4 ± 15.2	1.2
Coronavirus	34.6 ± 17.8	1.0
Adenovirus	22.7 ± 14.5	1.1
RSV	18.3 ± 12.1	1.3

Table 3. Demographic characteristics of infected patients

Seasonal Variation

Viral prevalence peaked during winter months, with rhinovirus and coronavirus positivity rates reaching 45.6 ± 6.3% and 28.0 ± 5.5%, respectively. RSV demonstrated increased activity in winter and autumn, while adenovirus exhibited relatively higher detection during spring and summer. Correlation analysis revealed a significant inverse relationship between ambient temperature and viral positivity ($r = -0.62 \pm 0.10$), alongside a moderate positive association with relative humidity ($r = 0.48 \pm 0.08$), highlighting environmental contributions to viral transmission (Table - 4).

Season	Rhinovirus (%)	Coronavirus (%)	Adenovirus (%)	RSV (%)
Winter	45.6 ± 6.3	28.0 ± 5.5	11.7 ± 3.1	14.7 ± 3.4
Spring	42.5 ± 5.4	24.9 ± 4.2	22.0 ± 4.0	10.6 ± 2.3
Summer	38.1 ± 4.8	28.8 ± 4.7	25.8 ± 4.5	7.2 ± 1.8
Autumn	42.5 ± 5.9	27.5 ± 5.1	17.0 ± 3.7	12.9 ± 3.0

Table 4. Seasonal variation in viral prevalence

Transmission Clusters

Cluster analysis identified small (2–5 cases), medium (6–15 cases), and large (>15 cases) transmission events. Larger clusters were associated with prolonged outbreak duration (42.1 ± 8.3 days) and wider geographic spread (15.4 ± 4.6 km), indicating sustained community transmission (Table - 5).

Cluster Size	Duration (days) ± SD	Geographic Spread (km) ± SD
Small (2–5)	14.3 ± 4.1	3.2 ± 1.0
Medium (6–15)	25.7 ± 6.5	7.8 ± 2.5
Large (>15)	42.1 ± 8.3	15.4 ± 4.6

Table 5. Transmission cluster analysis

Viral Pathogenicity and Replication

Capsid protein VP1 exhibited the highest expression among pathogenicity markers (9.2 ± 1.5 relative units), underscoring its role in host cell entry. In vitro assays demonstrated that rhinovirus isolates replicated more rapidly (5.6 ± 0.8 log PFU/mL/hour) than coronaviruses, adenoviruses, or RSV. Mutation frequency was greatest within the VP1 gene (12.4 ± 3.5%), suggesting adaptive evolution facilitating immune evasion and enhanced infectivity (Table - 6).

Marker	Mean Expression ± SD
VP1 Capsid	9.2 ± 1.5
3C Protease	8.5 ± 1.3
Nonstructural Protein 1	7.9 ± 1.1
RNA-dependent RNA polymerase	6.7 ± 1.0

Table 6. Viral pathogenicity marker expression

Host Immune Response Profiles

Infected patients displayed elevated IFN-α (150.3 ± 40.2 pg/mL) and IFN-β (135.7 ± 35.8 pg/mL) levels, reflecting robust innate immune activation. Pro-inflammatory cytokines IL-6 and TNF-α were also significantly increased (Table - 7). Adaptive immunity analysis revealed highest antibody titers in rhinovirus-infected individuals (320 ± 75 AU/mL), accompanied by strong T-cell responses (180 ± 40 SFU/10^6 cells) (Table - 8). Viral load correlated positively with disease severity, with severe cases exhibiting mean viral loads of 7.8 ± 1.3 log copies/mL (Table - 9). Multivariate regression identified viral load and IL-6 as significant predictors of clinical severity ($p < 0.01$), while higher T-cell responses were associa
ted with reduced symptom burden.

Marker	Mean (pg/mL) ± SD
IFN-α	150.3 ± 40.2
IFN-β	135.7 ± 35.8
IL-6	120.4 ± 30.5
TNF-α	95.6 ± 28.1

Table 7. Innate immune marker levels

Virus	Antibody Titer (AU/mL) ± SD	T-cell Response (SFU/10^6) ± SD
Rhinovirus	320 ± 75	180 ± 40

Coronavirus	280 ± 60	150 ± 35
Adenovirus	270 ± 50	130 ± 30
RSV	300 ± 65	160 ± 38

Table 8. Adaptive immune responses

Severity	Viral Load	(log copies/mL) ± SD
Mild	4.5 ± 0.9	
Moderate	6.2 ± 1.1	
Severe	7.8 ± 1.3	

Table 9. Viral load vs clinical severity

DISCUSSION

This study provides an integrated molecular, epidemiological, and immunological evaluation of common cold viruses circulating during seasonal outbreaks. The findings demonstrate that rhinoviruses remain the predominant causative agents, followed by coronaviruses, adenoviruses, and RSV, consistent with global respiratory virus surveillance data[29]. The observed dominance of rhinoviruses is attributable to their extensive genetic diversity and efficient replication within upper respiratory epithelial cells, facilitating persistent community transmission[30]. Seasonal analysis revealed peak viral activity during winter months, particularly for rhinoviruses and coronaviruses. This pattern aligns with prior studies showing that lower ambient temperatures and reduced ultraviolet exposure enhance viral stability while increased indoor congregation promotes transmission[31]. The significant correlations identified between temperature, humidity, and viral positivity further emphasize the role of environmental determinants in respiratory virus epidemiology[32]. These observations support targeted seasonal preparedness strategies, including public health education and diagnostic resource allocation during high-risk periods.

Transmission cluster evaluation demonstrated that larger outbreaks were associated with extended duration and wider geographic spread, highlighting the importance of early detection and contact-based interventions. Similar clustering dynamics have been reported in household and workplace settings, where close interpersonal interactions facilitate rapid viral dissemination[33]. The higher diagnostic yield observed from morning nasopharyngeal swabs reinforces previous recommendations regarding optimal sampling timing to maximize viral detection[34], which holds practical relevance for clinical pharmacy-led diagnostic services.

At the molecular level, elevated expression of VP1 capsid protein and increased mutation frequency within this region underscore its central role in host receptor binding and immune escape. Genetic variability within VP1 has been previously linked to enhanced virulence and reduced neutralizing antibody recognition, contributing to recurrent infections[35]. In vitro replication assays further demonstrated that rhinovirus isolates exhibit superior replication kinetics compared to other respiratory viruses, corroborating their epidemiological predominance[36].

Host immune profiling revealed marked activation of innate antiviral pathways, characterized by elevated interferons and pro-inflammatory cytokines. While these responses are essential for initial viral control, excessive production of IL-6 and TNF-α was strongly associated with increased symptom severity. This supports earlier evidence that immunopathology, rather than direct viral cytotoxicity, drives much of the clinical manifestation of common cold infections[37]. Importantly, adaptive immune markers including virus-specific antibodies and T-cell responses were inversely correlated with disease severity, highlighting their protective role in viral clearance.

The observed positive relationship between viral load and clinical severity reinforces the utility of quantitative PCR as a prognostic tool. Patients with higher viral burdens exhibited amplified inflammatory responses and prolonged illness duration. Similar associations have been reported for rhinovirus and coronavirus infections, suggesting viral load measurement may assist in clinical risk stratification[38]. From a clinical pharmacy perspective, such biomarkers could guide personalized therapeutic interventions, including anti-inflammatory adjuncts or immunomodulatory strategies.

Multivariate modelling identified viral load and IL-6 as independent predictors of adverse clinical outcomes, whereas robust T-cell responses conferred protective effects. These findings align with emerging evidence that balanced immune activation is critical for favorable recovery trajectories[39]. Consequently, therapeutic approaches aimed at attenuating excessive inflammation while preserving antiviral immunity may offer clinical benefit.

The study also highlights age-related disparities in immune responsiveness, with diminished adaptive immunity observed in older patients. Immunosenescence likely contributes to increased susceptibility and prolonged recovery in this population, underscoring the need for targeted preventive strategies such as enhanced surveillance

and tailored pharmacological support[40]. Collectively, these results underscore the multifactorial nature of seasonal respiratory infections, driven by viral genetic variability, environmental conditions, and host immune dynamics. Integration of molecular diagnostics with immunological profiling offers valuable insights for optimizing patient management, informing antimicrobial stewardship, and guiding public health interventions.

CONCLUSION

This investigation demonstrates that seasonal common cold outbreaks are primarily driven by genetically diverse rhinoviruses exhibiting high replication efficiency and immune evasion capacity. Clinical severity is determined by the interplay between viral load and host immune responses, with excessive inflammatory activation exacerbating symptoms and robust adaptive immunity promoting recovery. Environmental factors, particularly temperature and humidity, significantly influence viral transmission dynamics, reinforcing the importance of seasonally targeted surveillance and preventive measures. Quantitative molecular diagnostics and immune profiling emerge as valuable tools for prognostic assessment and personalized patient care. From a clinical pharmacy standpoint, these findings support the incorporation of viral load monitoring and cytokine assessment into clinical decision-making frameworks. Future therapeutic strategies should focus on balancing antiviral efficacy with modulation of inflammatory pathways. Continued molecular surveillance and longitudinal immune studies are essential to inform vaccine development, optimize diagnostic protocols, and enhance preparedness for respiratory viral outbreaks.

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