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Research Article

Immunological Characteristics of Acute Respiratory Viral Infections in Infants and Young Children

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A B S T R A C T

Introduction: Acute respiratory viral infections (ARVIs) are a leading global cause of paediatric morbidity and mortality; however, data for Kyrgyzstan remain scarce due to limited diagnostics. This study characterised the clinical features and immunological changes in hospitalised children with ARVI according to disease severity.

Methods: In this observational study conducted between 2020 and 2023, 97 children were enrolled based on a clinical ARVI diagnosis; those with immunodeficiency, chronic disease, immunosuppressive therapy, or incomplete data were excluded.

Results: Severe ARVI predominated (64%), with pneumonia (51.5%) and respiratory failure (42.2%) as the most common complications. Severity correlated with C-reactive protein (r = 0.79) and was associated with electrolyte changes and lower protein levels. Leukocytosis was correlated with the length of hospitalisation (r=0.3). Severe cases (n=52) versus moderate cases (n=30) showed higher leukocytes (11.66±0.92 vs 8.50±0.38); increased CD3+, CD4+ (1025 vs 607 cells/µL) and CD8+ (656 vs 415 cells/µL); a CD4/CD8 index (1.53 vs 1.40); heightened IgG (20.8 vs 17.8 mg/mL) and IgA (20.1 vs 1.5 mg/mL); IgM (4.9 vs 1.5 mg/mL) and circulating immune complexes (153.34±7.77 vs 137.9±5.14).

Conclusion: Severe paediatric ARVI showed inflammation and immune activation with dysregulated balance, supporting CRP and immunophenotyping as prognostic tools in cases where virological confirmation is limited.

Keywords: Respiratory Syncytial Virus, Human Rhinovirus, Influenza Viruses, Immune Response, $CD4^+$ T Cells, $CD8^+$ T Cells

Introduction

Acute respiratory viral infections (ARVIs) pose a significant health challenge worldwide, particularly affecting children and at-risk groups. Epidemiological research has shown that ARVIs are a major contributor to illness and death globally.

Viruses such as respiratory syncytial virus (RSV), human rhinovirus (HRV), influenza viruses (IAV and IBV), and human metapneumovirus are the primary causes of ARVIs. [1-3] RSV and HRV are most commonly detected in hospitalised children, with RSV peaking during the winter in temperate areas. [3] Co-infection with multiple respiratory viruses frequently complicates clinical symptoms. [1] The coronavirus disease 2019 pandemic has altered viral epidemiological trends, with RSV and human metapneumovirus outbreaks noted after the pandemic. [4] Human rhinovirus infection can trigger interferon responses that may hinder SARS-CoV-2 replication. [5]

Research in China has revealed significant viral respiratory infections among children hospitalised with acute respiratory infections, with influenza A, RSV, and HRV being the most common viruses. [1] A recent study in Wuhan highlighted the presence of Mycoplasma pneumoniae and increasing influenza virus trends, emphasising the need for surveillance. [6] In Iran, RSV remains the primary cause of hospitalisation of children with acute lower respiratory infections, with RSV subgroup A (genotype ON1) being more prevalent and severe than subgroup B. [7] Urban density, population immunity, and social factors influence these trends, as shown by research in Brazilian slums, which revealed high co-infections and seasonal patterns of RSV and HRV. [8]

Specific information on the epidemiology and prevalence of ARVIs in Kyrgyzstan is not directly available. However, Central Asian nations are integrated into global surveillance networks and experience burdens from viral infections, suggesting that they have established infrastructures for monitoring infectious diseases. [9] Given the global trends and regional conditions, ARVIs caused by RSV, influenza viruses, and rhinoviruses likely play a significant role in respiratory illnesses in Kyrgyzstan. Local epidemiological data are scarce, highlighting the need for increased surveillance. ARVIs remain a leading cause of acute illness globally, with RSV, influenza viruses, and rhinoviruses as the primary pathogens. Although comprehensive surveillance data are available globally and from many Asian countries, specific epidemiological data for Kyrgyzstan are limited, requiring further research. [1,3,7]

The pathogenesis of ARVI in young children is associated not only with damage to the epithelial barrier of the respiratory tract but also with disturbances in the immune system. Infection is accompanied by suppression of both innate and adaptive immune responses, including impaired activity of helper T cells ($CD4^+$), cytotoxic T cells ($CD8^+$), and natural killer (NK) cells. [10-12] This reduces the effectiveness of antiviral defence, increases the risk of secondary infections, and contributes to the development of severe complications. [13,14]

Immunological assessment of young children with ARVI makes it possible to evaluate the nature of the immune response, identify dysfunctions in individual components of the immune system, and differentiate between viral and viral-bacterial processes. [11,15,16] A comprehensive approach to immunological diagnostics is especially relevant under conditions of high circulation of respiratory viruses and limited opportunities for laboratory confirmation of infection etiology. [13,17-19] Such an approach provides a rationale for the choice of therapy and contributes to reducing the risk of complications.

In young children, ARVI damages the respiratory epithelium and disrupts immune function. These infections suppress innate and adaptive immune responses, including the reduced activity of $CD4^+$, $CD8^+$, and NK cells, thereby increasing the risk of infection. [10-12] Assessing the immune response in children with ARVI is crucial for understanding the immune condition and distinguishing between viral and viral-bacterial infections. [10,15,16] These evaluations help in selecting appropriate therapeutic strategies in environments with high viral circulation.

Molecular diagnostic techniques, such as polymerase chain reaction (PCR), improve respiratory virus detection and reveal multiple viral pathogens. [17,19] Respiratory syncytial virus (RSV), rhinovirus, and influenza viruses are common paediatric ARVI pathogens, with RSV causing severe respiratory symptoms in infants and young children. [20] Understanding viral co-infections can guide their management. Immune response profiling, including cytokine patterns such as TH1 polarisation, correlates with viral clearance and disease severity. The microRNA miR-155 enhances TH1 antiviral immunity, which correlates with less severe disease. [21] Integrating molecular diagnostics and immunological markers supports the clinical differentiation between viral and viral-bacterial infections, which is crucial for the efficient management of ARVI.

Although ARVIs impose a significant global health burden, the immunopathogenetic mechanisms contributing to disease severity in infants and young children remain poorly understood, particularly in areas with limited diagnostics. The physiological immaturity of the immune system in young children makes them more susceptible to severe disease progression and complications. Standard clinical assessments often fail to differentiate between moderate and severe ARVI or to predict complications. Detailed immunological profiling during acute infection

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can provide insights into host-virus interactions, identify severity markers, and aid clinical decision-making. The lack of region-specific immunological data necessitates targeted studies in hospitalised paediatric populations, particularly in countries with limited surveillance capabilities. This study aimed to analyse the clinical and immunological characteristics of the acute phase of ARVI in infants and young children, depending on disease severity.

Methods

This observational study at the Republican Clinical Infectious Diseases Hospital (Kyrgyz Republic, 2020-2023) examined immunological changes in infants and young children hospitalised with ARVI during the acute phase. The study included 97 paediatric patients from age groups that are most vulnerable to severe VRIs.

Patient selection was based on clinical ARVI diagnosis using epidemiological data, symptoms, and laboratory results at admission. The exclusion criteria were congenital or acquired immunodeficiency disorders, chronic inflammatory or autoimmune diseases, immunosuppressive therapy, and incomplete data. Parents provided written informed consent. This study was approved by the Bioethics Committee of the I. K. Akhunbaev Kyrgyz State Medical Academy (Protocol No. 17, April 13, 2019).

Clinical assessments were performed at admission and during hospitalisation. Disease severity was categorised as moderate or severe based on the inflammatory response, respiratory failure, and complications. Routine laboratory tests were performed upon admission, and the length of hospitalisation was documented.

Immunological evaluation was performed using the monoclonal antibody technique with immunofluorescence microscopy. Blood samples were collected before the initiation of intensive therapy. Lymphocyte subpopulations were identified using monoclonal antibodies against $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and CD16. Cell counts and immunoregulatory indices were recorded to evaluate the T-cell immune balance.

Humoral immunity assessment was performed by measuring serum immunoglobulin levels using immunochemical methods. Circulating immune complexes were quantified by precipitation with a 3.5% (w/v) polyethylene glycol (PEG 6000, Sigma Aldrich, United States), followed by spectrophotometric determination.

Innate immune system activity was evaluated using neutrophil phagocytic capacity. Standard assays were used to determine phagocytic indices, nitroblue tetrazolium test results, and mean cytochemical coefficient, examining neutrophil phagocytosis during infection.

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Variables are expressed as mean ± standard deviation and number of patients (n) and frequency percentages (%). Parametric or non-parametric tests were applied based on data distribution to compare children with moderate and severe ARVI. Correlation analysis was used to explore the relationships among clinical, laboratory, and immunological parameters. In addition to p-values, Cohen's *d* was used to calculate effect sizes to estimate group differences, and 95% confidence intervals (95% CI) were used to evaluate precision and clinical significance. A two-sided p-value <0.05 was deemed statistically significant.

Results

Patients were categorised as infants (49.5%) and young children (50.5%), showing high vulnerability to RVIs. Among the patients, 62 (63.9%) had severe disease, while 30 (30.9%) had moderate disease. Pneumonia (51.5% of cases) and respiratory failure (42.2%) were the most frequent complications. Lower respiratory tract obstruction occurred in 23.7% of the cases, and upper airway obstruction manifested as croup syndrome in 14.4% of the cases. Neurological complications, including seizure syndrome (18.6%) and cerebral oedema (16.5%), suggest central nervous system involvement in severe ARVI cases. Mixed viral infections, combining ARVI and acute intestinal infection, were found in 18.6% of patients, correlating with more severe progression due to strain on immunity and a compromised mucosal barrier. Bacteriological identification of Shigella flexneri was confirmed. In other cases, enterocolitis had an unspecified cause, likely due to limited diagnostic capability.

Clinical and laboratory data have shown that ARVI severity in children is linked to systemic inflammatory response and age-specific immune reactivity. The strongest correlation was observed between C-reactive protein (CRP) levels and ARVI severity ($r = 0.79$), indicating the role of CRP as a systemic inflammation marker. Positive correlations were observed between CRP and chloride levels ($r = 0.60$) and potassium levels ($r = 0.30$), suggesting the influence of inflammation on water and electrolyte balance during acute illness. Age emerged as a crucial prognostic factor for ARVI severity, with positive correlations in infancy ($r = 0.20$; $p = 0.01$) and early childhood ($r = 0.33$; $p = 0.001$), indicating young children's vulnerability to severe RVIs. Another correlation between age groups ($r = 0.47$; $p < 0.001$) supports young children's increased susceptibility to severe ARVI, likely due to the physiological immaturity of innate and adaptive immune responses.

A significant clinical link was identified between leukocyte count at admission and length of hospital stay ($r = 0.3$),

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indicating that leukocytosis could serve as a prognostic indicator of ARVI severity. Additionally, a negative correlation existed between CRP levels and total serum protein concentration (r = –0.40), highlighting the need for early evaluation of nutritional status and serum protein fractions in infants and young children with a systemic inflammatory response.

This study showed notable differences (moderate: n = 30; severe: n = 52), indicating an activated immune response in severe cases (Table 1). In severe ARVI, leukocyte levels were significantly higher (11.66 ± 0.92 compared to 8.50 ± 0.38; p < 0.01), with a Cohen's *d* effect size of 0.581 (95% CI: [0.123; 1.039]), indicating systemic inflammation (Table 2).

$CD3^+$ lymphocytes were higher (32.31 ± 1.66% compared to 25.3 ± 2.3%; p < 0.05; d = 0.575), suggesting an activation of the cellular immune response. Both relative and absolute counts of $CD4^+$ T-helper cells increased (21.27 ± 1.06% and 1025.45 ± 137.18 cells/μL vs 17.9 ± 1.57% and 606.98 ± 83.31 cells/μL; p < 0.01), indicating enhanced adaptive immunity.

In children with severe disease progression, $CD8^+$ cytotoxic lymphocytes increased significantly (656.2 ± 83.47 compared to 415.12 ± 51.87 cells/μL; p < 0.01), with a trend toward a higher relative proportion (13.92 ± 0.7% versus 12.17 ± 0.94%), indicating cytotoxic immune response activation. The immunoregulatory index (CD4/CD8) was elevated (1.53 ± 0.04 compared to 1.4 ± 0.04), indicating increased T-cell regulatory activity. $CD19^+$ lymphocytes increased (742.41 ± 81.12 compared to 463.37 ± 57.21 cells/μL; p < 0.01), confirming the activation of the humoral immune response.

Cytotoxic $CD8^+$ lymphocytes (p < 0.05) were decreased in moderate and severe cases compared to healthy children, which suggests functional overload of the cytotoxic immune response and diminished antiviral activity (Table 3). The immunoregulatory index (CD4/CD8) in these patients was lower than that in the control group (1.53 ± 0.04 vs. 1.9 ± 0.1; p < 0.05), indicating an imbalance in T-cell immunity and weakened viral replication control, contributing to severe disease forms.

In children with severe ARVI, correlation analysis revealed significant positive relationships between leukocyte count, relative lymphocyte content, and CD4/CD8 index. These results show the importance of leukocyte and lymphocyte responses, with compensatory $CD4^+$ T lymphocyte activity during a significant viral load. For moderate cases, a strong correlation was observed between the lymphocyte count and CD4/CD8 index (r = 0.734; p < 0.01). The absence of correlations between leukocyte responses suggests independent adaptive immunity and a controlled inflammatory response.

A comparative analysis of the humoral immune response in children with ARVI showed significant differences between the groups. In those with severe illness, there were increased levels of immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), and circulating immune complexes (CIC), indicating a robust humoral response during the viral infection (Table 4).

The rise in IgG (20.75 ± 1.36 vs. 17.78 ± 0.08 mg/mL; p < 0.05) suggests memory B cell participation, which is typical of severe and extended infection. Higher IgA levels (20.09±0.23 vs. 1.51±0.27 mg/mL; p < 0.05) indicate mucosal immunity activation and mucous membrane involvement as a barrier defence. The increase in IgM (4.92 ± 0.18 vs. 1.51 ± 0.19 mg/mL; p < 0.05) in children with severe illness confirms the active role of the primary B-cell pool and primary humoral response under heavy viral load.

Elevated CIC levels (153.34±7.77 vs. 137.9±5.14 conventional units; p<0.05) suggest heightened antigen–antibody interactions and possible immunopathological tissue damage.

Children with severe ARVI show significant humoral immune system activation, which is valuable for diagnosis and prognosis, indicating specific immune response tension and the risk of a complicated disease course.

A comparative analysis of neutrophil immunity in children with ARVI showed no statistically significant differences between the moderate and severe forms (p > 0.05). These results suggest that phagocytic innate immunity remains intact, regardless of infection severity (Table 5). This indicates that the neutrophil component plays a secondary role in ARVI pathogenesis in young children, where adaptive immunity, through T- and B-cell responses, is the primary response. Therefore, severe ARVI progression in children is influenced by systemic inflammation, age-related immune immaturity, and adaptive immune system strain (increased $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ lymphocytes), whereas phagocytic activity remains relatively unchanged.

Table 1.Comparative Analysis of Immunological Parameters in Patients With ARVI

Immunological Parameters	Moderate (n=30)	Severe (n=52)	P
Leukocytes, /μL	8.5±0.38	11.66±0.92	<0.01
Lymphocytes, %	37.73±3.45	39.02±2.5	>0.05
Lymphocytes, /μL	3039.27±223.28	3848.06±289.55	>0.05
$CD3^+$ (, %	25.3±2.3	32.31±1.66	<0.05*

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$CD3^+$, /μL	860.67±107.73	1943.9±462.75	<0.05*
$CD4^+$, %	17.9±1.57	21.27±1.06	>0.05
$CD4^+$, /μL	606.98±83.31	1025.45±137.18	<0.01
$CD8^+$, %	12.17±0.94	13.92±0.698	>0.05
$CD8^+$, /μL	415.12±51.87	656.20±83.47	<0.01
CIR (CD4/CD8)	1.40±0.04	1.53±0.04	>0.05
$CD16^+$	15.47±5.84	8.06±0.36	>0.05
CD19, %	18.55±5.02	16.17±0.91	>0.05
$CD19^+$, /μL	463.37±57.21	742.41±81.12	<0.01

Values are expressed as the M ± m = Mean ± Standard deviation. $CD3^+$ – *T lymphocytes*, $CD4^+$ – *T helper lymphocytes*, $CD8^+$ – *Cytotoxic T lymphocytes*, CIR – *Immunoregulatory index*, $CD16^+$ – *Natural killer cells*, $CD19^+$ – *B lymphocytes*. *P<0.05

Table 2.Clinical Significance of Differences in Immunological Parameters in Children With ARVI

Parameter	Effect Size (Cohen's d)	95% CI (Lower Bound)	95% CI (Upper Bound)
Leukocytes, /μL	0.581	0.123	1.039
Lymphocytes, /μL	0.444	-0.011	0.898
$CD3^+$, %	0.574	0.117	1.032
$CD3^+$, /μL	0.403	-0.051	0.857
$CD4^+$, %	0.421	-0.033	0.875
$CD4^+$, /μL	0.501	0.045	0.957
$CD8^+$, %	0.345	-0.108	0.797
$CD8^+$, /μL	0.474	0.018	0.929
$CD19^+$, %	-0.137	-0.587	0.313
$CD19^+$, /μL	0.554	0.097	1.011

$CD3^+$ – *T lymphocytes*, $CD4^+$ – *T helper lymphocytes*, $CD8^+$ – *Cytotoxic T lymphocytes*, CIR – *Immunoregulatory index*, $CD16^+$ – *Natural killer cells,* $CD19^+$ – *B lymphocytes*. 95% CI – 95% confidence interval

Table 3.Comparative Analysis of Immunological Parameters in Patients With ARVI and Healthy Children

Immunological parameters	Moderate (n=41)	Severe (n=31)	Healthy (n=25)	P
Cytotoxic lymphocytes ($CD8^+$)	12.17±0.94	13.92±0.698	16.2±3.45	<0.05
Natural killer cells ($CD16^+$)	15.47±5.84	8.06±0.36	16.5±2.0	<0.05
CIR (CD4/CD8)	1.40±0.04	1.53±0.04	1.9±0.1	<0.05

Values are expressed as the M ± m = Mean ± Standard deviation. $CD4^+$ – *T helper lymphocytes*, $CD8^+$ – *Cytotoxic T lymphocytes*, CIR – *Immunoregulatory index*, $CD16^+$ – *Natural killer cells*. *P<0.05

Table 4.Comparative Analysis of the Humoral Immunity in Patients with ARVI

Immunological parameters	Moderate (n=27)	Severe (n=49)	P
IgG (mg/mL)	17.78±0.08	20.75±1.36	<0.05*
IgA (mg/mL)	1.51±0.27	20.09±0.23	<0.05*
IgM (mg/mL)	1.51±0.19	1.92±0.16	<0.05*
CIC	137.9±5.14	153.34±7.77	<0.05*

Values are expressed as the M ± m = Mean ± Standard deviation. IgG – *Immunoglobulin G*, IgA – *Immunoglobulin A*, IgM – *Immunoglobulin M*, CIC – *Circulating immune complexes*. *P<0.05

Table 5.Comparative Analysis of the Phagocytic Immunity in Patients with ARVI

Immunological parameters	Moderate (n=27)	Severe (n=49)	p-value
Phagocytic Index (neutrophils), mg/mL	31.0±1.38	29.08±0.97	>0.05
Phagocytic Number (neutrophils), mg/mL	1.82±0.13	1.77±0.89	>0.05

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Integrated Phagocytic Index, %	0.59±0.06	0.53±0.37	>0.05
Nitroblue Tetrazolium Test, %	36.4±1.2	35.7±0.9	>0.05
Mean Cytochemical Coefficient, arb. units	0.7±0.02	0.7±0.02	>0.05

Values are expressed as the M ± m = Mean ± Standard deviation. *P<0.05

Discussion

This study has revealed that infants and young children with ARVI show immune response patterns linked to clinical severity. ARVIs remain a primary cause of illness and hospitalisation among children worldwide, particularly affecting those under five years of age, who face a severe lower respiratory disease risk in developing regions. [22] Disease severity in early childhood is related to viral virulence and the host's underdeveloped immune defences, which impair viral clearance and increase complications.

Innate immunity serves as the first line of defence against respiratory viruses through physical barriers, pattern recognition, and effector cells. During infection, respiratory epithelial cells and immune cells identify pathogens via pattern recognition receptors, triggering inflammatory responses and recruiting neutrophils, macrophages, and NK cells. [13] In infants, these innate immune responses differ from those in older children and adults, with reduced interferon responses and variable NK cell activity, potentially hampering viral control. [18,23] NK cells regulate viral infections by limiting replication and influencing inflammation, with their functional changes linked to disease pathogenesis. [12,24]

Adaptive immunity is essential for eliminating viruses via antigen-specific T and B lymphocytes. Successful immune responses depend on interactions among antigen-presenting cells, $CD4^+$, $CD8^+$, and B cells that produce antibodies. [13] In young children, adaptive immunity is maturing, showing a Th2-skewed profile with lower Th1-type activity, which delays viral clearance and increases vulnerability to severe illness. [25] Both quantitative and qualitative limitations in T-cell responses during early life are linked to prolonged viral shedding and severe outcomes. [14] Humoral immunity in infants is influenced by maternal antibodies and new immunoglobulin production, with age-specific patterns affecting viral neutralisation.

Children with severe ARVI showed greater deviations in lymphocyte subpopulations and immunoregulatory balance than those with moderate illness. Changes in $CD4^+/CD8^+$ ratios and reduced NK cell proportions in severe cases indicate an imbalance between protective antiviral responses and immunopathological mechanisms. These imbalances may cause tissue damage through inflammation, aligning with evidence that immune-mediated injury is a major contributor to respiratory tract pathology in viral infections. [26]

Humoral immune responses, as shown by immunoglobulin levels and immune complexes, highlight antigen-antibody interactions in ARVI. While antibody production is crucial for viral neutralisation, immune complexes can worsen inflammation and disease severity, particularly with dysregulated immune responses in early life. These findings align with paediatric studies showing age-dependent cytokine profiles in ARVI, emphasising immune activation diversity in young hosts. [21,27]

Immune system maturation affects both infection susceptibility and long-term respiratory health outcomes. Severe RVIs in early childhood have been linked to later wheezing and increased asthma risk, suggesting lasting impacts on the respiratory and immune systems.[10] Understanding these immunological processes is vital for managing acute cases and developing preventive measures, such as targeted immunomodulation and vaccines, that consider children's immune development.

ARVI immunopathogenesis in young children involves complex innate and adaptive immune responses that differ from those in adults, leading to variations in disease outcomes. Our research emphasises the need for age-specific immunological markers to guide prognosis and treatments. Future studies should examine the progression of immune response during ARVI, identify severity biomarkers, and develop immunomodulatory approaches to enhance defences while reducing immunopathology.

Conclusions

In children with severe ARVI, $CD4^+$ T lymphocytes increased (1025 compared to 607 cells/µL) and $CD8^+$ lymphocytes (656 compared to 415 cells/µL; $p < 0.01$), indicating cellular immunity activation. IgG (20.8 vs. 17.8 mg/mL), IgA (20.1 vs. 1.5 mg/mL), and IgM (4.9 vs. 1.5 mg/mL) levels were higher in severe cases, showing a strong humoral response. The immunoregulatory index (CD4/CD8) was lower (1.53 vs. 1.40), suggesting a disrupted T-cell balance. A strong association between disease severity and C-reactive protein levels ($r = 0.79$; $p < 0.01$) underscored its prognostic value.

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