



# Clinical and Laboratory Profiles of Rhinovirus-Infected Preschool Children: Identifying Risk Factors for Subsequent Asthma

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**Background:** Rhinovirus infection is considered a significant risk factor for the development of asthma in children. However, not all children with rhinovirus infections ultimately manifest asthma.

**Aim of Study:** To analyze the clinical and laboratory profiles of children under five years of age with proven rhinovirus infection and identify potential common factors predisposing them to an increased risk of future asthma.

**Materials and Methods:** A retrospective longitudinal study was conducted at the National Institute of Pediatric Tuberculosis and Respiratory Diseases in Slovakia. The study population consisted of 122 preschool children (mean age 2.5 years  $\pm$  1.84, 69% boys vs 31% girls) hospitalized with PCR-confirmed rhinovirus infection. The children were followed for a minimum of three years to monitor the potential development of bronchial asthma.

**Results:** Fifty of 122 children (41%) developed asthma (group 1), while 72 (59%) did not (group 2). Children in group 1 had a higher prevalence of family history of atopy ( $p < 0.001$ ), sensitization to allergens (especially house dust mites and grass;  $p = 0.0002$ ), elevated peripheral eosinophilia ( $p = 0.047$ ), and higher total IgE levels ( $p < 0.05$ ) compared to group 2. The use of inhaled corticosteroids was significantly higher in group 1 ( $p < 0.001$ ). No significant differences were found between the groups in terms of prematurity, pathological perinatal history, and upper respiratory tract colonization by common microbial pathogens.

**Conclusion:** Atopy, sensitization to aeroallergens, and inhaled corticosteroid use were significant risk factors for asthma development in children with rhinovirus infections. The early identification of these risk factors may help in the timely management of these children to mitigate the potential long-term consequences of chronic airway inflammation. This personalized approach allows for more intensive medical surveillance and targeted therapeutic interventions in high-risk individuals, potentially improving the long-term outcomes.

**Keywords:** rhinovirus, bronchial asthma, children, wheezing, atopy

## Introduction

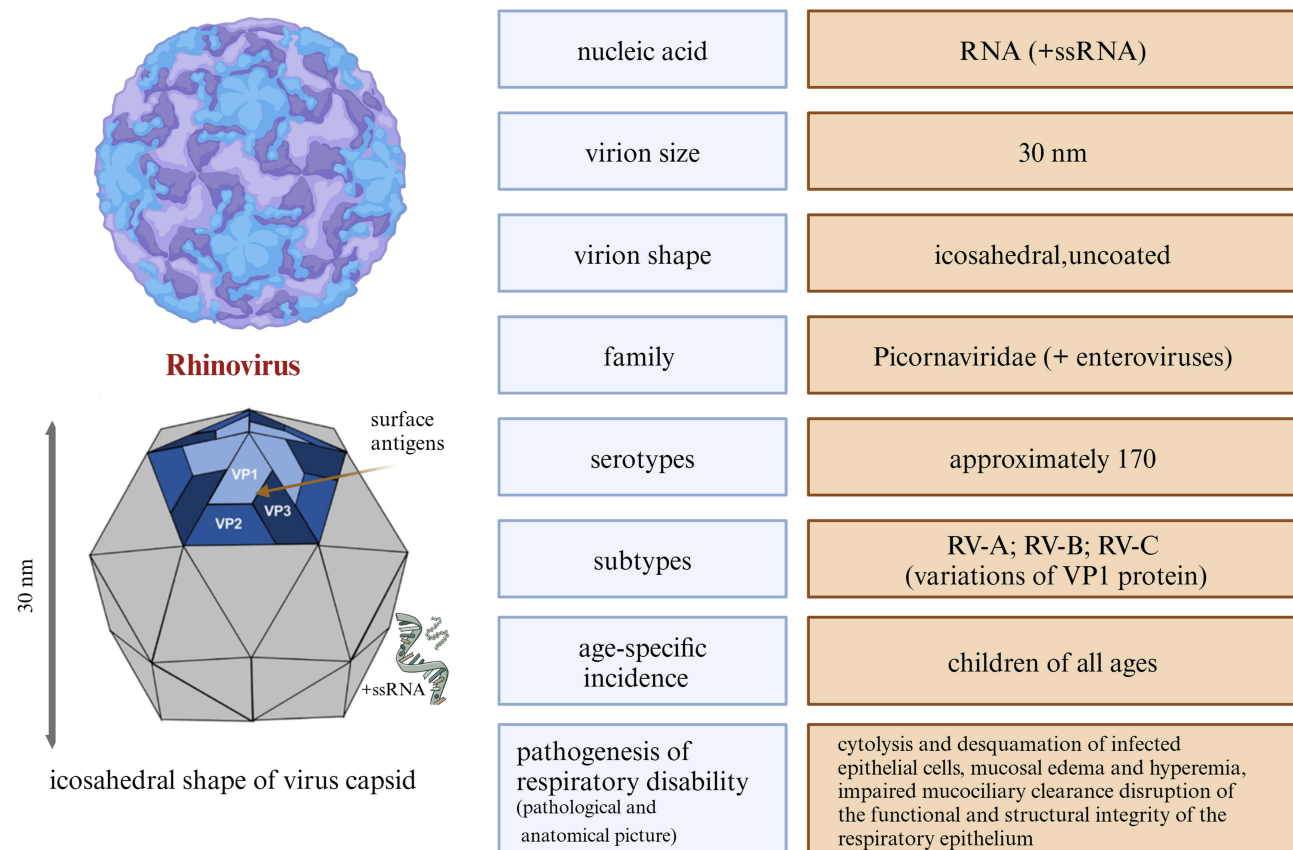
In the pediatric population, the prevalence of bronchial asthma, the most common chronic inflammatory airway disease, is steadily increasing. A Polish study, for instance, reported a significant rise in physician-diagnosed asthma from 3.4% in 1993 to 12.6% in 2014.<sup>1</sup> This clinical entity is characterized by a high degree of heterogeneity in clinical symptoms, course, and response to therapy. The interplay between genetic and environmental factors leads to chronic allergic or non-allergic airway inflammation, which underlies the development of reversible bronchial hyperresponsiveness. Approximately one-third of children experience wheezing within the first three years of life, but not all progress to asthma.<sup>2</sup> Preschool wheezing is a broad term encompassing various respiratory conditions with distinct phenotypes, each potentially linked to a unique underlying cause and molecular mechanism.<sup>3</sup> To simplify diagnosis and treatment, the European Respiratory Society (ERS) recommends classifying wheezing as either episodic viral wheezing or multiple trigger wheezing based on causative factors and frequency.<sup>4</sup> Rhinoviruses (RV) are common respiratory pathogens. As

illustrated in Figure 1, rhinovirus, a member of the *Picornaviridae* family, is an icosahedral non-enveloped virus with a single-stranded RNA genome. Recurrent RV lower respiratory tract infections associated with bronchial obstruction are considered risk factors for the subsequent development of bronchial asthma in children.<sup>5</sup> The present study aimed to analyze children under five years of age with proven RV infection to determine their clinical profile and identify potential common factors predisposing them to an increased risk of asthma.

## Materials and Methods

### Study Population and Design

This retrospective longitudinal study was conducted at the National Institute of Pediatric Tuberculosis and Respiratory Diseases in Dolny Smokovec, Slovakia. From the total number of children hospitalized between 2016 and 2022, we selected hospitalization cases with laboratory-confirmed RV infection, as determined by polymerase chain reaction (PCR). This served as the primary inclusion criterion for case inclusion in the analysis. We enrolled children with a history of recurrent respiratory infections who met at least one of the following criteria according to De Martino: experiencing six or more respiratory infections annually, having at least one upper respiratory tract infection monthly from September to April, or having at least three lower respiratory tract infections annually.<sup>6</sup> Additionally, we included participants with a history of recurrent wheezing episodes, defined as four or more episodes per year. We excluded participants with any of the following conditions: autoimmune disease, active malignancy, severe cardiovascular disease, significant congenital developmental defects, severe primary immunodeficiencies, clinically relevant malnutrition, cystic fibrosis, diffuse interstitial lung disease, and bronchiectasis.



**Figure 1** Characteristics of rhinovirus and its pathogenesis in the airways, created in Biorender.com.

**Abbreviations:** RNA, ribonucleic acid; RV-A, human rhinovirus type A; RV-B, human rhinovirus type B; RV-C, human rhinovirus type C; +ssRNA, Positive-sense single-stranded RNA; VP1, protein of the virus capsid type 1, VP2, protein of the virus capsid type 2, VP3, protein of the virus capsid type 3.

Based on the available anamnestic data within the hospital information system, the focus was on information relevant to RV infection. This study collected data on the following patient characteristics: age at confirmation of RV infection, sex, month of RV infection positivity, co-infections, and type of acute diagnosis associated with RV infection. Family history of allergic diseases, history of prematurity, pathological perinatal period, and recurrent respiratory tract infections was also recorded. Sensitization to aeroallergens was assessed *in vivo* and/or *in vitro*, and specific groups of aeroallergens were identified. The data included a history of bronchial asthma, regular use of inhaled corticosteroids (in patients with and without asthma), and a history of recurrent obstructive bronchitis. Non-specific atopic markers such as peripheral and tissue eosinophilia and total IgE antibody levels were evaluated. Finally, nasopharyngeal swabs were cultured to identify pathological microbial agents such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. In addition, among the confirmed RV infections in children under 5 years of age, we determined the proportion of cases that subsequently developed bronchial asthma.

The study protocol was approved by the Ethics Committee of the National Institute of Pediatric Tuberculosis and Respiratory Diseases. All research procedures involving human participants adhered to the ethical principles outlined in the Declaration of Helsinki (revised version 2000.09.01). Written informed consent was obtained from the parents or legal guardians of all participants prior to study commencement.

## Methods and Data Collection

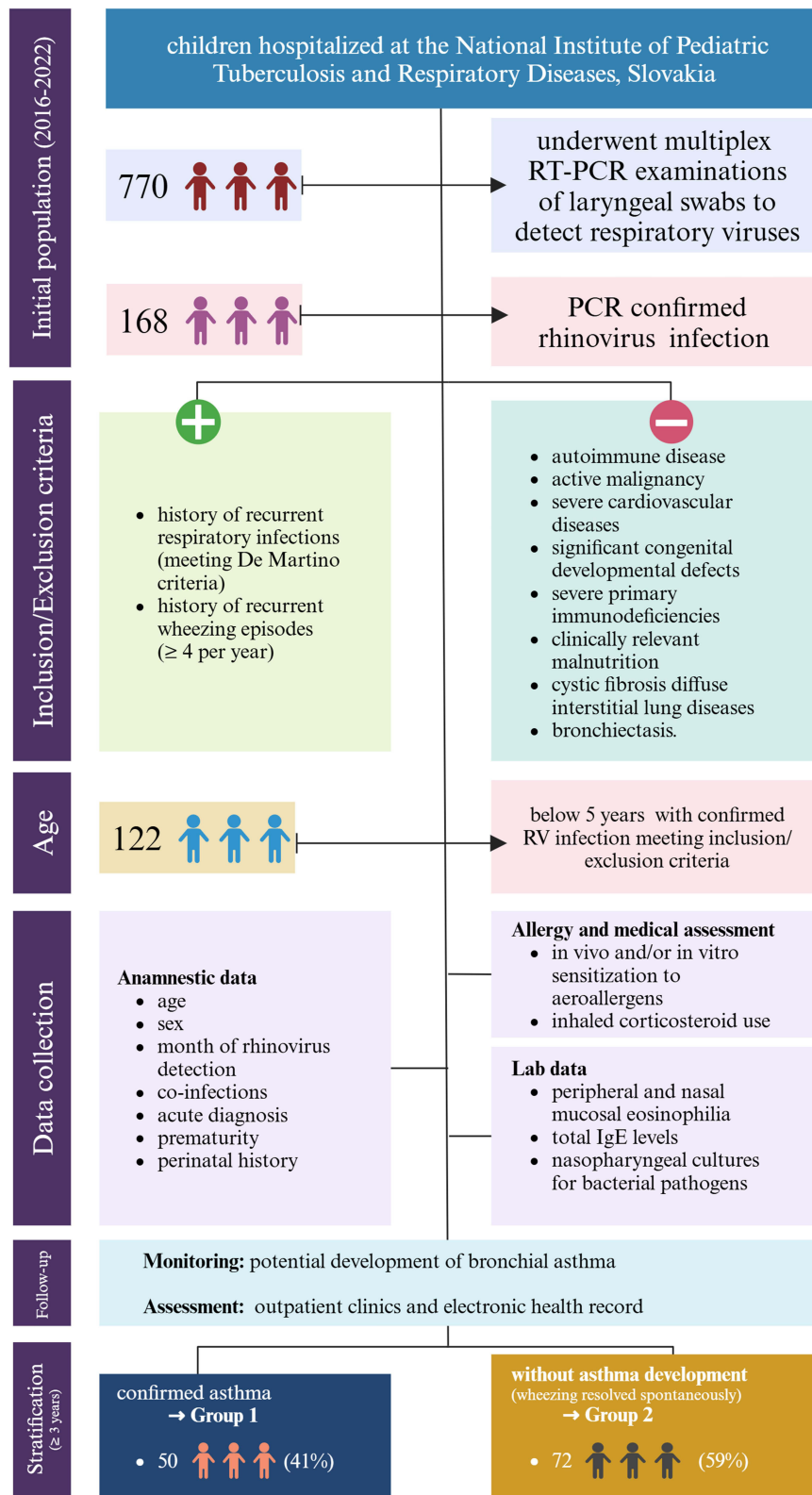
All evaluated patients underwent multiplex real-time polymerase chain reaction (RT-PCR) using the AmpliSens<sup>®</sup> ARVI-screen-FRT PCR kit (Ecoli Dx, Czech Republic) on nasopharyngeal swab specimens as indicated by the attending physician. Unlike traditional PCR, this method enables real-time quantification of the target DNA fragment and is currently the only diagnostic tool available for confirming RV infection in clinical practice. The multiplex panel simultaneously detected RV, adenovirus (ADV), respiratory syncytial virus (RSV), human coronavirus (HCoV), parainfluenza virus (PIV) 1–4, human bocavirus (HBoV), and human metapneumovirus (HMPV), allowing for the identification of both single and co-infections with multiple respiratory viruses.

Peripheral blood eosinophil counts were determined using a population hematology analyzer (MINDRAY BC-5120, Shenzhen Mindray Bio-Medical Electronics Co). Eosinophil levels were expressed as absolute numbers (thousands/ $\mu$ L of peripheral blood). Elevated eosinophil counts were defined as values exceeding 300 eosinophils/ $\mu$ L in peripheral blood. We selected a cut-off value of 300 eosinophils/ $\mu$ L of peripheral blood to identify individuals with elevated eosinophil levels, as this threshold has been widely used in clinical practice and research to identify patients with T2 positive endotype asthma who may benefit from inhaled corticosteroid therapy.<sup>7</sup> Nasal mucosal eosinophilia (Eo/nose) was assessed cytologically by microscopic examination of swab smears. After staining, the relative percentage of eosinophils among other cell types was qualitatively determined by counting the number of microscopic fields (400x magnification) containing at least one eosinophil in 10 randomly selected fields. Given that elevated serum IgE levels may indicate sensitization to environmental allergens and a potential predisposition to IgE-mediated hypersensitivity reactions, we included this parameter in our analysis despite its limited clinical relevance. To determine total IgE concentrations, we employed a nephelometric method.

Patients diagnosed with RV infection were proactively followed-up for a minimum of three years to monitor the potential development of bronchial asthma. Follow-up assessments for a subset of patients were conducted in specialized outpatient clinics at the institute. For those not receiving care at the institute, electronic health records were reviewed to determine if anti-asthmatic medications had been prescribed in the preceding 12 months for diagnoses consistent with bronchial asthma (ICD-10 codes J45.0, J45.8, and J45.9). This approach stratified the cohort into two groups: 50 out of 122 children (41%) with a confirmed diagnosis of bronchial asthma (group 1) and a comparative group of 72 out of 122 children (59%) without an asthma diagnosis or prescription for anti-asthmatic medication (group 2), whose wheezing episodes resolved spontaneously. A detailed flowchart of the study design and patient flow are shown in [Figure 2](#).

## Statistical Analysis

Data were analyzed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria; URL <https://www.R-project.org/>, version 4.0.3). The dataset comprised both categorical and continuous variables. For categorical



**Figure 2** Flowchart of the study design and participant selection, created in Biorender.com.

**Abbreviations:** IgE, immunoglobulin E; PCR, polymerase chain reaction; RT-PCR, real time polymerase chain reaction, RV, human rhinovirus.

data, results are presented as percentages. Descriptive statistics were used to summarize the patient characteristics. Where applicable, the chi-square test ( $\chi^2$ ) with 1 degree of freedom and a sample size of 122 was employed to assess the association between categorical variables. The critical value for 1 degree of freedom at a significance level of 0.05 was calculated as 3.84. Fisher's exact test was employed for small sample size comparisons. Independent sample *t*-tests were used to compare the means of continuous variables between the two groups. A significance level of  $p < 0.05$  was established to determine the statistical significance of observed differences between groups.

## Results

### Basic Demographic of Study Cohort

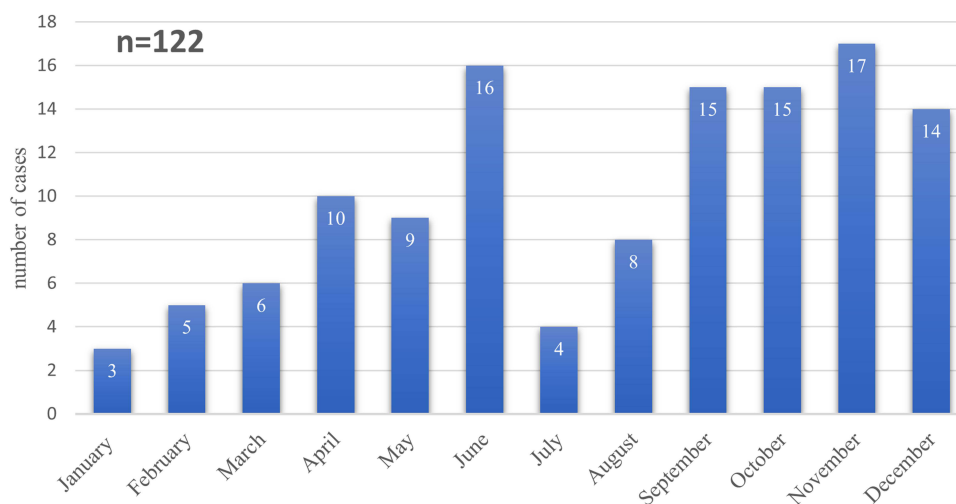
Between January 1, 2016, and December 31, 2022, 770 multiplex RT-PCR examinations of nasopharyngeal swabs were performed at the institute to detect respiratory viruses. Of these, 168 patient samples were positive for RV, either as a single infection or in combination with other respiratory viruses. From this group, 122 children under the age of 5 (preschool age) were selected for further analysis. The cohort consisted of 84 boys (69%) and 38 girls (31%), with a mean age of 2.5 years (SD  $\pm 1.84$  years).

### Epidemiological Aspects of Rhinovirus Positive Cases

RV infections exhibited a distinct seasonal pattern throughout the year (Figure 3). The peak incidence occurred in June in the first half of the year, accounting for 13.1% (16/122) of all cases, followed by September to December, which comprised 49.9% (61/122) of the total. The lowest incidence, representing only 2.5% (3/122) of the total, was observed in January.

Analysis of co-infections revealed a significantly higher prevalence in group 2 than in group 1, with 25 and 13 cases, respectively. The most frequent co-infection was ADV, comprising 15 cases (5 in group 1 and 10 in group 2). This was followed by RSV (8 cases; 2 in group 1; 6 in group 2) and RV with HBoV (6 cases; 2 in group 1 and 4 in group 2). Co-infections with parainfluenza viruses 2 and 3 and human coronaviruses represented a negligible proportion. Although four instances of co-infection with more than two pathogens were confirmed by PCR, they did not appear to be clinically significant.

To further investigate the impact of RV infection, we examined the clinical manifestations. For clarity, acute infections were categorized as upper airway infections (UAIs), bronchitis, or pneumonia. Group 2 exhibited higher number of pneumonia cases (9 vs 1) than group 1. This was confirmed by chi-square tests of independence, which revealed significant associations between group membership and the occurrence pneumonia ( $\chi^2$  (1,  $n = 122$ ) = 4.33,  $p < 0.05$ ). The prevalence of



**Figure 3** Monthly distribution of rhinovirus infections among the study participants.

bronchitis (29 in group 1 vs 31 in group 2;  $\chi^2(1, n = 122) = 2.637, p > 0.05$ ) and UAIs (20 in group 1 vs 32 in group 2;  $\chi^2(1, n = 122) = 0.239, p = 0.63$ ) was not statistically different between the two groups.

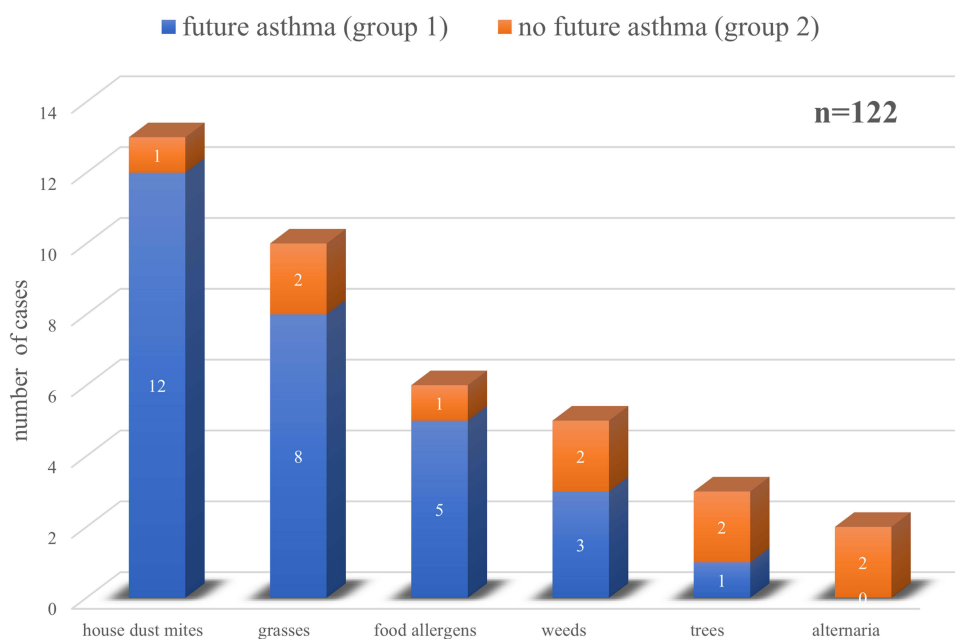
## Assessment of Selected Data from Patients' History

To assess the potential risk factors for asthma development, we examined selected medical history data from both groups, including prematurity (gestational age < 37 weeks), pathological perinatal course, and family history of atopy in first-degree relatives. No significant difference in the proportion of premature infants was observed between study groups 1 (7/50, 14%) and 2 (10/72, 13.9%) [ $\chi^2(1, n = 122) = 0.00023, p = 0.987$ ]. We arrived at similar conclusions after assessing the pathological perinatal history of probands. There was no significant difference in the proportion of infants with a pathological perinatal history between groups 1 (5/50, 10%) and 2 (5/72, 6.9%) ( $\chi^2(1, n = 122) = 0.37, p = 0.543$ ). Conversely, a strong significant difference in family history of atopy was observed between the two groups, with a higher prevalence in group 1 (38/50, 76%) than in group 2 (33/72, 45.8%) ( $\chi^2(1, n = 122) = 11.02, p < 0.001$ ).

## Atopy Markers, Inhaled Corticoids Use and Nasal Microbiota

Other key data included selected categories related to atopy and atopic predispositions. A significant difference was observed between the two groups in the proportion of sensitization to inhalants or food allergens ( $\chi^2(1, n = 122) = 13.91, p = 0.0002$ ), with 40% of pediatric patients in group 1 and 11.1% in group 2 exhibiting sensitization. Further analysis of the sensitization profiles revealed a predominance of house dust mite allergens, with 13 patients (46%) exhibiting specific IgE antibodies to these allergens. Grass allergens were also frequently observed, with 10 cases (35%). Together, these two allergen groups accounted for > 81% of the identified sensitivities. The remaining allergen categories, including food allergens, weeds, trees, and molds, were significantly less represented (Figure 4).

Next, we focused on the comparison of selected nonspecific atopic markers. When assessing peripheral eosinophilia (> 0.3thousand/ $\mu$ L), we again demonstrated a higher number of cases in the first group (28/50, 56%) than in the second group (28/72, 38.9%), and a chi-squared test of independence indicated a significant association between group membership and the presence of peripheral eosinophilia ( $\chi^2(1, n = 122) = 3.91, p = 0.047$ ). We also assessed nasal mucosal eosinophils, in addition to peripheral eosinophilia. Despite the higher proportion in the first group (10/50, 20% vs 5/72, 6.9%), this difference was not statistically significant ( $\chi^2(1, n = 122) = 3.49, p = 0.062$ ). Similarly, the mean percentage of eosinophils in the nasal mucosa did not appear to differ substantially between the groups (21% in group 1 vs 19% in



**Figure 4** Sensitization to common aeroallergens in both study groups.

group 2). Other potential markers of a possible atopic process or predisposition to atopy include the levels of total IgE antibodies. We observed a significant difference (independent samples *t*-test;  $p < 0.05$ ) in the total IgE levels between the two groups. Group 1 participants exhibited a mean total IgE level of 210 IU/mL (median, 33 IU/mL), while group 2 probands had a mean of 66IU/mL (median, 17 IU/mL). Significant differences were also confirmed in the therapeutic use of inhaled corticosteroids (regular use during treatment or on demand). In group 1, 88% of the patients regularly used inhaled corticosteroids compared with 54.2% in group 2 ( $\chi^2 (1, n = 122) = 15.49 p < 0.001$ ).

Furthermore, in this study, we investigated colonization of the upper respiratory tract by examining nasal swabs from pediatric patients. Our analysis focused on the prevalence of four common microbial pathogens, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. *Moraxella catarrhalis* proved to be the most prevalent, detected in 36% of the 168 samples collected from all RV positive children regardless of their age. *Staphylococcus aureus* was the second most abundant (27%), followed by *Streptococcus pneumoniae* (18%). *Haemophilus influenzae* was the least prevalent, found in only 7% of samples. Despite these variations in individual pathogen prevalence, no significant differences were found between the two patient groups (Fisher's exact test,  $p > 0.18$  for all comparisons). In addition, the overall detection rate of at least one pathogen was nearly identical in both groups (68% in group 1 vs 68.1% in group 2; Fisher's exact test,  $p = 1.00$ ), indicating that the colonization rates were comparable. Table 1 summarizes the main results.

**Table 1** Clinical and Laboratory Characteristics of the Study Participants<sup>a</sup>

	Future Asthma (group 1)	No Future Asthma (group 2)	p-value	Statistics
Rhinovirus infection peak (month)	November	November	-	*
Co-infection	13 (26%)	25 (34.7%)	-	*
Most frequent co-infection	ADV	ADV	-	*
Second most frequent co-infection	RSV	RSV	-	*
Upper airway infections	20 (40%)	32 (44.4%)	0.63	**
Bronchitis	29 (58%)	31 (43.1%)	> 0.05	**
Pneumonia	1 (2%)	9 (12.5%)	< 0.05	**
Prematurity	7 (14%)	10 (13.9%)	0.987	**
Pathological perinatal history	5 (10%)	5 (6.9%)	0.543	**
Family history of atopy	38 (76%)	33 (45.8%)	0.001	**
Sensitization to inhalant or food allergens	20 (40%)	8 (11.1%)	0.0002	**
Most frequent inhalant allergen	House dust mites	House dust mites	-	*
Second most frequent inhalant allergen	Grass pollen	Grass pollen	-	*
Peripheral eosinophilia (> 0.3 thousand/ $\mu$ L)	28 (56%)	28 (38.9%)	0.047	**
Nasal mucosal eosinophils	10 (20%)	5 (6.9%)	0.062	**
Total IgE levels (IU/mL)	156 (median 34)	61 (median 17)	< 0.05	***
Use of inhaled corticosteroids	44 (88%)	39 (54.2%)	< 0.001	**
Presence of selected microbial pathogens in nasal swab	34 (68%)	49 (68.1%)	1.00	****

**Notes:** <sup>a</sup>Statistical methods used: \*Descriptive analysis (frequencies/percentages). \*\*Chi-square test (compare proportions between groups). \*\*\*Independent samples *t*-test (compare means between groups). \*\*\*\*Fisher's exact test (analyze association between variables). Significance level:  $p < 0.05$  (bold values indicates statistically significant difference).

**Abbreviations:** ADV, adenovirus; IgE, immunoglobulin E; RSV, respiratory syncytial virus.

## Discussion

RV is a highly prevalent infectious agent that causes various respiratory illnesses, from mild “common colds” to severe bronchiolitis in infants. Over the past two decades, numerous clinical studies have examined the association between rhinovirus infections in early childhood, particularly in infants and toddlers, and the subsequent development of bronchial asthma. This association was further supported by a meta-analysis of 15 original articles, which confirmed the potential role of RV infection in predisposing individuals to asthma.<sup>8</sup> Wheezing is common in preschool children, with 30–50% experiencing at least one episode before the age of six years.<sup>9</sup> Developing organisms in young children are particularly susceptible to respiratory infections. The intricate and complex interactions between the RV and epithelial cells, along with various components of the immune system, are not yet fully understood. Although some specific pathomechanisms and their consequences induced by RV entry and replication in respiratory epithelial cells are known, identifying the precise extrinsic and intrinsic factors that predispose individuals to recurrent virus-induced bronchospasm and subsequent bronchial asthma remains a clinical challenge. Nevertheless some factors, such as a genetic predisposition to atopy, are beyond our control.<sup>10</sup> Early wheezing may be linked to altered immune responses, particularly during acute respiratory infections such as those caused by RV. Impaired and delayed interferon responses in early life have been implicated as potential immune dysfunctions associated with recurrent wheezing and subsequent asthma development.<sup>11</sup>

This study aimed to delineate the clinical and laboratory characteristics of children with recurrent wheezing and PCR-confirmed RV infection who were hospitalized at the National Institute of Pediatric Tuberculosis and Respiratory Diseases. Through statistical analysis of specific anamnestic data and investigation of laboratory test results, we sought to identify potential factors associated with RV infection and subsequent development of asthma in this well-defined pediatric population. The clinical manifestations and nature of RV infection vary among children of different ages. This variation is not solely attributable to age itself but also to the interplay between the child’s age, the developmental stage of the child’s immune system, and the influence of various extrinsic factors. These factors collectively impact the viral load, cellular penetration, and replication dynamics.<sup>12,13</sup> We specifically focused on children under 5 years of age.

Based on a synthesis of available clinical studies, we hypothesized, that atopy could play a central role in the interplay between rhinovirus infection and asthma development. The association between RV infection and allergic sensitization is a crucial aspect to consider in the context of asthma development. Studies have demonstrated that individuals with atopic characteristics who contract RV infections exhibit an increased susceptibility to developing post-viral wheeze, a precursor to asthma.<sup>14</sup> This suggests a synergistic interaction between RV infection and atopy in the pathogenesis of asthma. Novel findings are further supported by research indicating that patients with elevated eosinophil counts, eczema, atopic eczema, and a family history of allergic rhinitis are more prone to developing post-viral wheeze following RV infection.<sup>15</sup> According to Jackson et al research outcomes, children between the ages of 1 and 6 who have pre-existing allergic sensitization are more likely to experience wheezing with RV infection.<sup>16,17</sup> Among others, likelihood of rhinovirus-induced wheezing appears to be elevated in patients with pre-existing allergic sensitization.<sup>18</sup> This highlights the importance of considering both atopy and RV infection in the assessment and management of children at risk for asthma. Our key findings indicate that a positive family history of atopy, sensitization to inhalant or food allergens, peripheral eosinophilia, and elevated total IgE levels significantly predispose children infected with rhinovirus to the subsequent development of asthma, thus supporting our hypothesis.

RV infection exhibited a distinct seasonal pattern in the patient population. Most cases were observed in November, with the number of infections gradually increasing from the beginning of autumn and declining during the spring months. Interestingly, RV was detected throughout the year, demonstrating its ability to circulate year-round, in contrast to seasonal viruses such as RSV and influenza, which exhibit more defined periods of prevalence.<sup>19,20</sup> Analysis of co-infections revealed that ADV was the most frequent pathogen co-infecting RV, followed by RSV. This observation contrasts with epidemiological studies in pediatric populations, where RV is most commonly detected in conjunction with RSV.<sup>21,22</sup> Notably, previous research has indicated that in children with RV and ADV coinfections, the presence of ADV is associated with increased clinical severity, including leukocytosis and neutrophilia.<sup>23</sup>

Our findings indicated that RV infections manifest more frequently as pneumonia in children who do not develop asthma. Acute bronchitis presented as an acute diagnosis with similar frequency in the group that

developed asthma and the group that did not. Notably, 48% of studied children with rhinovirus-induced bronchitis progressed to bronchial asthma within a 3-year follow-up period. While prematurity and pathological perinatal history did not appear to be significant risk factors, family history of atopy was associated with an increased risk of asthma. The presence of atopy markers, particularly sensitization to house dust mites and grass allergens, along with elevated peripheral eosinophilia and total IgE levels, was also associated with an elevated risk of asthma development. The use of inhaled corticosteroids was significantly higher in children diagnosed with asthma than in those without. These findings highlight the significant influence of atopy on the development of bronchial asthma in the studied age groups of children.<sup>17,24</sup> Studies have shown that children with both RV infection and allergic sensitization during infancy have a significantly higher risk of developing recurrent wheezing and asthma. This risk is particularly pronounced in the more dangerous subtype of RV-C.<sup>25</sup> Furthermore, our results emphasize the potential benefits of inhaled corticosteroids in managing children with frequent wheezing associated with risk factors for asthma combined with proper adherence and correct medication administration for optimal outcomes.<sup>3</sup>

The composition of the respiratory microbiome and its intricate relationship with mucosal immunity have been recognized as key factors influencing susceptibility to respiratory infections.<sup>26,27</sup> However, the many complex interactions and their clinical implications remain poorly understood. For instance, respiratory viruses can exploit microbes during epithelial cell infections. This interaction may compromise the integrity and functional capacity of the epithelial barrier, effectively enhancing viral penetration into the cells.<sup>28</sup> The most common microbial pathogen cultured from the nasal swabs of participants was *Moraxella catarrhalis*, followed by *Staphylococcus aureus*. Our findings regarding microbiome composition align with those of McCauley et al, who observed a link between *Moraxella catarrhalis* infections and an elevated risk of both bronchospasm recurrence and asthma exacerbation in younger patients. This association was further coupled with the evidence of eosinophil activation.<sup>29</sup> Rhinovirus infection increases the detection of specific bacterial pathogens, not only *Moraxella catarrhalis* but also detected *Streptococcus pneumoniae* in our participants. This can contribute to the severity of respiratory tract illnesses in children with asthma.<sup>30</sup> Interestingly, no significant differences were observed in the colonization of the upper respiratory tract by common microbial pathogens between the two groups.

One limitation of this study is the relatively small sample size and uneven distribution of patients across comparative groups. A larger cohort would have enhanced the robustness of the data, allowing for more sophisticated statistical analyses, and yielding more definitive conclusions. Additionally, the ability to identify specific RV subtypes, particularly those within the RV-A and RV-C groups, with higher virulence, viral load, and lower respiratory tract affinity, could significantly enhance the assessment of individual cases. Future research should prioritize prospective studies that follow children under five years of age from the time of suspected RV primoinfection to either the development or exclusion of bronchial asthma. These studies might incorporate comprehensive data collection, including the modified asthma predictive index and eosinophil counts from bronchoalveolar lavage fluid as well as emerging novel potential asthma biomarkers. This approach provides valuable insights into the complex relationship between early RV infection and the subsequent risk of asthma.

## Conclusions

This study identifies potential risk factors associated with atopy, including a positive family history, sensitization to allergens, peripheral eosinophilia, and elevated total IgE levels, as well as the use of inhaled corticosteroids, that may predispose children with rhinovirus infections to the development of asthma. By assessing these factors, clinicians can identify high-risk individuals who may benefit from close monitoring and targeted interventions, such as early initiation of inhaled corticosteroids or more frequent follow-up visits, to mitigate the risk of long-term consequences associated with chronic airway inflammation.

## Data Access Statement

The datasets analyzed during the current study are available in the cloud centre (Microsoft One Drive) repository at: RHINO\_asthma\_study\_datasets.xlsx.

## Statements

The study was approved by the Ethics Committee of the National Institute of Pediatric Tuberculosis and Respiratory Diseases in Dolny Smokovec, Slovakia, and conducted as a prospective non-interventional comparative cohort study. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (1975; revised 2013) to ensure the protection and well-being of all human participants.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by a project of the Ministry of Education, Research, Development, and Youth of the Slovak Republic (VEGA 1/0024/23). The funder had no role in the design, data collection, data analysis, or reporting of the study.

## Disclosure

The authors declare no conflicts of interest.

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