





Risk Factors and Clinical Determinants in Bronchiolitis of Infancy

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Abstract

OBJECTIVES: The aims of this study was to demonstrate the viral pathogens, to evaluate the clinical prognosis, risk factors for recurrence, severity of acute viral bronchiolitis episodes among pediatric patients.

MATERIALS AND METHODS: Our study included 101 children aged between 2 months and 2 years diagnosed with clinical bronchiolitis between September 2011 and April 2012. The demographics and clinical, laboratory, and radiological results of the patients were recorded. Nasopharyngeal swab samples were collected and analyzed through polymerase chain reaction (PCR) method. The patients were followed up for at least one year for new episodes, existence of wheezing, frequency of pulmonary infections, and progression of asthma.

RESULTS: In half of the patients, determinants were indicated through the PCR method, with the most frequent being respiratory syncytial virus (44%). The frequency of bronchiolitis was higher in prematures ($p < 0.005$). There was a relationship between crowded family structure and the existence of wheezing ($p = 0.003$), increased recurrence ($p = 0.014$), and need for inhaler treatment ($p = 0.014$). The frequency was higher in patients living in urban cities ($p < 0.001$), in houses with heating stoves ($p = 0.001$), and in houses with smokers ($p = 0.001$). Patients living in houses with heating stoves had more severe episodes ($p = 0.018$). Recurrent wheezing and the need for regular inhaler usage were positively correlated with high API scores ($p = 0.008$ and $p = 0.002$, respectively).

CONCLUSION: Prematurity, exposure to smoking, living in a crowded house with heating stoves, and an urban life are the risk factors for frequent bronchiolitis. The API can be used to predict the recurrence of bronchiolitis.

KEYWORDS: Asthma, bronchiolitis, viruses

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INTRODUCTION

Acute bronchiolitis is the most frequent respiratory tract infection in infants. Although it is seen in more than 80% of infants younger than 6 months of age, it is at the same time the most frequent reason for hospitalization of children younger than 2 years [1]. The most commonly detected etiological agents of acute bronchiolitis include respiratory syncytial virus (RSV), parainfluenza (PIV), influenza (INF), and adenovirus (ADV). RSV is responsible for 60%-80% of acute bronchiolitis cases during fall and winter [2]. Within the last few years, new viral determinants, including human rhinovirus (HRV), enterovirus, human metapneumovirus (hMPV), coronavirus (HCov), and human bocavirus (HBoV), have been detected in infections of the lower respiratory tract in infants and children [1].

Acute bronchiolitis causes an increase in rates of morbidity related to childhood wheezing during the infantile period [3]. Some studies found a relationship between RSV and HRV triggered wheezing episodes in the infantile period and the development of childhood asthma and atopic dermatitis. Therefore, it is necessary to conduct research on the relationship between childhood acute bronchiolitis, wheezing, and asthma as well as on the prevention of the disease and early treatment. To do so, the etiology of the disease needs to be understood [4, 5]. Although they have shown differences in indicating certain viral determinants, viral culture and polymerase chain reaction (PCR) tests are the tests with the highest sensitivity [6].

In our study, we aimed to evaluate the association of viral etiological agent with the clinical presentation of bronchiolitis and to investigate the environmental factors that influence disease frequency and severity in children aged two months to two years. Moreover, we aimed to determine the prognosis in this group.

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MATERIALS AND METHODS

Our study covered 101 children aged between 2 months and 2 years who had been diagnosed with clinical bronchiolitis in the emergency and pediatric pulmonology departments and treated at inpatient or outpatient clinics between September 2011 and April 2012. The diagnosis of bronchiolitis was based primarily on each patient's history of preceding viral upper respiratory tract infections, restlessness, cough and/or rhinorrhea with signs of a respiratory illness including tachypnoea, intercostal and/or subcostal retractions, accessory muscle use, nasal flaring, grunting, color changes or apnea, wheezing or crackles, and lower oxygen saturations [7]. Subjects younger than two months and older than two years, subjects without clinical acute bronchiolitis, subjects whose parents did not agree to participate in the study, and those with other structural anomalies were excluded. The Institutional review board of our university approved our study. Informed consent was granted by all the parents.

Age at the time of admission, sex, and demographic characteristics were recorded at admission. Patient-related issues, such as the commencement date of complaints, existence of wheezing, gestational age, weight at birth, and whether they had a previous history of atopy diagnosed by a physician, were determined and recorded. Issues related to the patients' families and environments, such as the number of people residing at the house or apartment, the household's smoking status, the type of heating used (central heating or stove heating), the place of residence (urban or rural), and history of asthma in the family, were also questioned and recorded.

Viral symptoms, including fever, pulse, and respiratory rate, were recorded. For each patient, tachypnea was deemed as the respiratory rate above the normal respiratory rate limit according to age, while tachycardia was deemed as the pulse rate above the normal pulse rate limit according to age. Pulmonary sounds, including rales, rhonchi, wheezing, nasal flaring, and intercostal and subcoastal retractions, were recorded for each patient. Each patient was categorized upon their admission to determine bronchiolitis severity [7].

MAIN POINTS

- In half of the patients, viral determinants were indicated through the PCR method, with the most frequent being respiratory syncytial virus (RSV).
- Bronchiolitis is most frequent in winter.
- Lymphocytosis is observed to be dominant in all virus types except influenza (INF). Lymphopenia and high sedimentation rates are significantly higher for INF.
- Prematurity, exposure to smoking, living in a crowded house with heating stoves, and an urban life are the risk factors for frequent bronchiolitis.
- Patients living in houses with heating stoves have more severe episodes.
- The asthma predictive index (API) can be used to predict the recurrence of bronchiolitis.

Bronchiolitis severity was scored as follows:

1. Mild disease: The patient's respiratory rate per minute is below 50; heart rate is below 140 beats per minute; retractions are mild; pulse oximetric saturation (SpO₂) is above 93%. The patient has no apnea and cyanosis.
2. Moderate disease: The patient's respiratory rate per minute is between 50 and 70; heart rate is between 140 and 160 beats per minute; retractions are moderate; SpO₂ is between 86% and 92%. The patient has no apnea and cyanosis.
3. Severe disease: The patient's respiratory rate per minute is above 70; heart rate is above 160 beats per minute; retractions are severe; SpO₂ is below 85%. The patient has apnea and cyanosis. The severity score was determined according to the most severe criteria.

Baseline pulse oximetric saturation levels while breathing room air were measured and recorded.

Total blood count and serum C-reactive protein (CRP) were analyzed in all patients. Nasopharyngeal swab samples were taken at the time of presentation to pinpoint the determinant viruses in bronchiolitis. These samples were kept at 20°C before the analyses. Viruses were detected through the multiplex PCR method Seeplex RV 12 ACE detection kit (Seeplex; Seegene, Seoul, South Korea). A total of 12 different viral determinants, including human hMPV, ADV, HCov 229 e, HCovnl63, HCovoc43-hku1, PIV 1-2-3, INF A-B virus, HRV A/B, and human RSV A-B, were investigated.

Patients in follow-up were classified as either positive or negative according to the asthma predictive index (API) [8]. The durations of hospitalization for the inpatient treatments were recorded. Patients' new episodes, existence of wheezing, and duration of inhaler usage (none, intermittent, and persistent [usage for at least a year]) were evaluated. The clinical statuses of patients who had not been able to come in for follow-ups were determined and recorded through phone calls. Those patients who were not available for follow-ups were noted as well.

Statistical Analyses

To select statistical methods to be employed, the Shapiro-Wilk normality test was conducted; however, if any of the groups did not meet the assumption of normality, then non-parametric testing methods were selected. Within this scope, the Mann-Whitney U test was used to compare the variables obtained by measurement in two independent groups, while the chi-square and Fisher exact tests were used to analyze the relationships among categorical variables or intergroup differences. Logistical regression analyses were also conducted to determine the risk factors thought to affect bronchiolitis severity. The related variables and related odds, 95% confidence intervals, and p values are summarized in tables. The study's statistical analyses were conducted using Statistical Package for the Social Sciences 17.0 (SPSS Inc.; Chicago, IL, USA), and the statistical significance limit was set at $p < 0.05$.

RESULTS

Age at Admission, Gestational Age, and Sex

A total of 101 patients were included in the study. The male:female ratio was 1.46:1. In total, 10 patients did not

have enough follow-up periods. The patients were allocated into three different groups according to their ages. The mean age was 9 ± 2.4 months. The number of patients aged between 2 and 6 months was 25 (24.8%), while the number between 7 and 12 months was 28 (27.7%) and the number between 13 and 24 months was 48 (47.5%). Bronchiolitis severity, the existence of wheezing on follow-up, and the recurrence of bronchiolitis did not change according to age groups. The patients were then divided into two groups according to their gestational ages. While 28 (27.7%) patients were premature, 73 (72.3%) were mature. The frequency of bronchiolitis was higher in the premature patients ($p < 0.005$).

When the patients' bronchiolitis classified according to severity, it was seen that 12 (11.9%) had mild, 71 (70.3%) had moderate, and 18 (17.8%) had severe episodes. The severity of the bronchiolitis was re-classified at the second, sixth, and twelfth hours. Mild bronchiolitis was detected as 18.8% at the second, 30.6% at the sixth, and 54.4% at the twelfth hours. Bronchiolitis severity did not change statistically according to sex, age at admission, and gestational age.

In total, 77 (76.2%) of the 101 patients were hospitalized, and 24 (23.8%) of them were treated as outpatients. The mean hospitalization period was 4.57 ± 3.47 days; it was not statistically longer in premature than mature patients (5.2 ± 3.1 days versus 4.3 ± 3.5 days, respectively; $p = 0.19$).

Environmental Conditions and Factors Affecting Severity of Bronchiolitis

In total, 78 (77.2%) of the 101 patients lived in cities, while 23 (22.8%) patients lived in villages. Frequency of bronchiolitis was significantly higher among urban patients ($p < 0.001$). A total of 67 (66.3%) patients had heating stoves at their houses as the source of heat, while 34 (33.7%) patients had central heating. The frequency bronchiolitis was significantly higher in patients whose houses had heating stoves ($p = 0.001$).

A total of 50 (49.5%) patients had five or more people living in their houses. Upon follow-up, significant relationship was observed between crowded family structure and existence of wheezing ($p = 0.003$), increased bronchiolitis recurrence ($p = 0.014$), and an increased need for inhaler treatment ($p = 0.008$). However, there was, no relationship between the severity of the bronchiolitis episodes and family structure ($p = 0.10$).

A total of 67 (66.3%) patients had smokers among household members. The frequency of bronchiolitis was significantly higher in these patients ($p = 0.001$). The distribution of the patient's bronchiolitis scores upon presentation to the hospital, oxygen saturation measurements, duration of hospitalization, bronchiolitis recurrence, and the need for inhaler treatment did not change according to the patient's exposure to smoking. The frequency of both mild and moderate episodes was found to be significantly higher (89.5% and 67.6%, respectively) in those who were exposed to smoking than those who were not exposed to smoking ($p = 0.023$).

The risk factors affecting bronchiolitis severity were analyzed through a single variable logistical regression analysis. Heating with a stove at home ($p = 0.008$), smoking at home

Table 1. A single variable logistical regression analysis about the risk factors assumed to be affecting moderate and severe episode developments

Risk factors	Odds ratios (95% CI)	p
Sex (male)	1.731 (0.610-4.909)	0.302
Prematurity	1.190 (0.394-3.593)	0.757
Heating with a stove	5.854 (1.250-27.402)	0.025
Exposure to smoke	0.233 (0.079-0.687)	0.008
Living in urban areas	2.036 (0.650-6.372)	0.222
Crowded household population	0.316 (0.102-0.979)	0.046

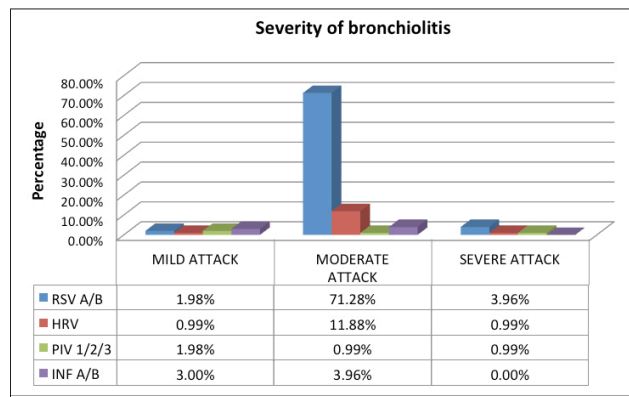


Figure 1. Distribution of viruses according to the severity of bronchiolitis

($p = 0.046$), and having a large household population ($p = 0.025$) were found to be the factors that increase bronchiolitis severity. Data are shown in Table 1.

The relationship between the four most commonly detected viruses and bronchiolitis severity classification was evaluated. Moderate and severe bronchiolitis episodes were significantly less frequent in the PIV virus ($p = 0.040$), and severe bronchiolitis episodes, specifically, were significantly less frequent in the INF A/AB virus ($p = 0.022$). Data are shown in Figure 1.

Viral Agents Detected

Viral etiological agents were detected in 50 (49.5%) patients. The viruses included hMPV, ADV, HCoV 229e/NI63-Oc43/Hku1, PIV, INF A, HRV, and RSV A-B. RSV was detected in 22 (44%) patients, HRV in 14 (28%), INF A in 7 (14%), hMPV in 4 (8%), PIV in 4 (8%), HCoV in 4 (8%), and ADV in 3 (6%). More than one agent was detected in 16% (8/50) of patients.

Seasonal Distribution of the Viruses

When the monthly distribution of bronchiolitis was investigated, it was determined that patients were admitted to hospitals most often in February (19.8%). Bronchiolitis was most frequent in winter (52.5%), and this rate was statistically significant ($p < 0.001$) (Figures 2 and 3). Viruses, most of which were RSVs, were also detected most often in winter. This was followed by HRV frequency. When the monthly distribution of RSV A/B was investigated, it was observed to peak in February. Regarding the monthly distribution of HRV, it was seen to have peaked in November and December, with

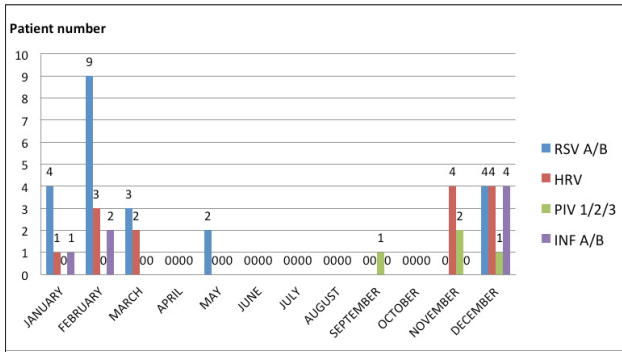


Figure 2. Distribution of viruses according to the months

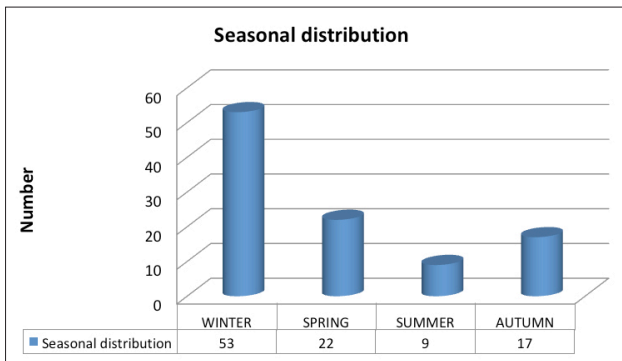


Figure 3. Distribution of patients according to the seasons

Table 2. Complaints and physical findings at admission

Complaint or finding	Values n (%)
Cough	101 (100)
Restlessness	96 (95)
Wheezing	90 (89.1)
Tachypnea	87 (86.1)
Difficulty in feeding	73 (72.3)
Tachycardia	65 (64.4)
Nasal discharge	54 (53.5)
Retraction	44 (43.6)
Fever	20 (19.8)
Cyanosis	11 (10.9)

the highest rate of detection in the wintertime. Similar to RSV A/B, HRV was not detected in summer.

Complaints and Physical Examination Findings at Admission

The distribution of complaints according to the etiological agents is shown in Table 2. Coughing was the most frequent complaint among all agents and was present in all patients. The second most common symptom was restlessness (95%) and the third was wheezing (89.1%). Cyanosis, which was the least common symptom, was seen most frequently in PIV (25%), while complaints of restlessness and nasal discharge were found to be significant for RSV ($p=0.034$ and $p=0.001$, respectively).

Laboratory Findings of the Patients

When the laboratory results of the patients were compared with regard to the four most commonly seen viral etiological

agents, lymphocytosis was observed to be dominant in all virus types except INF. Lymphopenia and high sedimentation rates were significantly higher for INF ($p=0.037$ and $p=0.025$, respectively). Neutrophil, monocyte, eosinophil, and platelet counts were similar among all the virus types.

Radiological Evaluation of the Patients

A chest x-ray was performed for all patients and was evaluated by an experienced pediatric pulmonologist. The most commonly detected radiological finding was hyperinflation, seen in 92 (91%) patients. The other significant findings were peribronchial infiltration in 68 (67.3%) patients, patchy consolidation in 8 (7.9%) patients, and atelectasis in 2 (1.9%) patients. There were no statistical correlations between radiological findings and the virus types.

Treatment Modalities of the Patients

A total of 77 (76.2%) patients were hospitalized. The mean duration of hospitalization was 4.57 ± 3.47 days, with durations ranging between 1 and 14 days. All the patients were given bronchodilators, 86 (85.1%) were given antibiotics, and 52 (51.5%) were given systemic steroid treatments. Antibiotic treatment was started if the patient had a high fever, showed consolidation in their chest x-ray or had high acute phase reactants. Steroids were started if the patient had a severe episode or did not respond to the bronchodilator. Antibiotic and systemic steroid usage were higher among the hospitalized patients ($p=0.034$ and $p=0.003$, respectively).

Clinical Follow-Up of the Patients

A total of 37 (40%) out of 91 patients who had been contacted and had adequate (at least one year) follow-up periods had wheezing problems. While no recurrent bronchiolitis episodes were seen in 21 (23%) of these patients, 41 (45%) had between one and three episodes and 29 (32%) had three or more episodes.

The patients were divided into two groups, positive and negative, according to API. Seventy-six (75.2%) patients were API negative, while 25 (24.7%) patients were API positive. Recurrent wheezing and the need for regular inhaler usage were positively correlated with high API scores ($p=0.008$ and $p=0.002$, respectively).

The recurrence of bronchiolitis was seen in 68% of the RSV positive, 78% of the HRV positive, 28.5% of the INF positive, and 25% of the PIV positive patients. The need for inhaler treatment was seen in 42% of the HRV positive, 31% of the RSV positive, 28.5% of the INF positive, and 25% of the PIV positive patients. Sex, age at admission, gestational age, API, recurrence of bronchiolitis, recurrence of wheezing, and the need for inhaler treatment were not statistically different between the virus types.

DISCUSSION

Acute bronchiolitis is a contagious infection of the lower respiratory tract often caused by viral agents or the inflammatory narrowing of small airways and is mostly seen in children younger than 2 years [9]. In a multi-centered study conducted by Mansbach et al. [10], the authors stated that overall children younger than 2 years with bronchiolitis who

admitted to emergency rooms had a median age of 6.3 months (IQR 3.1 to 10.2) and most were male (61%) consistent with our study.

Epidemic cases related to bronchiolitis typically begin in late fall in temperate climates and continue until the middle of spring. They are most commonly seen in winter and spring, especially in January, February, or March [11, 12]. Epidemics in Turkey are most frequently seen in winter and early spring [13]. In our study, 86% of the patients were admitted to our hospital between October and April, while 52% were presented in the winter (December, January, and February).

Day care center attendance, passive smoking, living in crowded houses, and poverty have been proven to be associated with the severity of bronchiolitis [14]. In our study, passive smoking, living in a crowded house, and living in a house with a heating stove were found to affect bronchiolitis severity. Recurrence of wheezing and bronchiolitis, as well as the increased need for inhaler treatment, were also found to be associated with living in a crowded house.

Passive smoking has a major influence on the risk of lower respiratory infections in infants, especially on bronchiolitis. This risk is particularly strong in relation to postnatal maternal smoking [15]. In our study, frequency of bronchiolitis was significantly higher in patients living in houses with smokers.

The results of a study conducted by Papadopoulos et al. [16] revealed no difference between patients with and without determinants regarding sex, age, fever, and bronchiolitis scores. Similar results were found in our study. Furthermore, there were no differences in our study with regard to gestational age, birth weight, and laboratory results.

The PCR is a sensitive molecular method in which nucleic acids of viruses can be shown in the microbiological diagnosis of bronchiolitis [17]. The multiplex PCR method, which analyses nasopharyngeal swab samples, enables the simultaneous detection of many viruses. The rate of virus detection, however, varies widely, according to the results of studies. In a study conducted by Templeton et al. [18] the multiplex PCR method used for respiratory tract viruses was only able to detect determinants in 24% of the patients. In a 3-year prospective study conducted among 318 patients receiving inpatient treatment in the infantile age group, the researchers investigated 16 virus types and detected determinants at a rate of 86.5%. They detected RSV in 52.9%, HRV in 17.4%, HBoV in 11.4%, ADV in 7.6%, and other viruses in 10.3% of the patients [1]. Mansbach et al. [10] detected RSV in 64%, HRV in 16%, hMPV in 9%, and other viruses in 6% of the patients. In our study, the PCR method detected determinants in 49.5% of the patients. The most frequently detected viruses in our study were RSV B (17.8%), HRV (13.8%), INF A (6.9%), and PIV 3 (2.9%). Viruses that were detected more infrequently in our study included hMPV, ADV, HCov, and RSV A. The fact that the vast majority of our patients were treated at primary and secondary healthcare centers at the commencement of their symptoms and were referred to us at later times can be listed among the reasons why our virus detection rate was particularly low. The most commonly seen determinant of bronchiolitis, RSV, is isolated in the nasophar-

ynx at the commencement of disease symptoms and it generally disappears within 7 days [19].

Several studies have demonstrated that severe viral infections in early childhood, especially RSV and hMPV infections, are related to recurrent wheezing and asthma in these patients' older ages [20]. Accordingly, the vast majority of our patients who followed up owing to recurrent wheezing were seen to have RSV followed by HRV; although it had been isolated, the rate of hMPV was found to be 1% (1 patient).

While RSV is known to be a determinant for wheezing in young children, HRV has proven to be a determinant in the exacerbation of asthma among older children [21]. In our study, although we did not detect statistically significant differences, recurrent bronchiolitis episodes were seen in 78% of HRV positive patients and 68% of RSV positive patients. In total, 42% of HRV positive patients had regular inhaler needs in their follow-ups, while in RSV positive patients, this rate was found to be 31%. Therefore, we believe that it is necessary to have an early diagnosis of asthma attacks caused by viral infections to avoid delays in treatment, to follow-up with patients regarding bronchiolitis episode recurrences, and to inform the patients' parents about these facts.

In their study, Ergin et al. [22] detected one episode in 68.7% of patients with bronchiolitis, two episodes in 13.4%, and three or more episodes in 18%. In our study, 23% of the cases had no recurrent episodes among 91 follow-up patients, 45% had less than three episodes, and 31% had three or more episodes.

The positivity of the API has a specificity of 97% and positive predictive index of 77% for the development of persistent asthma in children. While wheezing continues in 77% of children who have a high risk of contracting allergic diseases, it does not continue in 97% of children who have a low risk [8]. API positivity in our study was found to be 24.75%, and API-positive patients required regular inhaler use, as the presence of wheezy respiration in these patients was frequent.

Wheezy children can have diseases with different pathophysiological processes, progressions, and prognoses. The early differentiation of these diseases is necessary for patients to receive the correct follow-ups and modes of treatment. In children with recurrent wheezing, it is important to pinpoint the etiology to determine optimal treatment and prognosis early. In doing so, the rates of unnecessary antibiotic and inhaler treatment will decrease and therefore bring about a decrease in treatment costs. We thus believe that diagnostic methods through which early results can be obtained in viral infection diagnoses should be devised.

Chiappini [23] detected that lymphocytopenia is a marker for the influenza A/H1N1 2009 virus infection (H1N1 INF) in children. Wang et al. [24] found the diagnostic sensitivity of the rapid influenza diagnostic test to be 45.5%. Combining the lymphocyte counts and CRP levels provided a diagnostic sensitivity of 91.5%, and it was suggested to use a combination of lymphopenia and low-level CRP in the early diagnosis of H1N1 INF, especially for the patients with a false-negative rapid influenza diagnostic test. Lymphocytosis was observed

to be dominant in all virus types except INF and lymphopenia, and in our study, lymphopenia and high sedimentation rates were significantly higher for INF ($p=0.037$ and $p=0.025$, respectively).

There is a rising trend in the rate of bronchiolitis and bronchiolitis-related hospitalizations for preterm infants under 29 weeks of gestational age [25]. The lower the gestational age, the higher the hospitalization rate and the greater the likelihood of the patient requiring the highest level of neonatal care [26]. The frequency of bronchiolitis was also higher in premature patients in our study.

Studies have suggested that HRV, the agent of the common cold, may be more pathogenic than previously thought. Furthermore, comparative studies with larger populations are needed to determine the sensitivity of the PCR method in comparison with other diagnostic methods. Such studies will enable us to determine the prevalence and incidence of viral agents more clearly.

It could be considered a limitation of the study that we excluded infants under 2 months of age. We consider that infants under 2 months of age will require a higher degree of personalisation of oxygen saturation targets depending on their disease course. Another limitation is that the study was carried out in only one referral center. We suggest that future work include samples from a greater geographic area or be expanded to a multi-center analysis.

In conclusion, the parents of patients with bronchiolitis should be informed about the presence of new episodes, as these episodes could be followed by wheezy respiration and thus require follow-up hospitalization. Careful attention should be paid to probable asthma development, especially in API-positive patients, and no delays in the commencement of treatment should be allowed in patients requiring inhaler treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University Meram School of Medicine (2011/108).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept- S.P.; Design - S.P., O.A.; Supervision - S.P., O.A.; Resources - S.P., M.O.; Materials - O.A., M.O.; Data Collection and/or Processing - O.A., S.P., M.O.; Analysis and/or Interpretation - O.A., S.P.; Literature Search - O.A., S.P., B.G.; Writing Manuscript - O.A., S.P.; Critical Review - S.P., B.G.; Other - O.A., S.P., B.G., M.O.

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