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Title: Risk factors and clinical determinants in bronchiolitis

Short Title: Acute bronchiolitis

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Abstract

Objective: Our primary aim was to demonstrate the viral pathogens, clinical symptoms and findings of acute viral bronchiolitis attacks of child patients aged between 2 months and 2 years. Our secondary aim was to evaluate the clinical follow-up prognoses and detect the risk factors for recurrence and severity of bronchiolitis among them.

Material and Methods: Our study covered 101 children aged between 2 months and 2 years who had been diagnosed with clinical bronchiolitis between September 2011 and April 2012. The demographic, clinical, laboratory and radiological results of the cases were recorded.

Nasopharyngeal swab samples were collected from the patients for virus studies and analyzed through polymerase chain reaction (PCR) method. Within the framework of at least one-year follow-ups with the patients, new attacks, existence of wheezing, frequency of pulmonary infections and progression of asthma were evaluated.

Results: In 50 of the 101 patients (49.5%), determinants were indicated through the PCR method, with the most frequent being respirarory syncytial virus (RSV) (44%). The frequency of bronchiolitis was higher in premature patients ($p < 0.005$). There was a significant relationship between crowded family structure and the existence of wheezing ($p = 0.003$), increased bronchiolitis recurrence ($p = 0.014$) and increased need for inhaler treatment ($p = 0.014$). The frequency of bronchiolitis was significantly higher in patients living in urban cities ($p < 0.001$), patients using heating stoves ($p = 0.001$) and patients living in houses with smokers ($p = 0.001$). Patients living in houses with heating stoves had more severe attacks than patients with central heating ($p = 0.018$). The asthma predictive index (API) levels of the wheezing patients in their follow-ups were found to be statistically significant ($p = 0.008$).

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

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Keywords: Viruses, bronchiolitis, infancy, asthma.

INTRODUCTION

Acute bronchiolitis is the most frequently occuring respiratory tract infection in infants. While 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 hospitalisation of children younger than 2 years [1]. The most commonly detected aetiological 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 gives way to a increase in rates of morbidity related to childhood wheezing during the infantile period [3]. Some studies on the subject found a relationship between wheezing attacks triggered by RSV and HRV in the infantile period and the development of childhood asthma and atopic dermatitis. Therefore, it is necessary to conduct careful research on the relationship between childhood acute bronchiolitis, wheezing and asthma as well as prevention of the disease and early treatment. In order to do so, the aetiology 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 aim to determine the viral pathogens of acute bronchiolitis in order to demonstrate the differences in their symptoms and signs, to point out the environmental factors that influence the frequency and severity of the clinical status, and to evaluate the follow-up prognoses of patients with acute bronchiolitis aged between 2 months and 2 years.

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MATERIAL 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 rhinorrhoea with signs of respiratory illness including tachypnoea, intercostal and/or subcostal retractions, accessory muscle use, nasal flaring, grunting, colour changes or apnoea, wheezing or crackles, and lower O_2 saturations [7]. Those younger than 2 months and older than 2 years, those without clinical acute bronchiolitis, those whose parents did not want them to participate in the study, and those with other structural anomalies confused with bronchiolitis were exluded from the study. The Board of Ethics at our university granted their consent for our study (Consent no:2011/108). Before the study's initiation, all the parents were given a fully informed concent form, and all granted their consent. The data, which were collected prospectively in this study, were characterized by the study's analytical approach.

Each patient's age at the time of admission, sex, and demographic characteristics were determined. 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 also recorded. For each patient, tachypnoea was deemed as a respiratory rate above the normal respiratory rate limit according to age, while tachycardia was deemed as a pulse rate above the normal pulse rate limit according to age. Pulmonary sounds, including rales, rhonchus, wheezing, nasal flaring and intercoastal and subcoastal

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retraction, were recorded for each patient. Each patient was categorized upon their admission in order to determine the severity of their bronchiolitis case [7].

Bronchiolitis severity was scored as follows:

1) Mild disease: The patient's respiratory rate per minute is below 50; heart rate is below 140 per minute; retractions are mild; O2 saturation 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 140-160 per minute; retractions are moderate; O2 saturation 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 per minute; retractions are severe; O2 saturation is below 85%. The patient has apnea and cyanosis.

   The severity should be accepted according to the most severe criteria.

Patients' presenting SpO2 levels at room air were measured, and the results were 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 in order 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® RV12 Multiplex PCR Kit). Twelve different viral determinants, including human hMPV, ADV, HCov 229 e, HCov nl63, HCov oc43-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 hospitalisation for the inpatient treatments were recorded. Patients' new attacks, existence of wheezing, and duration of inhaler usage [none, intermittant, 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.

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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's exact test 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 SPSS 17.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, United States) 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. Ten of the 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%). The 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%) of the patients were premature, 73 (72.3%) were mature. The bronchiolitis frequency was higher in the premature patients ($p < 0.005$).

When the patients' bronchiolitis classifications were carried out according to severity, it was seen that 12 (11.9%) had mild, 71 (70.3%) had moderate and 18 (17.8%) had severe attacks. The severity of the bronchiolitis was re-classified at the 2nd, 6th and 12th hours. Mild bronchiolitis was detected as 18.8% at the 2nd, 30.6% at the 6th and 54.4% at the 12th hours. The bronchiolitis severity did not change statistically according to sex, age and gestational age.

Seventy-seven of the 101 patients (76.2%) were hospitalised, 24 of them (23.8%) were treated as outpatient. The mean hospitalisation period was 4.57 ± 3.47 days; it was not statistically longer in premature than mature patients (5.2 ± 3.1 versus 4.3 ± 3.5 days, p = 0.19)

Environmental conditions and factors affecting severity of bronchiolitis:

Seventy-eight of the 101 patients (77.2%) lived in cities, while 23 (22.8%) lived in villages. The bronchiolitis frequency was significantly higher in the urban patients (p < 0.001). Sixty-seven patients (66.3%) had heating stoves at their houses as the source of heat, while 34 (33.7%) had central heating. The bronchiolitis frequency was significantly higher in patients that used heating stoves (p = 0.001).

Fifty of the 101 patients (49.5%) each had five or more people living in their houses. Upon the follow-ups, there was a significant relationship observed between a crowded family structure and the existence of wheezing (p = 0.003), increased bronchiolitis recurrence (p = 0.014) and an increased need for inhaler treatment (p = 0.008). There was, however, no difference with regard to the severity of the bronchiolitis attacks (p = 0.10).

Sixty-seven (66.3%) of the patients had smokers living in their homes. 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 hospitalisation, bronchiolitis recurrence, and need for inhaler treatment did not change according to the patient's exposure to smoking. The frequency of both mild and moderate attacks was found to be significantly higher (%89.5 and 67.6%) in those who were exposed to smoking than those who were not exposed to smoking (p = 0.023)

Risk factors affecting bronchiolitis severity were analyzed through single-variable logistical regression analysis. Heating with a stove at home, smoking at home and having a large household population were the factors that increase the severity (p = 0.025, 0.008 and 0.046, respectively). Data were shown in Table 1.

The patients' cases were compared regarding the four most commonly detected viruses according to the patients' bronchiolitis classifications. Moderate and severe bronchiolitis attacks were significantly

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less frequent in the PIV virus (p = 0.040), and severe bronchiolitis attacks specifically were significantly less frequent in the INF A/AB virus (p = 0.022). Data was shown in Figure 1.

Viral agents detected:

Viral determinants were detected in 50 (49.5%) of the 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%), ADV in 3 (6%). More than one determinant was detected in 8 (16%) of 50 patients.

Seasonal distrubition of the viruses:

When the distribution of bronchiolitis as per month was investigated, it was detemined that patients were admitted to hospitals most often in February (19.8%). Bronchiolitis was most frequently detected 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; however, during the summer. Regarding the monthly distribution of HRV, it was seen to have peaked in November and December, with the highest rate of detection in the wintertime. Like RSV A/B, HRV was not detected in summer.

Complaints and physical examination findings at admission:

The distribution of complaints according to the determinants is shown in Table 2. Coughing was the most frequent complaint among all determinants 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 0.001, respectively).

Laboratory findings of the patients

When the laboratory results of the patients were compared according to the four most commonly seen viral determinants, lymphocytosis was observed to be dominant in all virus types except INF.

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Lymphopenia and high sedimentation rates were significantly higher for INF (p = 0.037 and 0.025, respectively). Neutrophil, monocyte, eosinophil and platelet counts were similar among all the virus types

Radiological evaluation of the patients:

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

Treatment modalities of the patients:

Seventy-seven of the patients (76.2%) were hospitalised. Mean duration of hospitalisation 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, exhibited leucocytosis or had high acute phase reactants. Steroids were started if the patient had a severe attack or did not respond to the bronchodilator. Antibiotic and systemic steroid usage were higher in the hospitalised patients (p = 0.034 and 0.003, respectively)

Clinical follow-up of the patients:

Thirty-seven (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 attacks were seen in 21 (23%) of these patients, 41 (45%) had between 1 and 3 attacks and 29 (32%) had 3 or more attacks.

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

Recurrence of bronchiolitis was seen in 68% of the RSV (+), 78% of the HRV (+), 28.5% of the INF (+), and 25% of the PIV (+) patients. The need for inhaler treatment was seen in 42% of the HRV(+), 31% of the RSV (+), 28.5% of the INF (+) and 25% of the PIV (+) patients. Sex, age, gestational age, API, recurrence of

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bronchiolitis, recurrence of wheezing and 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. [11], the authors stated that 59% of the patients younger than 2 years admitted to emergency rooms due to bronchiolitis were males with a mean age of 8 months. The percentage of male patients (59.4%) and the mean age in our study were similar to those of other studies.

Epidemic cases related to bronchiolitis typically begin in the 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 [12,13]. Epidemics in Turkey are most frequently seen in the winter and early spring [14]. In our study, 86% of the patients were admitted to our hospital between October and April, while 52% were presented in the winter.

Attending day care centers, experiencing second-hand smoke, living in crowded houses and living in poverty have been proven to be associated with the severity of bronchiolitis [15]. In our study, inhaling second-hand smoke, livig in a crowded house and heating with stove were found to be factors that affected the severity of the patients' bronchiolitis. 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 in the family home has a major influence on the risk of lower respiratory infections in infants and especially on bronchiolitis. This risk is particularly strong in relation to post-natal maternal smoking [16]. In our study, the frequency of bronchiolitis was significantly higher in patients living in houses with smokers.

The results of a study conducted by Papadopoulos et al. [17] 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 method is a highly sensitive molecular method by which nucleic acids of viruses can be shown in microbiological diagnosis of bronchiolitis [18]. 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.. the multiplex PCR method used for respiratory tract viruses was only able to detect determinants in 24% of the patients [19]. 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 53%, 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. [11] detected RSV in 64%, HRV in 16%, hMPV in 9%, and other viruses in 6% of the paients. 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, 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 nasopharynx at the commencement of disease symptoms and it generally disappears within 7 days [20]. Moreover, another reason why our determinant isolation rates were low might be related to the fact that some of our patients followed-up because of bronchiolitis were wheezy infants. Also the fact that a significant portion of these had recurrences within their one-year-follow-ups supports this idea.

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 [21]. Accordingly, the vast majority of our patients who followed up due to recurrent wheezing was 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 very young children, HRV has proven to be a determinant in the exacerbation of asthma among older children (22). In our study although we did not

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detect statistically significant differences, recurrent bronchiolitis attacks were seen in 78% of HRV (+) patients and 68% of RSV (+) patients. Forty-two percent of HRV (+) patients had regular inhaler needs in their follow-ups, while in RSV (+) patients, this rate was found to be 31%. Therefore, we believe that it is necessary to have an early diagnosis of asthma attacks brought by viral infections in order to avoid delays in treatment, to follow-up with patients regarding bronchiolitis attack recurrences, and to inform the patients'parents about these facts.

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

The positivity of the API has a specifity 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 patophysiological 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 aetiology to determine each patient's most 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 detected that lymphocytopenia is a marker for the A/H1N1 2009 virus infection in children [24]. Wang et al found that 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 suggested to use a combination of lymphopenia and low-level CRP in the early diagnosis of H1N1 INF, especially for the patients with false negative rapid influenza diagnostic test [25]. Lymphocytosis was observed to be dominant in all virus types except INF and lymphopenia and in our study, high sedimentation rates were significantly higher for INF.

There is a rising trend in rate of bronchiolitis and bronchiolitis-related hospitalisation in preterm infants under 29 weeks of gestational age [26]. The lower the gestational age, the higher the hospitalisation rate and the greater the likelihood of the patient requiring the highest level of neonatal care [27]. 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. Further comparative studies with larger populations are needed in order to determine the sensitivity of the PCR method in comparison to other diagnostic methods. Such studies will enable us to determine the prevalence and incidence of viral agents more clearly.

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

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Table 1: Single-variable logistical regression analysis about the risk factors assumed to be affecting moderate and severe attack developments.

Risk Factors	*O.R.(%95 G.A.)*	*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	2.036 (0.650-6.372)	0.222
Crowded household population	0.316 (0.102-0.979)	0.046

Table 2: Complaints anf phisical findings at admission

Complaint or finding	**n**	**%**
Cough	101	100
Restlessness	96	95
Wheezing	90	89.1
Tachypnoea	87	86.1
Difficulty in feeding	73	72.3
Tachycardia	65	64.4

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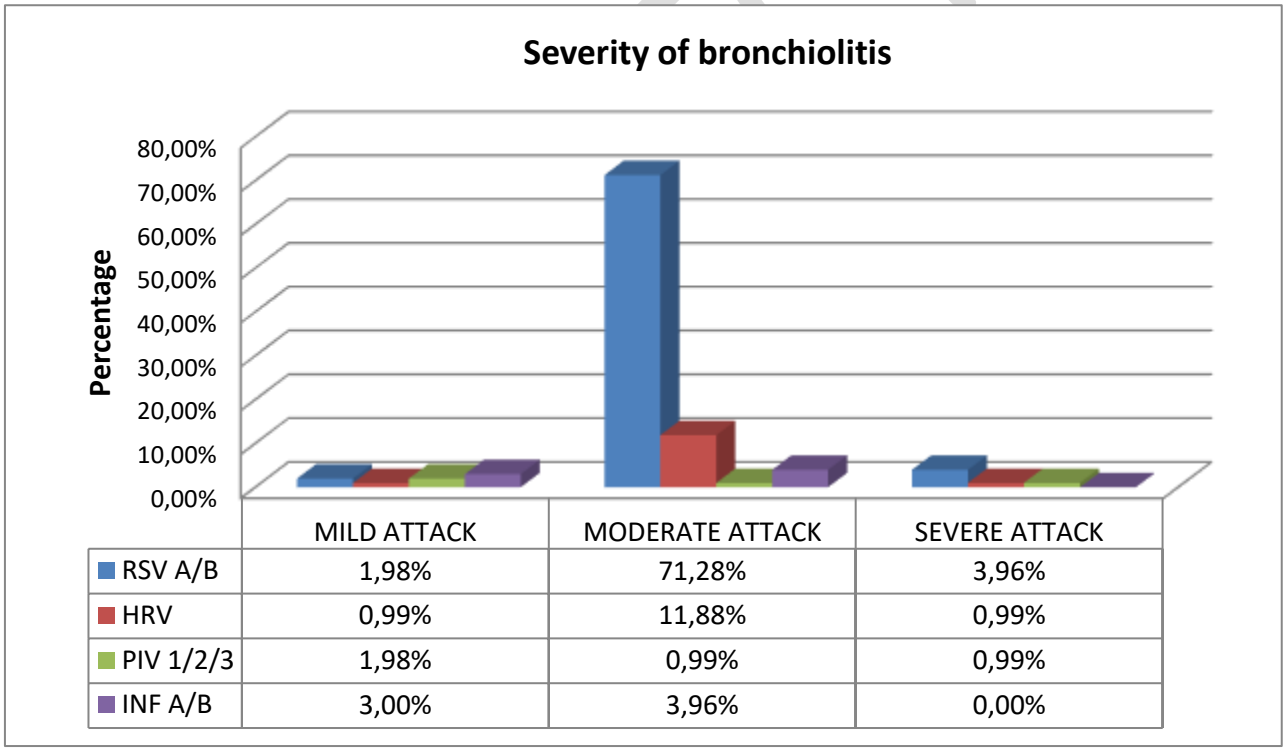
Nasal discharge	54	53.5
Retraction	44	43.6
Fever	20	19.8
Cyanosis	11	10.9



	MILD ATTACK	MODERATE ATTACK	SEVERE ATTACK
RSV A/B	1,98%	71,28%	3,96%
HRV	0,99%	11,88%	0,99%
PIV 1/2/3	1,98%	0,99%	0,99%
INF A/B	3,00%	3,96%	0,00%

Figure 1: Distrubition of viruses acording to the severity of bronchiolitis

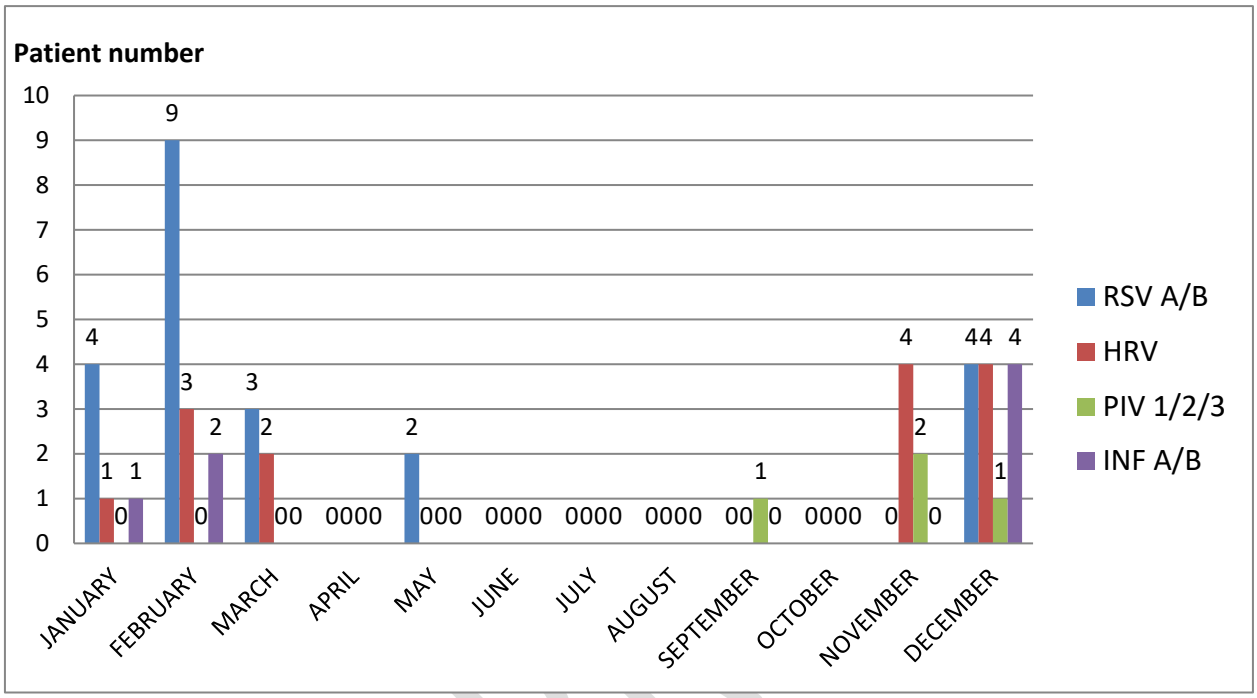


Figure 2: Distrubition of viruses according to the months

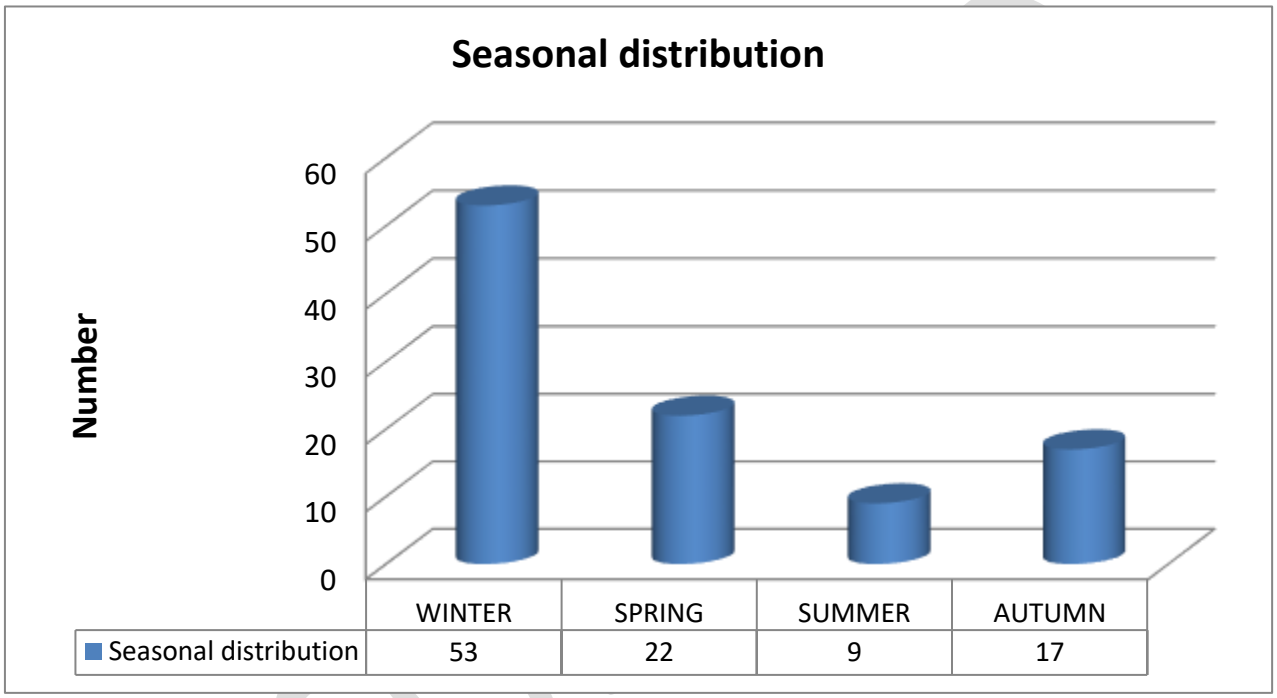


Figure 3: Distrubition of patients according to the seasons

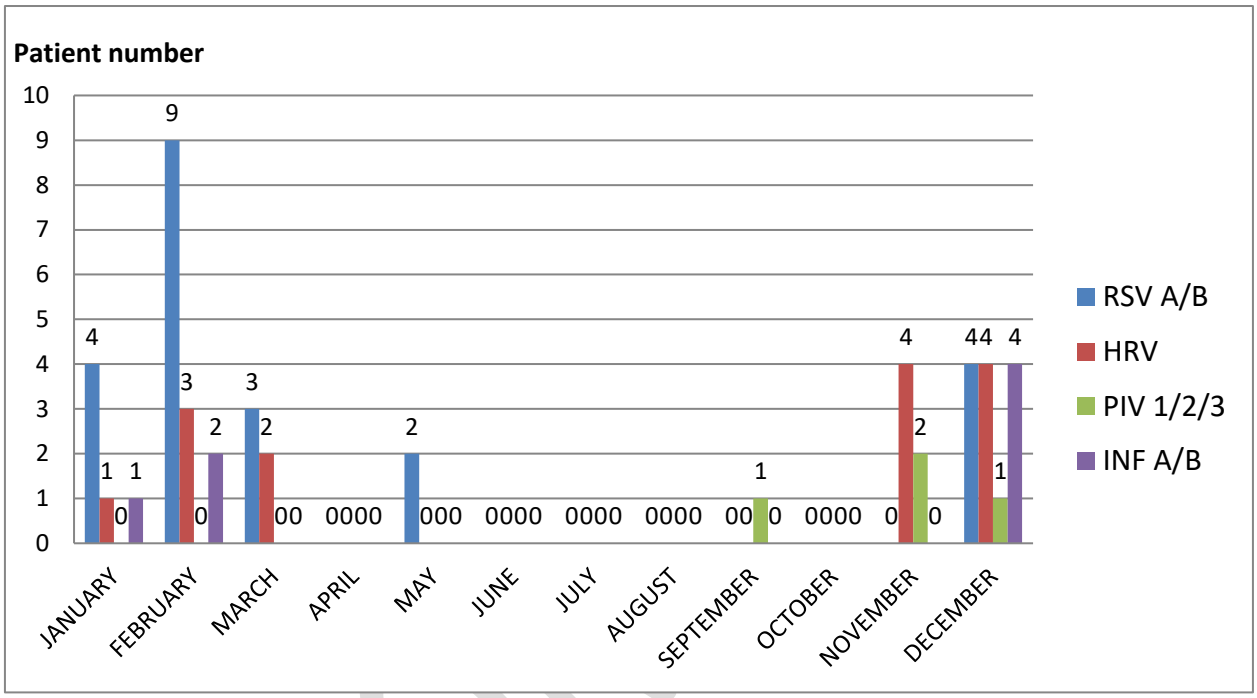


Figure 4: Distrubition of viruses according to the months

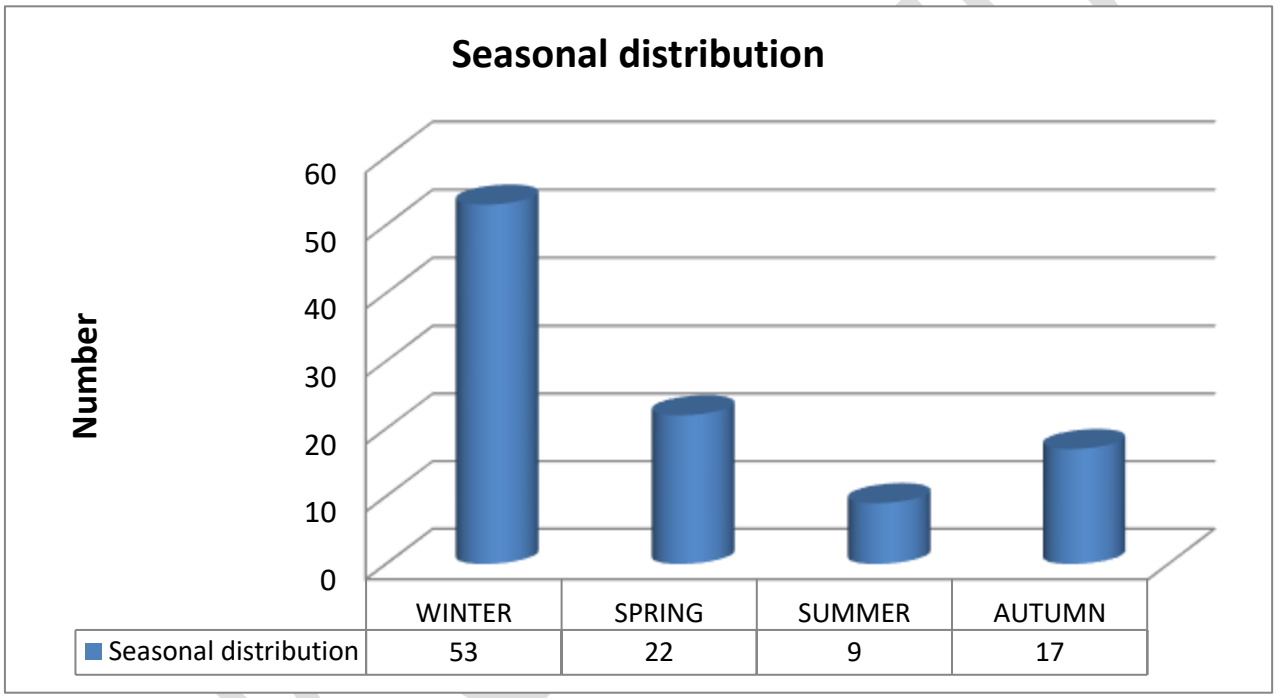


Figure 5: Distrubition of patients according to the seasons

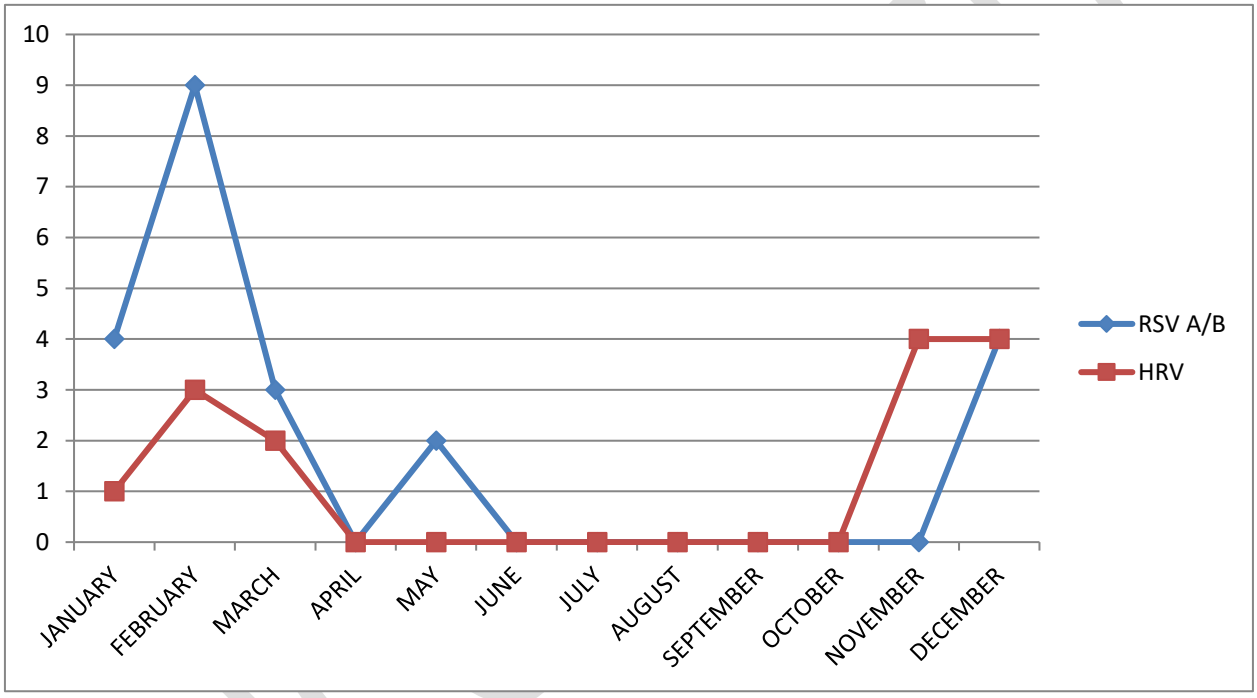


Figure 6: Distrubition of number of patients with RSV A/B and HRV according to the months