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Respiratory Viruses in Pediatric Patients with Acute Bronchiolitis: Analysis of 6 Consecutive Epidemic Seasons

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Abstract

Acute bronchiolitis is a clinical entity that may cause morbidity and mortality in infants. The aim of the study was to assess the viral frequency, seasonality, effect of viral pathogens in the course of the disease. A total of 516 pediatric patients under 2 years of age with acute bronchiolitis were evaluated for the study. The most common virus identified was Respiratory syncytial virus in 203 subjects (45%) as in other studies. Furthermore, human rhinovirus (n=105/451, 23.2%), human metapneumovirus (n=35/451, 7.7%), and influenza virus (n=32/451, 7%) were determined. 203 of the 516 RSV-positive cases, 133 (65.5%) were sole pathogens for RSV and 70 (34.5%) patients had RSV–coinfection, which was responsible for respiratory tract infection. The patients with RSV tended to have a need for supplemental oxygen, systemic steroid treatment. Although our study and the other studies in the literature showed that the most common viral agent was Respiratory syncytial virus; many different viral respiratory pathogens might be potential causative agents responsible for acute bronchiolitis. It should be considered an attack of bronchiolitis caused by the Respiratory syncytial virus or multiple agents in pediatric patients who have presented with wheezing, have longer hospitalizations, and have a need for more oxygen.

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Introduction

Bronchiolitis is one of the common lower respiratory tract diseases that usually caused by many different respiratory viruses in infants younger than 12 months of age. The entity commonly occurs following an infection that is usually an upper airway infection during the winter season. Inflammation and a partial obstruction resulting from several respiratory pathogens like RSV in the epithelium of bronchus creates the typical symptoms of bronchiolitis [1,2]. Even if lots of studies have stated that Respiratory Syncytial Virus (RSV) is the most common responsible virus for acute bronchiolitis (50% to 80%), it has been detected many different respiratory viruses that cause acute bronchiolitis as the sole or as coinfection [3-5]. The frequency of co-infections - dual and/or more

has been reported from 10% to 40% in hospitalized children [6-8]. Hospital admissions for bronchiolitis account for 18% in infants aged <1 year around the world. Due to the fact that the epidemiological data is insufficient in developing countries, the definitive incidence of bronchiolitis is unknown. However, it is known that the risk of bronchiolitis increase in children who receive less breast milk and live in low socioeconomic level regions, overcrowded societies, and smoking [9-12].

Despite the high hospitalization rate of bronchiolitis, there are not much-defined studies that have evaluated the burden of respiratory viral tract infection agents for bronchiolitis in childhood. This study was designed to evaluate the epidemiology and clinical characteristics of the respiratory viruses and to assess whether there could be a clinical difference and presence of several factors associated with disease severity of the viruses in patients who were hospitalized with the diagnosis of acute bronchiolitis.

Materials and methods

Patients and sample collection

Study population

The clinical records for 516 full-term infants (315 boys, median age 4.5 months, interquartile range: 9 months) hospitalized for bronchiolitis in of Ege University, Children's Hospital (a 200 bed, tertiary-care facility in İzmir, for six consecutive years, 2013 and 2019) were reviewed. The study was approved by the institutional review board named The Ethics Committee of Ege University (**20-1.1T/42**). This study also includes a retrospective study of bronchiolitis published in 2017 (DOI number 10.1177/2333794X17714378).

Bronchiolitis was clinically defined as the first episode of acute lower respiratory tract infection, characterized by the acute onset of cough, tachypnea, retraction, and diffuse crackles on chest auscultation in infants [13]. Exclusion criteria were prematurity and underlying chronic diseases, such as cystic fibrosis, interstitial lung disease, congenital heart disease, and immunodeficiency.

In order to inform about the age, gender, breastfeeding history, family smoking habits, family history for asthma, and atopy of the study patients from their parents, a structured questionnaire was devised. On admission, the records the following clinical and serological data: total white blood cell count, blood lymphocyte count, blood eosinophil count, C - reactive protein (C-RP), chest radiological findings, and the number of days hospitalization were collected. Wang respiratory score has been utilized to evaluate the severity of the disease with the parameters (wheezing, retraction, respiratory rate, and general situation) on hospital admission [14].

The detection of respiratory pathogens

In order to clarify the respiratory viruses [RSV, human rhinovirus (RV), Influenza Virus (INF), Adenovirus (ADV), Parainfluenza Viruses (PINF), human coronavirus (COV), Human Metapneumovirus (HPMV) and human bocavirus (HBOV)], the multiplex reverse transcription PCR method has been utulized (RealAccurate®, Respiratory RT PCR, PathoFinder, Netherlands and Seeplex® RV15 ACE Detection, Seegene, South Korea). Polymerase Chain Reaction, nasal swab samples were obtained from each patient and tested for the presence of Samples were frozen at −20°C and transported on ice to the Department of Clinical Microbiology and Virology Laboratory of the University for Viral nucleic acid Amplification using a standardized protocol [15].

Statistical analyses

Descriptive statistics were used to summarise demographics, frequency of respiratory viruses, and clinical featof the patients. Chi-square test and Fisher Exact test was handled to assess for associations between two or more qualitative variables in categorical variables. Continuous values were described as frequency (percentage) and mean ± SD or median and Interquartile Range (IQR) as appropriate. Quantitative data between the two independent groups were examined using unpaired "T" and "Mann Whitney *U*" tests. The logistic regression methods were used to assess and compute the predictive values of each predictor or risk factors for RSV status. The results of logistic regression analyses were reported as Odds Ratios (OR) with 95% Confidence Intervals (CI). A two-sided *P* value <0.05 was considered to be statistically significant. Data analyses were performed using SPSS version 21.0 and all analyses were conducted using personal computers (Chicago, IL, USA).

Results

Patients

Five hundred sixteen pediatric patients were admitted to clinic. **Table 1** shows that the demographic data, 315 males (61%) and 201 females (39%) with an age ranging between 1 month and 2-year old (median age of 4.5 months, IQR 9 months). The most frequent age range of patients with bronchiolitis was 1-6 months, accounting for 62.7% of all included cases. One-third of patients were exposed to passive smoking. The median duration of symptoms among infected children was 4 days and the median length of their length of stay in hospitalization (LOS) was 6 days (IQR 3.75 days).

Clinical Symptoms of the Patients

Table 1 also shows the clinical data and laboratory results, severity scores of bronchiolitis, and hospitalizations length of the patients. On admission, 489 (94.8%) of all patients presented with cough and 355 (68.8%) suffered from wheezing. One hundred seventy-seven (34.3%) cases needed oxygen supplementation. More than half of the patients had moderate bronchiolitis and the median respiratory score was 5.0. Overall, fever presentation on admission was observed in 31% of patients with bronchiolitis. Detected respiratory viruses in patients with bronchiolitis were checked for presence of single or multiple infections. From the total 516 patients diagnosed with bronchiolitis; 18 (3.4%) were admitted to the pediatric intensive care unit and 5 of them were intubated, and the others were implemented non-invasive mechanical ventilations.

Table 1: Demographic characteristics, clinical presentations, laboratory measurements, and management of patients with bronchiolitis (n=516).

Demografic characteristics	
Age, months, [median, (IQR)]	4.5 (9)
Age disturbution, n (%)	
1 – 6 months	324 (62.7)
7-15 months	94 (18.4)
16-24 months	98 (18.9)
Gender, n (%)	
Male	315 (61)
Female	201 (39)
Personal history of atopy, n (%)	50 (9.7)
Passive smoking exposure, n (%)	168 (32.6)
Seasons, n (%)	
Winter	291 (56.4)
Spring	157 (30.4)
Fall	35 (6.8)
Summer	33 (6.4)
Clinical and presenting symptoms, n (%)	
Cough	489 (94.8)
Wheezing	355 (68.8)
Crepitation	321 (62.2)
Retraction	393 (76.1)
Fever	160 (31)
Apnea	24 (4.6)
Respiratory score, [median (IQR)]	5.0 (3.0)
Max. Respiratory rate (br/m)	62.51 ± 13.65
Max. Temperature (°C)	38.4 ± 0.1
Max. Pulse (beat/m)	167.3 ± 22.8
Supplemental oxygen therapy	177 (34.3)
Assisted ventilation	18 (3.4)
Respiratory score, n (%)	
Mild	100 (19.4)
Moderate	369 (71.5)
Severe	47 (9.1)
LOS, [median (IQR)]	6 (3.75)
LOS >5 days, n (%)	385 (74.6)
Treatment data, n (%)	
β agonist	484 (93.7)
Adrenaline	122 (23.6)
Antibiotic treatment	210 (40.6)
Systemic steroid treatment	324 (62.8)
Duration of systemic steroid treatment, [median (IQR)] days	5 (3.2)
Laboratory Findings	
White blood cell, [median (IQR)] /mm^3	10690 (5665)
Lymphocyte count, (%), [median (IQR)]	46 (28.3)
C-reactive protein, [median (IQR)] mg/dl	0.5 (3.3)
Co-morbidity diagnosed during hospitalization, n (%)	75 (14.1)
Cardiac defects and anomalies	42
Respiratory system and aquired pathologies	19
Immunologic	14

*IQR: I*nterquartile Range; *LOS:* Length of stay in hospital.

Respiratory viruses

The PCR method was utilized to determine the etiology in diagnosed with acute bronchiolitis 516 patients. From the total 516, PCR data of 65 (12.6%) patients did not achieve due to technical problems. Except for sixty-five patients, at least one virus was detected in 78.7% (355/451) of patients **(Figure 1)**. In total samples, 50.3% (n=227/451) were found as a positive for single pathogen; 28.3% (n=128/451) contained two or more viruses. Viral PCR was negative in ninety-six (21.3%) patients.

The incidence of respiratory viruses in patients in this study were shown in **Figure 2A**. Respiratory syncytial virus was identified in 203 (45%) of the 451 patients and RSV was the most common agent. Furthermore; RV (n=105/451, 23.2%), HMPV (n=35/451, 7.7%), INF (n=32/451, 7%), HBOV (n=30/451, 6.6%), ADV (n=29/451, 6.2%), , PINF (n=28/451, 6.2%), COV (n=15/451, 3.3%) were determined. Of the 203 RSV-positive cases, 133 (65.5%) were sole pathogens for RSV and 70 (34.5%) patients had RSV–coinfection **(Figure 2B)**. The second virus was RV, identified in 105 (23.2%) of the patients, and as a single pathogen in 49 (46.6%). A single virus in 227/355 (63.9%), dual infections, triple or more combinations in 128/355 (36%) were detected. Among dual co-infections [n=114/355, (89%)] the combination of RSV and RV had the the highest number (n=33/114, 28.9%). Of the dual infections, 23 patients had positivity for RV + non-RSV co-infection (20.1%).

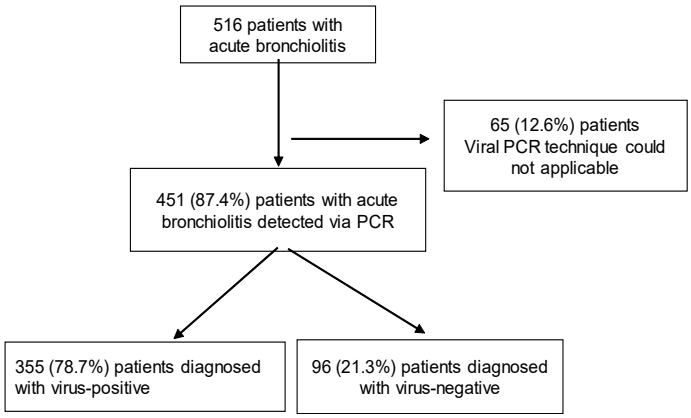

Figure 1: The distribution of the patients

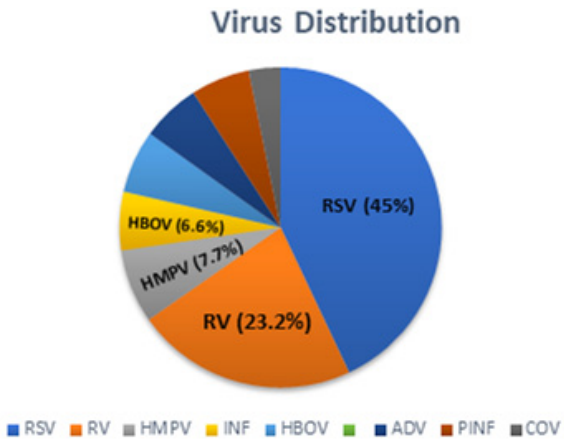

Figure 2A: The detected respiratory viruses in hospitalized patients.

RSV; Respiratory Syncytial Virus; RV: Human Rhinovirus; INF: Influenza virus: ADV: Adenovirus; PINF: Parainfluenza viruses; COV: Human Coronavirus; HPMV: Human Metapneumovirus; HBOV: Human Bocavirus (The rates include all viruses and co-infections; triple and more viruses combinations).

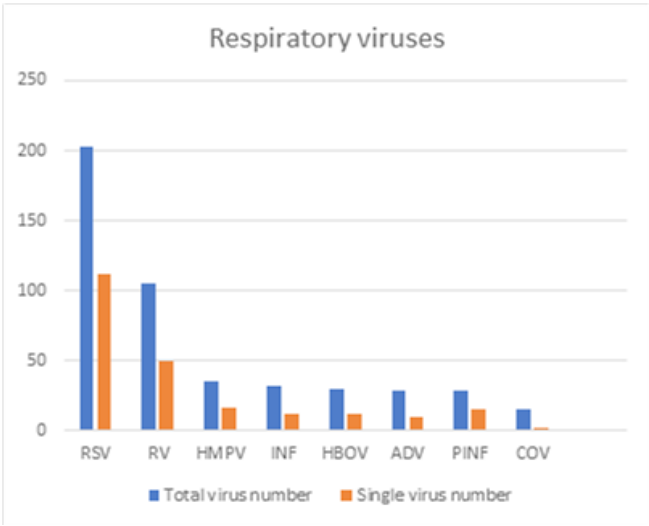

Figure 2B: Distribution of respiratory pathogens identified as sole or co-pathogen in acute bronchiolitis.

RSV; Respiratory Syncytial Virus; RV: Human Rhinovirus; INF: Influenza virus; ADV: Adenovirus; PINF: Parainfluenza viruses; COV: Human Coronavirus; HPMV: Human Metapneumovirus; HBOV: Human Bocavirus.

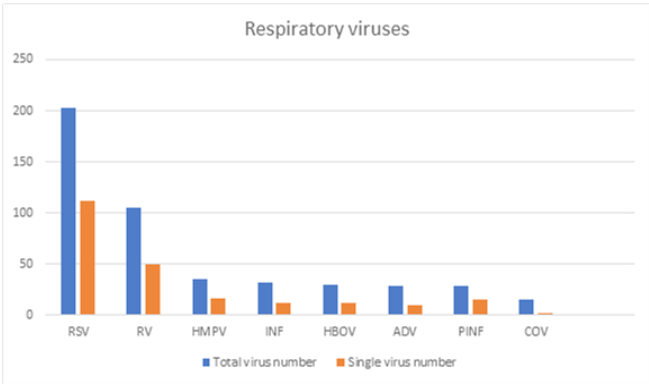

Figure 3: Distribution of respiratory pathogens identified as sole or co-pathogen in acute bronchiolitis (n=355).

RSV; Respiratory Syncytial Virus; RV: Human Rhinovirus; INF: Influenza virus; ADV: Adenovirus; PINF: Parainfluenza viruses; COV: Human Coronavirus; HPMV: Human Metapneumovirus; HBOV: Human Bocavirus.

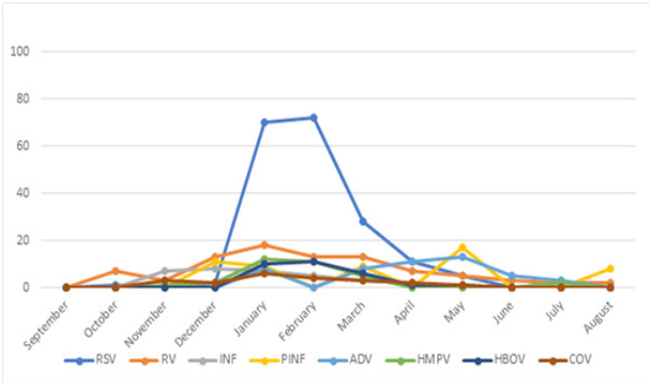

Figure 4

Seasonal distribution

The seasonal pattern of bronchiolitis outbreaks spans the winter months, with peaks in January and February in the study. The respiratory syncytial virus was the most dominant virus in the winter. Human Metapneumovirus (HMPV) circulated predominantly during the spring and winter. Human bocavirus infection occurred in all seasons except spring; ADV and RV were distributed all year round. The parainfluenza virus also occurred sporadically throughout the year. The findings indicated a peak in hospital admission rates during the winter season account for 291(56.4%) patients, followed by the spring 157 (30.4%) patients.

RSV vs. non-RSV

To determine if infection with RSV was particularly associated with differences in outcome compared to infection with other pathogens, the demographic and clinical characteristics were compared **(Table 2)**. Respiratory syncytial virus infection was more common in younger infants aged under 6 months; seventy percent of the patients with RSV bronchiolitis were under 6 months of age compared with 49.3% of those without RSV ($P < 0.001$). The patients with RSV were admitted to the hospital with two main symptoms significantly being needed for oxygen (n = 88; 43.3%) and wheezing (n = 149; 73.4%). There was a statistically significant difference in the bronchiolitis respiratory score of patients with RSV compared with the respiratory score of the non-RSV group [6 (3) vs. 5 (3.7), p =0.003]. There was no significant difference between the clinical features such as fever and cough of the two groups. No statistically significant difference was observed in other clinical findings between the study groups (data not showed). The number of patients hospitalized for more than 5 days was significantly high in RSV positive group compared to RSV negative patients ($p < 0.001$).

The binary logistic regression model for RSV or non-RSV was indiacted in **Table 3** controlling for demographic and clinical characteristics. Class with the pediatric patients with RSV, subjects with any other agents without RSV, were highly likely to have, wheezing, supplemental oxygen therapy. Respiratory syncytial virus increased the risk of the need for systemic steroid treatment by 1.2 times in patients compared to those infected with non-RSV infections [95 % CI (Lower-Upper) 1.056-1.445; Exp(B): 1.2; p = 0.011], also there was a significant difference in the length of stay hospital between those with RSV and those without RSV [95 % CI (Lower-Upper) 0.725-0.993; Exp(B): 0.8; p = 0.041]. An extensive analysis was conducted to study the correlation between other viral infection and no specific clinical signs were detected.

Table 2: Comparison of demographic and clinical characteristics of the RSV and Non-RSV group.

Data	RSV (n=203)	Non-RSV (n=152)	*P value*
Gender, n (%)			
Male	110 (54.1)	107 (70.4)	0.12
Female	93 (45.7)	45 (29.6)	
Age, n (%)			
0–2 months	82 (40.4)	42 (27.6)	
3–5 months	58 (28.6)	33 (21.7)	**< 0.01**
6–11 months	39 (19.2)	26 (17.1)	
12–24 months	24 (11.8)	51 (33.6)	
Fever> 38°C on admission, n (%)	61 (30)	40 (26.3)	0.104
Cough, n (%)	193 (95.1)	140 (92.1)	0.239
Wheezing, n (%)	149 (73.4)	102 (67.1)	**< 0.01**
Oxygen need, n (%)	88 (43.3)	40 (26.3)	**0.004**
Retraction, n (%)	167 (82.2)	103 (67.2)	0.344
Respiratory score, [median, (IQR)]	6 (3)	5 (3.7)	**0.03***
LOS >5 days, n (%)	139 (68.5)	87 (57.2)	**< 0.01**
Passive smoking, n (%)	72 (35.5)	50 (32.9)	**< 0.01**

IQR: Interquartile range; LOS: Length of stay in hospital; RSV: Respiratory syncytial virus; * Mann whitney -U test.

Table 3: The logistic regression model of demographic features, clinical findings, and laboratory markers according to RSV status.

	Exp (B)	95 % CI (Lower-Upper)	*P value*
Gender (Male predominance)	1,19	0.953-1.313	NS
Fever	0,916	0.776-1.081	NS
Cough	0,883	0.615-1.268	NS
Wheezing	1.256	1.065-1.480	**0.007**
Oxygen need	1.206	1.020-1.425	**0.029**
Antibiotic requirement	1.135	0.971-1.327	NS
Systemic steoid requirement	1.233	1.056-1.445	**0.011**
LOS> 5 days	0.849	0.725-0.993	**0.041**

LOS: Length of stay in hospital; RSV: Respiratory syncytial virus; NS: Not significant.

Differences between patients with single, multiple viruses and virus-negative

Table 4: Comparison between patients infected with Single, multiple pathogens and negative.

Data	Single pathogen (n=227)	Co-infections [dual and more] (n=128)	Virus negative (n=96)	*P value*
Gender				**0.005**
Male, n (%)	153 (67.4)	64 (50)	62 (64.6)	
Female, n (%)	74 (32.6)	64 (50)	34 (35.4)	
Age, n (%)				0.283
0–2 months	79 (34.8)	45 (35.1)	29 (30.3)	
3–5 months	56 (24.6)	35 (27.3)	25 (26)	
6–11 months	41 (18)	24 (18.7)	17 (17.7)	
12–24 months	51 (22.6)	24 (18.9)	25 (26)	
Fever> 38°C on admission, n (%),	68 (30)	33 (25.7)	31 (32.2)	0.177
Cough n (%)	209 (92.1)	124 (96.8)	92 (95.8)	0.147
Duration of cough before admission, [median, (IQR)], days	3 (3)	3.5 (4)	4 (4.4)	0.758*
Wheezing, n (%)	150 (66)	101 (78.9)	50 (52.1)	**< 0.01**
Oxygen need, n (%)	81 (35.6)	47 (36.7)	31 (32.3)	0.527
Retraction, n (%)	198 (87.2)	109 (85.1)	54 (56.2)	0.344
Passive smoking, n (%)	82 (36.1)	40 (31.5)	40 (41.7)	**< 0.01**
Respiratory score	6 (3)	5 (3.7)	4.5 (3)	0.840*
LOS >5 days, n (%)	138 (60.7)	88 (68.7)	47 (48.9)	**< 0.01**

*Mann Whitney – U test; LOS: Length of stay in hospital

The study determined that it was statistically significant in gender for all three groups. The patients infected with dual or more viruses had tended to present with wheezing ($p < 0.01$). Compared with single, multiple viruses and virus-negative patients; the patients infected with dual or more virus infections have had longer hospitalization time ($P < 0.01$). The further analysis using other parameters, however, there were no significantly different results.

Discussion

The study has assessed the clinical records for 516 pediatric patients hospitalized for bronchiolitis. The study of the patients hospitalized with bronchiolitis has proved once again that acute bronchiolitis is a major occasion of hospitalization in infants mostly younger than 6 months of age and young children. It was demonstrated that at least one respiratory viral pathogen was responsible for bronchiolitis in 78.7% of the cases via multiplex real-time PCR technique in Ege University Children's Hospital.

Bronchiolitis is one of the most important inflammatory diseases characterized by affecting the small airways (less than 2 mm in diameter) and presented with acute wheezing in children. A pathogen or other potential agents cause the commencement of the inflammation of the bronchial epithelium and lead to epithelial necrosis. After the invasion, degenerated squamous epithelium secretions accumulate in the lumen, so the classical symptoms including wheezing, crackles, and bronchospasm take place due to partial obstruction of the lumen. Generally, there is a typical contact history with an adult or older child with minor respiratory manifestations. Followed by symptoms of viral upper respiratory infection, increased respiratory rate accompanied by the loss of appetite, restlessness, lethargy might be seen [16,17]. There are characteristic clinical characteristics such as tachypnea, nasal flaring, chest retractions, and wheezing, and/or rales on examination. The 2014 American Academy of Paediatrics bronchiolitis guideline does also not recommend the routine laboratory studies for the diagnosis of acute bronchiolitis. However, respiratory pathogen

panels able to show us a reasonable therapy in the clinical setting, monitoring clinical progress. In this context, the detection of specific viral nucleic acids enabled a better understanding of the viral etiology through antigen detection or immunofluorescence of nasal secretion wash or nasal aspiration, rapid antigen test, and various Polymerase Chain Reaction (PCR) techniques [18-20]. The multiplex polymerase chain reaction for the detection the respiratory viruses is a commonly used procedure that able to get a facilitating cost-effective diagnosis [21].

The study showed that the respiratory viral agents demonstrated seasonal patterns with the number of RSV cases peaking in January and February. It has been reported that the seasonal distribution of respiratory agents may directly be related to the meteorological conditions, spreading of infectious pathogens, and pathogen transmission by the host behavior due to different meteorological conditions [22,23]. It is also hypothesized that ultraviolet light radiation could affect the spread of RSV by inactivating. The viral prevalence in the summer was low in thes tudy due to the fact that it can be associated with less symptomatic children during the summer months [24].

During the first year of life, 20% of infants develop acute bronchiolitis, and the most common etiologic virus is RSV (60-80% of cases); however, human metapneumovirus, parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, and enteroviruses have also been shown a responsible association[22]. It has also been reported that the other pathogens like mycoplasma and chlamydia, and other fungal and mycobacterial infections might rarely be detected in acute bronchiolitis [25]; in particular, rhinovirus is the second most common virus inducing acute bronchiolitis [22]. The findings of the study are in agreement with the results of several studies previously reported, RSV was the most common virus detected in 203 children (45%). It has been also found that the patients less than 6-month-old have frequently infected with RSV resulting from a lack of passively acquired immunity from their mother or the antibodies to prevent the virus from all samples tested. A comparable prevalence of Stempel et al[26] showed that RSV incidence was 77% and Antunes et al[27] found this as 58.1% in the epidemic season of the RSV. In addition, 23.2% of the cases in the study were positive for Rhinovirus, followed by human metapneumovirus (7.7%), influenza virus (7%), human bocavirus (6.6%), adenovirus (6.2%), parainfluenza virus (6.2%), and human coronavirus (3.3%). In keeping with previous studies this current study has shown that the respiratory viruses could occur as co-infection with other respiratory viruses; within a range of 19-35% dual, triple or more [28]. A study by Papadopoulos et al[29] stated that 19.5% of 119 infants were dual-infected, 69% of whom had RSV with rhinovirus co-infections. Another study conducted by Ong et al [30] showed that RSV bronchiolitis associated with other pathogens was present in 10% of the infants.

A study from the United States showed that previously healthy infants with RSV had more severe bronchiolitis than those hospitalized with non-RSV bronchiolitis [31]. A study by Hervas D et al [32] evaluated the clinical features of RSV infection in infants hospitalized with acute bronchiolitis and stated that RSV infection played an important role in the increased severity of acute bronchiolitis. It has also been reported that RSV acute bronchiolitis was associated with a longer hospital stay and greater oxygen requirement compared with non-RSV acute bronchiolitis. Bamberger et al stated that a higher clinical score on admission and a significant difference in length of stay for the patients with RSV alone compared to those who were non-RSV [33]. Similar to the aforementioned results, the present study, it was found that if a patient infected with RSV, they tended to have more wheezing, and had needed more oxygen. However, there was no difference in the clinical findings, including fever and cough on admission, for RSV positive compared to those non-RSV patients.

Some studies propose that co-infection is in relation to more severe diseases. However, it is sometimes hard to define the pathogenicity of co-infecting viruses. Because respiratory viruses may be persistent in the nasal secretions of the asymptomatic person for several days and/or months [34,35]. A previous study conducted by Stemple et al [26] demonstrated that coinfection increase by 10-fold the risk of admission for the intensive care unit. According to the outcomes and in accordance with previous studies, several differences in clinical severity between patients hospitalized with a single infection and those with viral co-infection were found. However, no significant association between single or multiple infections except for hospitalization days and wheezing.

It may be said that there could be seen several limitations in the study. First of all, it was only investigated hospitalized patients with acute bronchiolitis and not the patients who applied to the emergency services or outpatient policlinics, so the study group was small in number. Secondly, the subjects in a single unit and retrospectively examined data from an existing database, medical charts, and diagnostic testing results. Therefore, there could be some missing data. It was not also investigated the prevalence of the pathogen in asymptomatic individuals, which could have explained the silent role of a single or a co-infection. In addition, it was unable to identify whether bacterial or other viral pathogens were present in all samples, including negatives. In the study, it was used a nasal swabs rather than a nasopharyngeal swab, which has been a more invasive procedure with a higher sensitivity [36]. This could also explain the negative results in 12.6% of the children.

In conclusions, the index study indicated that the causative viruses of acute bronchiolitis are quite varied in inpatient cases in Ege University Children's hospital during a period of 6 years. Where viral agents were determined via PCR in pediatric patients, molecular diagnostic techniques uncovered a high frequency of viruses and viral combination infections. Respiratory syncytial virus remained the most frequent causative pathogen, followed by rhinovirus. Even if the results of diagnostic methods show that the most common pathogen is RSV; the single or multiple viral infections should also be considered the potential significance in patients hospitalized with acute bronchiolitis, as sole or co-pathogen. Another possible result from the study, it may be proposed that when patients, particularly under 6 months of age, presented with wheezing, had longer hospitalization and had a need for more oxygen, it should be considered an attack of bronchiolitis caused by RSV or multiple agents. Finally, further studies are needed to study the influence of single or co-infection in these cases and to find new microorganisms that may play a role in subjects with severe respiratory infection with unknown etiologies.

With the best of knowledge, acute bronchiolitis associated with COVID-19 infection has never been reported, however, there is a possibility of togetherness COVID-19 and RSV or a single infection with COVID-19. Because there have recently been observed lung lesions compatible with bronchiolitis in a recent experimental model of ferrets with COVID-19 [37]. Hopefully, there will be a significant reduction in hospitalization for acute

bronchiolitis in children under one-year-old in the next winter season due to an important impact of social distance on reducing the transmission of viruses related to acute bronchiolitis with the ongoing new coronavirus pandemic.

Conflict of interest

All authors have no conflict of interest

Ethics

The study was approved by the institutional review board named The Ethics Committee of Ege University (**20-1.1T/42**).

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