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Acute Bronchiolitis To Pediatric Inpatient Clinic In Patients Under 2 Years Old, Installed with Diagnosis Investigation of the Relationship of Bronchiolitis and Asthma

Pediatri Servislerine Akut Bronşiolit Tanısıyla Yatırılan 2 Yaşından Küçük Hastalarda Bronşiolit ve Astım İlişkisinin Araştırılması

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ABSTRACT

Objective: Previously considered a uniform disease, bronchiolitis has been revealed through research as heterogeneous, displaying varied phenotypes and clinical-histopathological differences among patients. Our study aimed to explore distinctions among children hospitalized with acute, severe bronchiolitis and identify potential asthma risk factors.

Methods: Between January 2017 and November 2022, we examined hospitalized children under 2 years with moderate to severe acute bronchiolitis. Disease severity was assessed using the bronchiolitis severity score developed by the Turkish Thoracic Society. The asthma risk was evaluated using the modified Asthma Predictive Index (mAPI) designed for predicting future asthma in bronchiolitis cases.

Results: A total of 156 patients were studied, with 41% having previous bronchiolitis hospitalizations (multiple hospitalization group) and 59% having first-time hospitalizations (first hospitalization group). Middle rales, wheezing, and tachypnea were more frequent in the multiple hospitalization group, with a 1-unit increase in respiratory rate, increasing readmission risk by 1.048 times. Assessing patients by "API", 64.1% were "API" (+) and 35.9% were "API" (-). Among "API"

ÖZ

Amaç: Bronşiolit klinik olarak tek hastalık olarak görülmüşsede, yapılan çalışmalar gerek viral etken özellikleri gerek hastalar arasında klinik ve histopatolojik farklılıklar bulunduğunu ve değişik fenotipleri olan, heterojen hastalık olduğunu göstermektedir. Amacımız; akut bronşiolit sebebiyle hastaneye yatırılan çocuklarda, hastalar arasındaki farkları araştırmak ve astım risk faktörlerini belirlemeye çalışmaktır.

Yöntemler: Hastanemiz pediatri servislerine Ocak 2017-Kasım 2022 tarihlerinde, 2 yaşından küçük, orta-ağır şiddette akut bronşiolitle yatırılan 156 hasta alınmıştır. Hastaların atak şiddetleri, Türk Toraks Derneği tarafından oluşturulan bronşiolit şiddet skoruna göre belirlenmiştir. Hastalarımızda bronşiolitlerde olası astımı öngörebilmek için kullanılan "modified Asthma Predictive Index" (mAPI) skoruna göre astım riski değerlendirilmiştir.

Bulgular: Yüz ellli altı hasta değerlendirilmiştir. Akut bronşiolitle daha önceden hastane yatışı öykülerine, ve mAPI özelliklerine göre değerlendirilmiştir. Hastalarımızın %41'i bronşiolit nedeniyle önceden hastaneye yatırılmış olup (çoklu yatış grubu) %59'u ilk kez yatırılmıştır (ilk yatış grubu). Orta ral, hışıltı ve takipne çoklu yatış grubunda daha fazla olup, aradaki fark istatistiksel olarak anlamlıdır. Hastalarımız,

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(+) patients, 69% were male, compared to 48.3% among "API" (-) patients-a significant difference. Wheezing occurred in 48% of "API" (+) patients and 30.3% of "API" (-) patients - also significant.

Conclusion: The majority of bronchiolitis cases were linked to asthma, with a significant 48.7% having a family history. This major risk factor implies a prevalent asthma phenotype. Moreover, 41% of patients with repeated hospitalizations and 64.1% API (+) reinforce this view. In summary, an early identification of patients at risk of asthma is crucial for tailoring appropriate treatment and safeguarding lung function.

Keywords: Astma, bronchiolitis, phenotyphe, child, viruses, wheezing

"API"e göre değerlendirildiğinde; hastaların %64,1'inin "API" (+), %35,9'unun "API" (-)'tir. "API" (+) hastaların %69'u erkek, "API" (-) hastaların %48,3'ü erkek olup aradaki fark istatistiksel olarak anlamlıdır. "API" (+) hastaların %48'inde hışıltı, "API" (-) hastaların %30,3'ünde hışıltı duyulmuş, aradaki fark istatistiksel olarak anlamlıdır.

Sonuç: Çalışmamızda bronşiolit geçirenlerde birçoğunun astımla ilişkili olduğunu düşündüren bulgular görülmüştür. Ailede astım öyküsünün %48,7 olup bu durum astım yönünden bilinen en büyük risk faktörüdür. Bu sebeple hastalarımızın birçoğunun astım fenotipinde olduğunu düşünmekteyiz. Ayrıca %41 çoklu yatış öyküsü, %64,1 API (+) olması bu görüşümüzü desteklemektedir. Astım yönünden riskli hastaların erken dönemde belirlenmesi, doğru tedavinin ayarlanması ve hastanın akciğer fonksiyonlarının korunması önemlidir.

Anahtar Sözcükler: Astım, bronşiolit, fenotip, çocuk, hırıltı

INTRODUCTION

Bronchiolitis is an acute obstructive infection characterized by bronchospasm, necrosis of epithelial cells, increased mucus production, submucosal edema, and inflammation in the small airways (bronchioles) caused by viruses (1,2). This terminology is used for children under the age of 2 in the United States and our country, whereas in Europe, Canada, and Australia, it is applied to children under the age of 1 (2-4). The bronchioles form a large area of 140 m² throughout the lungs. Their total volume is 4.500 mL (5). Bronchioles, which create such a large volume and area, have two significant differences from other airways: first, their lumen diameters are very narrow, ranging from 0.5 to 1 mm. Second, cartilage, which provides the tone of the airways and is abundantly present in medium- and large-sized bronchi, is absent in bronchioles. This absence makes them prone to collapse during illness (5,6). Although all respiratory viruses can cause acute bronchiolitis, severe cases are often associated with respiratory syncytial virus (RSV) and rhinovirus (RV) (7). Throughout the world, all infants encounter respiratory viruses soon after birth. This case usually presents as a simple upper respiratory tract infection (URI). However, in 20-50% of cases, instead of URI, lower URI or bronchiolitis is diagnosed (1,2,4). The most important symptoms include cough, mucus (wheezing), shortness of breath, and wheezing respiration (wheezing). Decreased feeding and restlessness may accompany. Nasal flaring and retraction due to the use of accessory respiratory muscles may be observed. Expiration may be prolonged. On auscultation of the lungs, the rales, medium rales, and wheezing can be heard, depending on the severity of the obstruction (1,4,8).

Approximately 3.2-7.8% of bronchiolitis cases are severe and require hospitalization for treatment (4). In 16-60% of patients hospitalized with an acute bronchiolitis diagnosis, it is observed that bronchiolitis attacks recur after recovery, and many of these patients are later diagnosed with asthma (1,9). It has even been reported that long initial attacks can be classified as bronchiolitis (10). Although bronchiolitis has long been seen clinically as a single disease, it is now understood that not every patient with bronchiolitis has the same characteristics (11,12). Recent studies have increasingly revealed both clinical and histopathological differences among patients (13,14). This evidence indicates that bronchiolitis is a heterogeneous disease with various phenotypes. Identifying the phenotypes associated with asthma is crucial for ensuring appropriate treatment and preventing future impairment of respiratory function and development of chronic persistent asthma (12).

The aim of our study was to investigate differences among children hospitalized for the treatment of acute severe bronchiolitis to identify risk factors for asthma.

MATERIALS AND METHODS

Case Selection and Study Design

Our study included patients aged below 2 years who were hospitalized for acute bronchiolitis between January 2017 and November 2022 at Gazi University Medical Faculty Hospital's Pediatrics department. All hospitalizations were reviewed, and a total of 156 cases. Patients were initially assessed using emergency department records, while subsequent evaluations relied on file records during admission to pediatric and infection services.Initial attack severity was determined using the Turkish Thoracic Society's bronchiolitis severity score (8). Patients with moderate to severe attacks were included and categorized as mild, moderate, or severe. Starting from 2020, all hospitalized patients underwent a COVID-19 polymerase chain reaction test; those who were negative were placed in the wards. The study excluded outpatients with treated bronchiolitis and children with non-bronchiolitis chronic or systemic illnesses.

Work Plan

For each patient, a "case report form" was created, documenting disease history from parents, personal and family history, initial emergency department examination, and laboratory results. Upon admission, patient SpO_2 was measured using a Covidien Nellcor pulse oximetry device. Prior to any treatment, complete blood counts were conducted on peripheral venous blood samples at our hospital's hematology laboratory. For patients investigated for causative agents, PCR analysis of nasopharyngeal samples (Fast Tract Respiratory Pathogens 21; Siemens Healthcare GmbH, Germany) detected causative agents. The test covered RSV A/B, Rhinoviruses, Influenza A/B Viruses, H1N1, Parainfluenza (PIV 1, PIV 2, PIV 3, PIV 4), Coronaviruses (NL63-229E-OC43-HKU1), Metapneumoviruses A/B, Bocaviruses, Adenoviruses, and Parechoviruses. A multiplex real-time PCR panel simultaneously detected Enteroviruses, Mycoplasma pneumoniae, *Bordetella Pertussis*, and Legionella Pneumonia.

All patients underwent assessment using the "modified Asthma Predictive Index" (mAPI) score based on recorded data (15). The asthma risk score (Table 1) gages asthma risk in under-three-year-olds with recurrent bronchiolitis. A major criterion and two minor ones indicate high future asthma risk (15). All 156 patients were categorized as "API" positive or negative, facilitating comparison. However, blood-specific IgE and skin prick tests for aeroallergen sensitization were not performed during hospitalization. Thus, the first two parameters were used as the major criteria for our patients.

Ethics Committee Approval

Our study was approved by the Gazi University Faculty of Medicine Local Ethics Committee (approval number: 805, date: 14.12.2020).

Statistical Analysis

Data analysis employed the "SPSS for Windows 11.5" software. The parameters were categorized as categorical or numerical variables. The frequency distribution (count, percentage) and descriptive statistics (mean, standard deviation) were applied. Pearson's chi-square test, Fisher's chi-square test, continuity correction chi-square test, Student's t-test, and Mann-Whitney U test were used. Significance was determined at $p<0.05$, considering Type 1 error levels below 5% as statistically significant.

RESULTS

Patient Characteristics

Table 2 Assesses the traits of patients aged below 2 years admitted to the Gazi University Faculty of Medicine Hospital's Pediatrics departments from January 2017 to November 2022.

Previous Hospitalization Status of Patients With Bronchiolitis (Number of Hospitalization Groups)

Patients were categorized by prior acute bronchiolitis hospitalization history. Among the 156 patients, 64 (41%) had prior hospitalizations (multiple hospitalization group), while 92 (59%) had first-time acute bronchiolitis admissions (first hospitalization group). When the two groups were compared in terms of age and gender, no statistically significant difference was found (p=0.25 and p=0.25, respectively) (Table 3).

Evaluation of Hospitalization Number Groups Based on Respiratory System Examinations At Admission

Patients in both the multiple and initial hospitalization groups underwent respiratory examination. Patients in the multiple hospitalization group exhibited higher rates of moderate rales and wheezing compared with those in the initial hospitalization group, with a significant difference (p=0.04, p=0.037, respectively), as indicated in Table 4. Increased respiratory rate (tachypnea) was also found in more patients in the multiple hospitalization group, and there was a statistically significant difference between the groups (p=0.008) (Table 4). Upon analyzing patients in the multiple hospitalization group based on physical examination, a rise of one unit in the respiratory rate amplified readmission risk by 1.048 times. Alternatively, tachypnea heightened readmission likelihood by a factor of one [p=0.004, OR: 1.048, CI: 95% (1.015-1.081)], detailed in Table 5.

Bronchiolitis Agents in Our Patients (PCR Results)

Respiratory tract PCR was performed in 92 (58.9%) of the 156 patients included in this study. The viral agent results are presented in Table 6. In a total of 48 (71.6%) of 67 patients hospitalized with a diagnosis of acute bronchiolitis and PCR positivity, RSV or RV was found to be the causative agent. These 48 patients were defined as "RSV+RV group". Another 19 (28.4%) patients with bronchiolitis associated with other viral agents were defined as "other agents group". No causative agent was detected in 25 (27.2%) of 92 patients in whom PCR was performed. These patients were defined as "PCR (-) group". When the RSV+RV Group was compared with the "other factors group", no statistically significant difference was found in age and gender (p=0.32, p=0.58, respectively). No statistically significant age or gender differences existed between the PCR (+) and PCR (-) groups (p=0.26, p=0.60, respectively). Upon assessing hospitalization duration, no statistically significant distinctions emerged among the groups (p=0.55, p=0.40, respectively), as shown in Table 7.

Table 1. Modified "asthma predictive index" (15)

Major criteria	Minor criteria
1. Doctor-diagnosed asthma in the mother or father	1. Accompanied by food allergy
2. Doctor-diagnosed atopic dermatitis	2. Wheezing outside the URTI
3. At least 1 aeroallergen sensitivity	3. Eosinophilia in peripheral blood (≥4%)

URTI: Upper respiratory tract infection.

Table 2. Patient characteristics (n=156)

Age, month (± SD)	11.8 (±7.06)
Gender, n (%)	
Female	59 (37.8)
Male	97 (62.2)
Number of hospitalizations with a previous diagnosis of bronchiolitis, n (%)	
First hospitalization	64 (41)
Multiple hospitalizations	92 (59)
Duration of hospitalization	
Mean days (± SD)	4.7 (±3.1)
Median, day (range)	4 (1-17)
Mode of delivery, n (%)	
Cesarean section	89 (57.1)
Vaginal	67 (42.9)
Premature birth	36 (23)
Low birth weight (< 2500 g)	3 (1.9)
Mechanical ventilation during the neonatal period	17 (10.8)
Premature	14 (8.9)
Term	3 (2.4)
Atopic Dermatitis, n (%)	34 (22.4)
Asthma in the family, n (%)	76 (48.7)

SD: Standard deviation

Evaluation of Bronchiolitis Agents According To Physical Examination Findings

The physical examination findings of 67 patients hospitalized with acute bronchiolitis and PCR (+) and 25 patients with PCR (-) were assessed. In the PCR (+) group, no statistically significant variation was noted in physical examination findings between patients with RSV+RV-related bronchiolitis and those linked to other viral agents (p=0.81, p=1.00, p=0.96, p=0.74, p=0.54, p=0.43, respectively).

Table 3. Characteristics of patients with previous hospitalization for bronchiolitis

	Multiple hospitalization (n=64)	First hospitalization (n=92)	p
Age			p=0.25*
Mean, months (± SD)	12.6 (±7.1)	11.4 (±7.1)	
Median, month (range)	11.5 (1-24)	10 (1-24)	
Gender, n (%)			p=0.25**
Female	21 (32.8)	39 (42.3)	
Male	43 (67.2)	53 (57.7)	

*Mann-Whitney U test, **Student t-test, SD: Standard deviation

Table 4. Respiratory system examinations at first admission according to hospitalization groups

	Multiple hospitalization (n=64)	First hospitalization (n=92)	p
Rhonchus, n (%)			p=0.52*
Yes	61 (95.3)	84 (91.3)	
No	3 (4.7)	8 (8.7)	
Medium rale, n (%)			p=0.04**
Yes	36 (56.2)	37 (40.2)	
No	28 (43.8)	55 (59.3)	
Wheezing, n (%)			p=0.037**
Yes	33 (50.8)	32 (34.7)	
No	31 (34.1)	60 (5.9%)	
Breath retraction, n (%)			p=0.33***
Yes	53 (82.8)	69 (75)	
No	11 (48.5)	23 (25)	
Respiratory rate			p=0.008****
Mean, min. (± SD)	58.5 (±10.8)	53.4 (±12.4)	
Median, min. (range)	60 (34-84)	55 (30-90)	
SpO_2 (%)			p=0.45****
Mean, min. (± SD)	92.4 (±4.2)	92.1 (±3.9)	
Median, min. (range)	93 (84-100)	93 (82-100)	

*Fisher's exact chi-square test, **Pearson's chi-square test, ***Yates's correction chi-square, ****Independent group t-test, min.: Minimum, SD: Standard deviation

There was no statistically significant difference between the PCR (-) group and the PCR (+) group in terms of physical evaluation (p=0.66, p=0.43, p=1.00, p=1.00, p=1.00, p=0.15, p=0.76) (Table 8)

Evaluation of The Patients Regarding The "Asthma Predictive Index" Status

All 156 patients hospitalized with a diagnosis of acute bronchiolitis were evaluated according to the "API" criteria described in detail in Table 2 in the materials and methods section.

Of the 156 patients included in our study, 100 (64.1%) were "API" positive, and 56 (35.9%) were "API" negative. When the groups were compared, there was no significant difference between them in terms of age (p=0.28), but there was a significant difference in terms of gender, with more male patients in the "API" positive group (p=0.017) (Table 9).

Respiratory Examination Findings of The "API" Groups At The Initial Presentation

When comparing "API" positive and "API" negative patients' physical evaluations, wheezing was significantly more prevalent in the "API" positive group (p=0.048) as indicated in Table 8. Similarly, comparing "API" positive and "API" negative patients based on physical evaluations, tachypnea was notably higher in the "API" negative group, with a significant difference (p=0.014), as detailed in Table 10.

Agents Detected By PCR Test In "API" Groups

The agents of bronchiolitis detected by PCR in our patients were analyzed in detail according to their API status. When the patients in whom PCR-detected bronchiolitis agents were compared based

Table 5. Association between hospitalization group and risk factors

Risk factor	OR	95% CI	p
Respiratory rate (min.)	1.048	1.015-1.081	0.004
Wheezing	1.71	0.85-3.47	0.13
Medium ral	1.85	0.92-3.69	0.81
Food allergy	2.63	0.83-8.34	0.10

OR: Odds ratio, CI: Confidence interval, min.: Minimum

Table 6. Results of 92 patients who underwent PCR test

Positive PCR , n (%)	67 (72.8)
RSV (single agent)	27 (40.3)
Rhinoviruses	21 (31.3)
Rhinovirus (single agent)	15 (71.4)
Rhinovirus + Parainfluenza virus	3 (14.2)
Rhinovirus + Adenovirus	2 (9.5)
Rhinovirus + Metapnomovirus	1 (4.7)
Adenoviruses	2 (2.9)
Bocaviruses (single agent)	6 (9)
Bocavirus + Adenovirus	1 (16.6)
Influenza viruses A/B	10 (15)
Mycoplasma	1 (1.5)
Negative PCR	25 (27.2)

PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus

on their "API" status, no statistically significant difference was found between them (p=0.53) (Table 11).

DISCUSSION

In this study, 156 patients admitted to the pediatric health and disease departments of our hospital with a diagnosis of moderate to severe acute bronchiolitis were analyzed. The aim of this study was to determine common features among these patients as well as clinical differences, specifically to identify those with asthma-like phenotypes. It is known that asthma often begins with recurrent bronchiolitis in childhood (10,16). A family history of asthma is the most well-established risk factor (15-17). In our patients, the rate of family history of asthma was as high as 48.7%. No biomarker predicts which young children with recurrent bronchiolitis will develop asthma (17). To identify such children in advance, indices that include certain risk factors are used. One commonly used index is the modified "API" (15). According to the modified "API", the probability of developing asthma after the age of 3 years in patients with API positivity is 90% (15). In our study, the prevalence of modified "API" positivity criteria was as high as 64%. The high rates of recurrent attacks and "API" positivity suggest that there is a significant number of children with asthma phenotypes in our study group. Our analysis revealed that 62.2% of patients were male. Mansbach et al. (18) reported that 59%

Table 7. Evaluation based on the causative agents of bronchiolitis

	PCR (+) (n=67)			PCR (-) (n=25)	
	RSV + RV (n=48)	Other factors (n=19)	p		p***
Age					
Mean, months (± SD)	12.3 (±7.4)	14.5 (±7.7)	p=0.32**	11 (±6.5)	p=0.26*
Median, month (range)	10.5 (1-24)	17 (1-24)		9 (1-24)	
Gender, n (%)					
Female	23 (47.9)	7 (36.8)	p=0.58*	9 (36)	p=0.60**
Male	25 (52.1)	12 (63.2)		16 (64)	
Duration of hospitalization				4.7 (±3)	
Mean, days (± SD)	5.5 (±3.4)	5.5 (±4.3)	p=0.55**	5 (1-10)	p=0.40*
Median, day (range)	5 (1-15)	4 (1-17)			

*Mann-Whitney U test, **Yates's correction chi-square, ***Evaluation of PCR (-) group and PCR (+) group, PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus, RV: Rhinovirus, SD: Standard deviation.

Table 8. Evaluation of respiratory system findings based on bronchiolitis agents

	PCR (+) (n=67)			PCR (-) (n=25)	
	RSV + RV (n=48)	Other factors (n=19)	p		p****
Rale, n (%)					
Yes	22 (45.8)	10 (52.6)	p=0.81*	10 (23.8)	p=0.66*
No	26 (54.2)	9 (47.4)		15 (76.2)	
Rhonchus, n (%)					
Yes	42 (87.5)	17 (89.5)	p=1.00**	24 (96)	p=0.43**
No	6 (12.5)	2 (10.5)		1 (4)	
Wheezing, n (%)					
Yes	18 (37.5)	10 (52.6)	p=0.96*	10 (23.8)	p=1.00*
No	30 (62.5)	9 (47.4)		15 (76.2)	
Breath retraction, n (%)					
Yes	38 (79.2)	16 (84.2)	p=0.74**	21 (84)	p=1.00**
No	10 (21.8)	3 (15.8)		4 (16)	
Respiratory rate					
Mean, min. (± SD)	54.7 (±12.5)	55.9 (±13.3)	p=0.54***	60.5 (±12.5)	p=0.15***
Median, min. (range)	57 (30-80)	58 (30-72)		60 (40-90)	
SpO_2					p=0.76***
Mean, % (± SD)	92.4 (±3.8)	93.1 (±4.5)	p=0.43***	93 (±4)	
Median, % (range)	92 (82-98)	95 (82-100)		94 (84-100)	

*Yates's correction chi-square, **Fisher's exact chi-square test, ***Mann-Whitney U test, ****Evaluation of PCR (-) group and PCR (+) groups, min.: Minimum, PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus, RV: Rhinovirus, SD: Standard deviation.

of patients under the age of 2 with acute bronchiolitis were male. It is believed that bronchiolitis is more common in boys because of the narrower bronchial diameters, higher airway resistance, and slower airflow rates in men (2,4). In our study, 89 out of 156 patients (57.1%) were born by cesarean section. The high rate of cesarean births was consistent with the findings of Douglas et al. (19) reported that the

Table 9. Evaluation of patients according to the "API"

	API (+) n=100	API (-) n=56	p
Age			
Mean, months (± SD)	12.1 (±7.1)	11.5 (±7.1)	
Median, month (range)	11 (1-24)	10.5 (1-24)	p=0.28**
Gender, n (%)			
Female	31 (31)	29 (51.7)	p=0.017*
Male	69 (69)	27 (48.3)	

*Mann-Whitney U test, **Yates's correction chi-square, API: Asthma predictive index, SD: Standard deviation.

Table 10. Physical examination findings of "API" groups at admission

	API (+) n=100	API (-) n=56	p
Rhonchus, n (%)			
Yes	93 (93)	52 (92.8)	p=1.00*
No	7 (7)	4 (57.2)	
Rale, n (%)			
Yes	49 (49)	24 (42.8)	p=0.46**
No	51 (51)	32 (57.2)	
Wheezing, n (%)			
Yes	48 (48)	17 (30.3%)	p=0.048***
No	52 (52)	39 (69.7%)	
Breath retraction, n (%)			
Yes	78 (78)	44 (78.5)	p=1.00***
No	22 (22)	12 (21.5)	
Respiratory rate (min.)			
Mean, min. (± SD)	53.8 (±12.2)	58.8 (±11.1)	p=0.014****
Median, min. (range)	56 (30-84)	60 (35-90)	
SpO_2			
Mean, (± SD) %	92,6 (±4.1)	92.9 (±3.8)	p=0.67****
Median, (range) %	93 (82-100)	94 (85-99)	

*Fisher's exact chi-square test, **Pearson's chi-square test, ***Yates's correction chi-square, ****Mann-Whitney U test, API: Asthma predictive index, SD: Standard deviation.

Table 11. Bronchiolitis agents detected by PCR test in "API" groups

	API (+) n=41	API (-) n=26	p
RSV+RV (n, %)	31 (75.6)	17 (65.4)	p=0.53*
Other factors (n, %)	10 (24.4)	9 (34.6)	

*Yates's correction chi-square, PCR: Polymerase chain reaction, API: Asthma predictive index, SD: Standard deviation.

incidence of bronchiolitis was 15-37% higher in patients who had a cesarean delivery than in those born vaginally. Contact with the mother's vaginal flora in vaginally born infants leads to more diverse and healthy microbiota colonization in both the gastrointestinal and respiratory tracts (20). This treatment may also protect against bronchiolitis. A study conducted by Alan et al. (21) in our country, evaluating 20,183 newborns, reported a higher incidence of RSV-associated bronchiolitis in premature or low birth weight newborns. In our study, we had 3 low birth weight patients, and a sample size comparable to that of normal birth weight infants could not be established. The survival rates of premature infants have significantly increased in recent years, and the associated conditions have become better understood. Lung development begins before birth and continues until the age of 2 years, indicating that premature infants are born with less developed lungs and are at higher risk of severe RSV infections during the first year (21,22). Additionally, the frequent occurrence of bronchopulmonary dysplasia in premature infants increases the risk of severe bronchiolitis (23). Mechanical ventilation during the neonatal period can lead to lung cell damage, inflammation, surfactant dysfunction, and persistent lung damage (23). In our study, 23% of patients had a history of premature birth, and 10.8% had a history of mechanical ventilation during the neonatal period. This may represent an additional risk factor for the development of moderate to severe bronchiolitis.

It is known that children with atopic dermatitis and food allergies during infancy have an increased risk of developing asthma (15). Although all our patients were a selected group with severe bronchiolitis, the rates of atopic dermatitis and food allergies were lower than expected (22.4% and 9.6%, respectively). These conditions may be missed if they are clinically mild or enter remission significantly during the first year (1,2,21,24). Because our study included patients aged up to 2 years and assessed retrospective records, the observed rates for these risk factors may be lower than expected. Among the 156 patients in our study, 64 (41%) were previously hospitalized for acute bronchiolitis and were classified as having multiple hospitalizations. The relationship between recurrent bronchiolitis and asthma development becomes causal, especially in severe cases. A cohort study involving 38 centers across Europe, Africa, and the Americas tracked 343 children with bronchiolitis and reported that the severity of previous bronchiolitis was the most important risk factor for future asthma development ($p<0.05$, OR: 1.21, CI% 95) (25). Epidemiological studies have reported that 16-60% of severe bronchiolitis requiring hospitalization experience recurrent attacks (1,9). As all patients with bronchiolitis in our study were in infancy, this period corresponds to the time when lung and immune system maturation is at its fastest (26,27). In cases of severe and recurrent attacks, inflammation, airway epithelial damage, and necrosis can also occur, leading to barrier loss and airway fibrosis. The emergence of chronic structural changes is important as it lays the groundwork for persistent asthma (13). In this relationship, genetic predisposition, prenatal risk factors, and environmental factors also play a role as epigenetic factors (4,17). Given these findings and the fact that 64 patients with recurrent attacks had a history of severe attacks, we considered these patients to have asthma phenotypes. A comparison of respiratory system examination findings recorded at the time of initial presentation, significant differences were observed. The frequency

of respiratory rate, wheezing, and rales was higher in the multiple hospitalization group than in the first hospitalization group, and the differences were statistically significant (p=0.008, p=0.037, p=0.04, respectively). These significant differences suggest that patients in the multiple hospitalization group experienced more severe bronchiolitis than those in the first episode. Wheezing, even during the initial attack, provides prognostic and phenotypic clues. Arroyo et al. (28) conducted a clinical study with 50 children under 2 years old hospitalized for acute viral bronchiolitis confirmed by PCR and found that the wheezing group had higher levels of asthma-specific Th2 cytokines (IL-13, IL-4) in nasal secretions. They also showed that children with wheezing during an attack had more frequent hospital admissions for asthma later. These authors highlighted that different phenotypes exist among patients with severe bronchiolitis, and those with wheezing during the attack might have asthma. In our study, wheezing was more frequently observed in the recurrent bronchiolitis group, which was associated with a higher number of children with asthma phenotypes. When these three examination findings with statistical significance were evaluated with linear regression analysis, only the respiratory rate was significantly more important in our patients with recurrent bronchiolitis, with each unit increase in the respiratory rate increasing the hospitalization rate by 1.07 times. This indicates that the respiratory rate is an important predictor of hospitalization. In fact, respiratory rate is also considered a major risk factor for mortality in pediatric intensive care units, as indicated by the "PRISM" score (29). The etiology of bronchiolitis was investigated using PCR in 92 patients (58.9%). Among the 67 patients who tested positive by PCR, 71.6% had RSV or RV as the pathogen of bronchiolitis, or both. RSV or RV are commonly found in severe bronchiolitis cases (7). Many epidemiological studies have investigated the relationship between bronchiolitis pathogens and later asthma development. Sigurs et al. (30) conducted a long-term follow-up study and reported that infants with RSV bronchiolitis before the age of 1 had a 7.2-fold higher risk of asthma at age 18, and RSV bronchiolitis in infancy was a stronger risk factor than a family history of asthma. In a study including 349 children under 2 years with acute bronchiolitis, those with RV bronchiolitis were reported to use more prophylactic asthma medications than those with other pathogens, with this difference being statistically significant (31). Overall, most controlled, long-term cohort studies have shown that RSV is a more frequent bronchiolitis pathogen in younger infants, while RV is more common in older children, and both are closely related to asthma phenotypes (12). Considering all other data, the high rates of RSV and RV in our patients may indicate a higher risk of asthma among the children in our study group. Additionally, among the 100 patients with positive "API" considered to be at high risk for asthma, RSV or RV was isolated in 75.6% of the PCR results. Routine PCR testing is not recommended for acute bronchiolitis (4). In our study, nearly half of the patients (41%) did not undergo PCR testing. If pathogen investigations had been conducted in these patients, we might have found statistically significant differences based on "API" characteristics and previous bronchiolitis attacks. Among the 67 patients for whom we could identify the bronchiolitis pathogen using PCR, no significant differences in respiratory system examination findings were found between different pathogens. Guilbert et al. (32) conducted a long-term follow-up study in a birth cohort with asthma risk factors and found that children with RV bronchiolitis had significantly impaired respiratory function compared with those with other viral pathogens (p<0.001 for FEV1; p<0.001 for FEF25-75), and this was related to future asthma development. They did not find any relationship with RSV or other pathogens. Since there was no difference between pathogen groups in our study and it was not a long-term follow-up study, we cannot comment on this matter. Comparison of respiratory system physical examination findings at initial presentation with "API" evaluations revealed no statistically significant difference in some aspects. However, the higher number of crackles, medium rales, and rhonchi in the "API" positive group caught our attention. Wheezing was more frequently reported in the "API" positive group, and the difference was statistically significant. It is known that wheezing may not always be present in every bronchiolitis attack, even if severe (4,8). However, epidemiological studies have shown that wheezing attacks are more closely associated with future asthma development (9,13,14). In our study, although there was no statistically significant difference between the "API" positive and negative groups, the presence of more patients with previous bronchiolitis and more frequent PCR positivity for RSV and RV in the "API" positive group suggests that wheezing in this group may indicate an asthma phenotype. Currently, bronchiolitis is recognized as not a single disease but one that varies in clinical severity and prognosis depending on the viral pathogen, along with the patient's respiratory function, immune response, and genetic characteristics. Acute bronchiolitis may recur frequently in some patients, and these patients are often diagnosed with asthma later in life. Therefore, more extensive long-term studies involving larger patient populations are needed to identify high-risk patients early and adjust treatment accordingly.

Study Limitation

We can consider the limited number of cases a constraint in our study. Moreover, the inability to conduct respiratory viral PCR tests for each patient can also be regarded as a limitation.

Ethics

Ethics Committee Approval: Our study was approved by the Gazi University Faculty of Medicine Local Ethics Committee (approval number: 805, date: 14.12.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.K., İ.T., Design: S.K., İ.T., Supervision: T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Resources: S.K., İ.T., Material: T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Data Collection or Processing: S.K., İ.T., T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Analysis or Interpretation: S.K., İ.T., Literature Search: S.K., İ.T., T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Writing: S.K., İ.T., T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Critical Review: İ.T.

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