



The epidemiologic and clinical features of viral agents among hospitalized children with lower respiratory tract infections

Alt solunum yolu enfeksiyonu tanısı ile hastanede yatan çocuklarda viral etkenlerin epidemiyolojik ve klinik özellikleri

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The known about this topic

Acute respiratory tract infections are among the most common causes of infectious diseases. Viruses are the leading cause of respiratory tract infections during childhood. Viruses are widespread and very contagious.

Contribution of the study

Timely and accurate diagnosis of viruses is necessary for public health because of their high socioeconomic burden. A definite differentiation cannot be made by clinical and radiologic findings among the various types of viruses, though there are some differences.

Abstract

Aim: Acute respiratory tract infections are among the most common infectious diseases worldwide. Respiratory viruses are the leading cause of respiratory infections in children. Herein, we aimed to determine the epidemiologic and clinical features of viral agents among hospitalized children with lower respiratory tract infections.

Material and Methods: Nasopharyngeal swab specimens were obtained from the 422 patients hospitalized with a diagnosis of lower respiratory tract infections between December 2012 and December 2016. Multiplex reverse-transcription polymerase chain reaction was performed for the detection of viruses.

Results: Viral respiratory pathogens were detected in 311 patients (73.7%). In regard to respiratory virus subtypes, 103 patients (33.1%) had respiratory syncytial virus, 102 (32.7%) had human rhinovirus, 49 (15.7%) had multiple viruses, 15 (4.8%) had parainfluenzavirus, 13 (4.1%) had adenovirus, nine (2.8%) had human metapneumovirus, eight (2.5%) had human coronaviruses, six (1.9%) had bocavirus, five (1.6%) had influenza

Öz

Amaç: Solunum yolu enfeksiyonları tüm dünyada en yaygın görülen enfeksiyon hastalıkları arasındadır. Virüsler çocuklardaki solunum yolu enfeksiyonlarının en sık nedenidir. Bu yazıda, alt solunum yolu enfeksiyonu nedeniyle hastanede yatan çocuklarda viral etkenlerin epidemiyolojik ve klinik özelliklerinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Fakültemiz çocuk enfeksiyon servisinde Aralık 2012–Aralık 2016 tarihlerinde akut solunum yolu enfeksiyonları tanısı ile yatırılan 422 hastadan nasofarengeal sürüntü örnekleme alındı. Virüslerin saptaması için multiplex polimeraz zincir reaksiyonu yöntemi kullanıldı.

Bulgular: Viral solunum yolu virüsleri 311 hastada saptandı (%73,7). Solunum yolu virüslerinin tiplendirilmesi yapıldığında; 103 hastada (%33,1) respiratuvar sinsitiyal virüs, 102 hastada (%32,7) insan rinovirüs, 49 hastada (%15,7) çoklu virüs, 15 hastada (%4,8) parainfluenza virüs, 13 hastada (%4,1) adenovirüs, dokuz hastada (%2,8) metapnömovirüs, 8 hastada (%2,5) koronavirüs, altı hastada (%1,9) bokavirüs, beş hastada (%1,6) influenza virüsü ve bir hastada enterovirüs saptandı. Çoklu virus saptanan

Cont. ➔

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virus, and one patient (0.3%) had enterovirus. The median age was lower in patients with multiple viruses ($p<0.001$). The respiratory syncytial virus was more commonly detected in patients with a history of prematurity ($p<0.001$). Stridor was more common in other viruses including parainfluenza viruses ($p<0.001$).

Conclusion: Respiratory viruses are the main causative agents of respiratory tract infections in children. Timely and accurate detection of viruses is necessary in terms of public health. The detection of respiratory viruses also contributes to epidemiologic results and vaccine studies.

Keywords: Children, respiratory tract infections, respiratory viruses

Introduction

Acute respiratory tract infections (RTI) are among the most common causes of infectious diseases that cause significant morbidity and mortality all over the world (1, 2). Respiratory tract infections also have significant socioeconomic effects due to school and work loss, increased hospital admissions, and health charges. Viruses are the leading cause of RTIs and hospitalization during childhood. The disease spectrum of respiratory viruses changes from simple upper RTIs to acute respiratory failure. Viral infections can be epidemic, pandemic, and can even result in death depending on the age and the immune status of the child (3, 4). Although the distribution of viruses varies by season, geographic region, and age group, the respiratory syncytial virus (RSV), human rhinovirus (HRV), parainfluenza viruses (PIV), and seasonal influenza viruses are the most common causative respiratory viruses around the world (3, 4).

Cell culture is the gold standard method for the detection of viruses, but the low sensitivity, inefficacy in coinfections, and the necessity of cold chain logistics are the main handicaps. Multiplex polymerase chain reaction (PCR), a new molecular method, enables the determination of respiratory viruses rapidly and accurately (5, 6). The detection of viruses is important to avoid unnecessary antibiotic use, to begin antiviral treatment in time, to decrease the spread of the viruses, and to shorten the duration of hospitalization. The detection of respiratory viruses also contributes to epidemiologic results and vaccine studies. Herein, we aimed to determine the rate and clinical features of viruses among hospitalized children with lower RTIs.

Material and Methods

Study participants

This study was performed at Cerrahpasa Medical Faculty, Pediatric Infectious Disease Department between December 2012 and December 2016. The records of 422 patients hospitalized with findings of lower RTIs were evaluated retrospectively. Lower RTIs were subgrouped as acute bronchiolitis and bronchopneumonia. The diag-

nosis of patients was made by pediatricians according to standard clinical criteria. The diagnosis of bronchiolitis was established in patients with lower respiratory symptoms of wheezing, tachypnea, chest retractions, and/or rales. Bronchopneumonia was considered with clinical findings of fever, respiratory distress with crepitations, decreased vesicular sounds, and accompanying radiographic findings.

Çıkarımlar: Solunum virüsleri, çocuklarda solunum yolu enfeksiyonlarının ana nedenlerindedir. Toplum sağlığı açısından virüslerin zamanında ve doğru saptanması gerekmektedir. Solunum yolu virüslerinin saptanması epidemiyolojik sonuçlara ve aşı çalışmalarına da katkıda bulunmaktadır.

Anahtar sözcükler: Çocuklar, solunum yolu enfeksiyonları, solunum yolu virüsleri

The detailed medical records of patients were listed as age, sex, hospitalization states and times, breast feeding, exposure to smoking, the presence of atopy, number of siblings, school attendance, contact with anybody with upper RTIs, and influenza vaccination status. The physical examination findings, laboratory tests, radiologic findings, and viral PCR results were recorded from patient files.

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Analysis of respiratory tract virus

Nasopharyngeal swab samples were obtained by inserting swabs into both nostrils, progressing up to the nasopharyngeal region and rotating the swabs 360 degrees. The swabs were sealed in capped tubes that contained UTM™ Viral Transport medium (Copan Diagnostics Inc. Italy). Nucleic acids were extracted from 200 µL of specimens using High Pure Viral Nucleic Acid Kit (Roche, Germany) according to the manufacturer's instructions. Following nucleic acid purification, cDNA synthesis was performed using a RevertAid First Strand cDNA synthesis kit (Fermentas, Canada) according to the manufacturer's instructions. Multiplex PCR test in three tubes (A, B, and C) was performed for investigation of respiratory viruses. A Seplex® RV15 ACE Detection kit was used for testing, which covers 15 of the most common respiratory viruses (influenza A and B viruses, parainfluenza virus 1, 2, 3 and 4, coronavirus 229E/NL63 and OC43, rhinovirus A/B/C, respiratory syncytial virus A and B, metapneumovirus, enterovirus adenovirus and bocavirus 1/2/3/4), and based on multiplex PCR technology. Multiplex PCR was conducted in a final volume of 20 µL containing 3 µL cDNA sample, 4 µL ACE primer, 3 µL 8-MOP solution, and 10 µL master mix. Amplified PCR products were analyzed using 1.5% agarose gel electrophoresis.

Ethical approval for the study was provided by the Local Ethics Committee of Cerrahpasa Medical Faculty in 2017 (identification code: 367965) and detailed informed consent was obtained from the parents. The study was performed according to the principles of the Helsinki Declaration.

Statistical Analysis

The SPSS program (version 21.0, IBM company, SPSS Inc.) was used for statistical analysis. Continuous variables are presented as median (with interquartile range) and categorical variables as frequencies (with percentages). In the comparison of categorical data, the Chi-square test and Fisher's exact test was used where appropriate. Distribution of continuous data was analyzed using the Kolmogorov-Smirnov test, and the Kruskal-Wallis test was used to compare continuous data because normal distribution could not be achieved. Post hoc analyses for continuous variables were performed using the Mann-Whitney U test. A value of $p < 0.05$ was considered statistically significant.

Results

Demographic, clinical, and laboratory data

Four hundred twenty-two patients hospitalized at the Pediatric Infectious Disease Department were enrolled in the present study. There were 183 females (43.4%) and 239 males (56.6%). The median age of the patients was 10.0 (range, 4.0–48.0) months. In terms of age distribution, 98 patients (23.2%) were aged ≤ 3 months, 139 (32.9%) were aged between 4 and 12 months, 95 (22.5%) were aged between 13 and 60 months, and 90 patients (21.3%) were aged ≥ 60 months.

Bronchiolitis was diagnosed in 257 (61%) patients and bronchopneumonia was diagnosed in 165 (39.0%) patients.

A history of premature birth was present in 102 (24.2%) patients, and asthma was present in 38 (9%) patients. One hundred eighty-five (43.8%) patients were breastfed. In total, 124 (29.4%) patients had a household member with an upper RTI and 143 (33.9%) patients had sibling continuing daycare center or school. Two hundred two (47.9%) families were smoking in their homes. Overall, 132 patients (31.3%) had an underlying chronic disease, the most common were chronic lung disease, gastroesophageal reflux disease, congenital heart disease, and cystic fibrosis, respectively. The demographic findings of patients are listed in Table 1.

At presentation, 125 (29.6%) patients had tachypnea. The symptoms of the hospitalized children were cough ($n=369$, 87.4%), fever ($n=240$, 56.9%), wheezing ($n=152$, 36%), nasal discharge ($n=97$, 22.9%), expectoration ($n=69$,

Table 1. Demographic findings of the patients (n=422)

	n	%
Sex		
Male	183	43.4
Female	239	56.6
Ages of patients		
<3 months	98	23.2
4–12 months	139	32.9
13–60 months	95	22.5
>60 months	90	21.3
Diagnosis of patients		
Bronchiolitis	257	61
Bronchopneumonia	165	39.0
Premature birth history	102	24.2
Underlying chronic disease	132	31.3
Asthma	38	9
Breastfeeding	185	43.8
Household member daycare center or school	143	33.9
Household member with URTI	124	29.4
Smoker in family	202	47.9
Season		
Winter	161	38.1
Spring	126	29.8
Autumn	84	19.9
Summer	51	12.0

URTI: Upper respiratory tract infection

16.4%), cyanosis ($n=18$, 4.2%), and stridor ($n=10$, 2.3%). In physical examinations, 206 patients (48.8%) had focal or diffuse crackles, and 208 (49.2%) had prolonged expiration.

In the radiology, 130 (30.8%) patients had peribronchial findings, 248 (58.8%) had consolidation, and 168 (39.8%) patients had increased aeration. The symptoms, physical, and radiologic findings of the patients are listed in Table 2.

In laboratory tests, the median leukocyte count was 11,200 (range, 8100–15,100) mm^3 , the median neutrophil count was 5550 (range, 3000–8800) mm^3 , the median lymphocyte count was 3400 (range, 2100–5600) mm^3 , the median platelet count was 339,000 (range, 254,000–416,000) mm^3 , the median aspartate aminotransaminase (AST) concentration was 32.0 (range, 24.0–41.0) IU/L, and the median alanine aminotransaminase (ALT) level was 20.0 (range, 14.0–29.0) IU/L.

Prevalence of respiratory agents and seasonal patterns

Viral respiratory pathogens were detected in 311 (73.7%)

Table 2. Symptoms, physical and radiologic findings of patients (n=422)

	n	%
Tachypnea	125	29.6
Cough	369	87.4
Fever	240	56.9
Wheezing	152	36
Nasal discharge	97	22.9
Expectoration	69	16.4
Stridor	10	2.3
Cyanosis	18	4.2
Focal or diffuse crackles	206	48.8
Prolonged expirium	208	49.2
Peribronchial findings	130	30.8
Consolidation	248	58.8
Increased aeration	168	39.8

Table 3. Viral respiratory pathogens (n=311)

	n	%
Respiratory syncytial virus	103	33.1
Human rhinovirus	102	32.7
Multiple viruses	49	15.7
Parainfluenzavirus	15	4.8
Adenovirus	13	4.1
Human metapneumovirus	9	2.8
Human coronaviruses	8	2.5
Bocavirus	6	1.9
Influenza	5	1.6
Enterovirus	1	0.3

patients. In regard to the respiratory virus subtypes, 103 (33.1%) patients had RSV, 102 (32.7%) had HRV, 49 (15.7%) had multiple viruses, 15 (4.8%) had parainfluenzavirus (PIV), 13 (4.1%) had adenovirus (AdV), nine (2.8%) had human metapneumovirus (MPV), eight (2.5%) had human coronaviruses (HCoV), six patients (1.9%) had bocavirus (BcV), five patients (1.6%) had influenza virus, and one patient (0.3%) had enterovirus (EV). Viral respiratory pathogens are listed in Table 3.

HRV and RSV were identified in 19 of 47 patients with multiple infections, and a combination of HRV and BcV was identified in eight patients; the remainder had multiple types of respiratory viruses. Blood cultures were negative in all patients in whom viruses were detected.

With regard to seasonal distribution, 161 patients (38.2%) were hospitalized in winter, 126 (29.9%) in spring, 84 (19.9%) in autumn, and 51 (12.1%) patients were hospi-

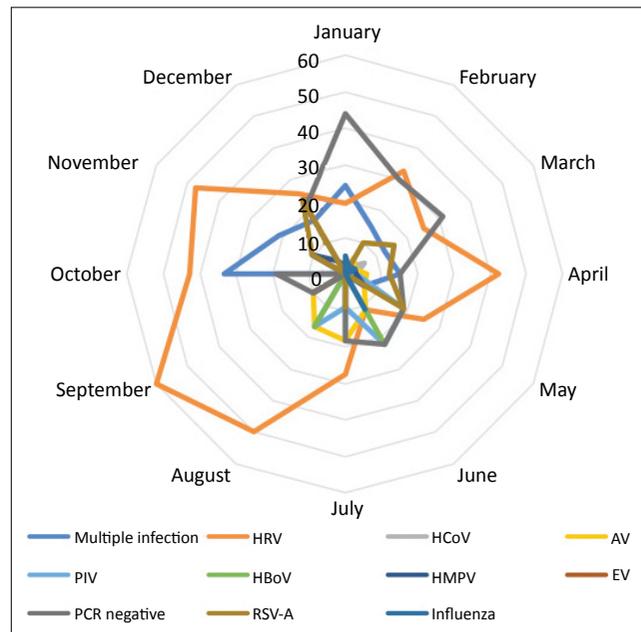


Figure 1. The comparison of respiratory viruses with regard to seasonal distribution

talized in summer. Influenza, RSV, and HRV were more common in cold and rainy periods, with HRV mostly in September and RSV in January. Multiple viruses were also more common in winter. Metapneumovirus and HCoV were not detected in summer. EV was only detected in autumn and BcV was present only in winter and summer (Fig. 1).

The comparison of demographic results in terms of virus detection revealed that the distribution of respiratory tract viruses by the age of patients was found to be statistically different. The median age was lower in patients with multiple viruses ($p < 0.001$). Respiratory syncytial virus was more commonly detected in patients with a history of prematurity ($p < 0.001$).

According to signs and symptoms at presentation, stridor was strikingly more common in other viruses including PIV ($p < 0.001$).

No difference was found between the viruses in terms of diagnosis as bronchiolitis and bronchopneumonia. No significant difference was also demonstrated relevant to demographics including sex, presence of asthma or atopia, family history of smoking, upper RTI in the family, and hospitalization duration. We also found no significant difference among the viral pathogens in terms of other clinical and radiologic findings. Although all the influenza cases (only 5) involved leukopenia and lymphopenia, there was no significant statistical difference among the viruses with regard to laboratory findings.

Table 4. Comparison of demographic and clinical findings of viruses

	Multiple (n=49)		HRV (n=102)		Other viruses (n=57)		No virus (n=111)		RSV (n=103)		p
	n	%	n	%	n	%	n	%	n	%	
Sex (male)	28	57.1	63	61.7	32	56.1	58	52.3	58	56.3	0.740 ^a
Age (months)*	6.0 (3.0–14.0)		15.5 (5.0–70.0)		11.0 (6.0–40.0)		18.0 (3.0–68.0)		7.0 (3.0–16.0)		<0.001^{b,+}
Bronchiolitis	33	67.3	66	64.7	30	52.6	69	62.1	59	57.2	0.440 ^a
Prematurity	4	8.2	22	21.6	11	19.3	19	17.1	46	44.7	<0.001^a
Breastfeeding	26	53.1	35	34.3	19	33.3	47	42.3	58	56.3	0.006 ^a
Chronic disease	12	24.5	35	34.3	17	29.8	42	37.8	26	25.2	0.239 ^a
Asthma	3	6.1	16	15.6	6	10.5	6	5.4	7	6.7	0.072 ^a
Smoking in the family	34	69.4	52	51.0	26	45.6	43	38.7	47	45.6	0.009 ^a
URTI in the family	16	32.6	35	34.3	17	29.8	33	29.7	23	22.3	0.416 ^a
Sibling continuing day care center	19	38.7	30	29.4	22	38.6	38	34.2	34	33.0	0.728 ^a
Fever	31	63.3	57	55.9	35	61.4	70	63.1	47	45.6	0.079 ^a
Wheezing	15	30.6	32	31.4	19	33.3	38	34.2	48	46.6	0.140 ^a
Nasal discharge	14	28.6	27	26.5	10	17.5	21	18.9	25	24.3	0.455 ^a
Cough	42	85.7	84	82.3	54	94.7	98	88.3	91	88.3	0.244 ^a
Expectoration	9	18.4	17	16.7	9	15.8	18	16.2	16	15.5	0.994 ^a
Tachypnea	15	30.6	28	27.5	13	22.8	32	28.8	37	35.9	0.475 ^a
Stridor	1	2.0	2	2.0	7	12.3	0	0.0	0	0.0	<0.001^c
Cyanosis	3	6.1	5	4.9	5	8.8	4	3.6	1	1.0	0.126 ^c
Consolidation	24	49.0	54	52.9	32	56.1	73	65.8	65	63.1	0.160 ^a
Peribronchial findigs	14	28.6	29	28.4	12	21.1	44	39.6	31	30.1	0.135 ^a
Increased aeration	28	57.1	31	30.4	27	47.4	37	33.3	45	43.7	0.008^a
Hospitalisation period*	10.0 (8.0–15.0)		10.0 (7.0–14.0)		12.0 (8.0–18.0)		10.0 (7.0–14.0)		10.0 (7.0–13.0)		0.849 ^b
Laboratory findings											
Leucocyte (x10 ³)*	10.2 (7.8–6.6)		12.2 (8.7–5.7)		10.6 (8.1–5.4)		11.2 (8.3–4.4)		10.2 (7.6–4.3)		0.408 ^b
Neutrophil (x10 ³)*	5.1 (2.7–7.9)		5.9 (3.4–9.4)		5.6 (3.4–9.1)		5.8 (3.4–9.8)		4.9 (2.9–7.4)		0.155 ^b
Lymphocyte (x10 ³)*	3.3 (2.4–5.7)		3.3 (1.8–5.7)		3.2 (2–3–54)		3.1 (1.7–4.9)		3.8 (2.2–5.9)		0.096 ^b
Platelet (x10 ³)*	341 (258–416)		344 (248–416)		337 (250–430)		336 (260–430)		332 (253–411)		0.895 ^b
AST*	32.0 (25.0–41.0)		29.0 (21.0–39.0)		32.0 (24.0–41.0)		33.0 (25.0–42.0)		34.0 (25.0–42.0)		0.075 ^b
ALT*	21.0 (16.0–30.0)		18.0 (12.0–25.0)		21.0 (14.0–27.0)		20.0 (13.0–33.0)		21.0 (14.0–32.0)		0.459 ^b

a: Pearson Chi-square test; b: Kruskal-Wallis test; c: Fisher's exact test; *Data presented as Median (Interquartile Range); +: Post Hoc Analysis are done with Mann Whitney U test; AdV: Adenovirus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; HRV: Human rhinovirus; MPV: Metapneumovirus; PIV: Parainfluenza virus; RSV: Respiratory syncytial virus

Discussion

In this study, we aimed to determine the prevalence and clinical features of respiratory viruses among hospitalized children with a diagnosis of lower RTI. Viral respiratory

pathogens were detected in 73.7% of patients. Respiratory viruses are the most common cause of respiratory infections during childhood, the rate of which varies between 48–88.7% (7–11). There are many epidemiologic studies in

the literature with similar results investigating the clinical and epidemiologic impact of viruses (7, 8, 10, 11). However, there is not yet any reported definite distinction between the severity of the disease and the type of viruses. So, to report the different clinical experiences can further contribute to composing a standardized definition of severity of RTIs, as Fretzayas and Moustaki suggested (12).

In the present study, RSV and HRV were the most commonly detected causative agents in the etiology of RTI. Respiratory syncytial virus is responsible for over 30 million acute lower RTI episodes in children aged under 5 years and it induces more than 3.4 million hospital admissions and 160 000 deaths every year (13–15). There are several studies reporting the rate of RSV ranging from 40.1–77% worldwide. For our country, the frequency of RSV in hospitalized infants is between 20–63% (16, 17).

Human rhinovirus is also known as the most common respiratory virus responsible for most upper RTIs, but HRV may also cause severe lower RTI and asthmatic exacerbations (18, 19). Human rhinovirus can even lead to bronchiolitis, more severe than RSV as Papadopoulos et al. (18) reported. Human rhinovirus and RSV are also related with persistent wheezing and respiratory disease, thus the detection of viruses is important for the diagnosis and follow-up of wheezing infants.

Multiple viruses were the third most frequent respiratory pathogens. Goka et al. (20) stated that the frequency of multiple viruses was between 5% and 62%. It has been postulated that prolonged nasopharyngeal shedding and asymptomatic persistence of viruses can be the reason of rather than the actual infection. Even though some studies suggest that identification of multiple viral agents can present with a more severe clinic than single pathogens, the relation between disease severity and coinfection remains unclear (21, 22). We experienced no clinical or radiologic difference between single and multiple viruses, but the median age of patients was lower for multiple viruses. Cilla et al. (23) also reported multiple viruses in younger children. The younger age group tended to develop viral infections more compared with adults due to immature immune status and prolonged viral shedding period. The RSV is also detected in younger age group (1–170 months), the median age of our patients with RSV was 7.0 (range, 3.0–16.0) months, consistent with the literature. It is already known that RSV is more likely to progress into severe lower RTIs in premature infants. We also detected RSV more commonly in patients with a history of prematurity.

Viruses show a seasonal distribution, especially in temperate climates. Most respiratory viruses are reported to

be active during the cold and rainy seasons. In particular, the activity of RSV is thought to be inversely correlated with high temperatures and ultraviolet light. Besides, HRV prefers high humidity (24–26). As in previous reports, RSV and HRV were detected in winter and autumn, and despite being rarely identified, all influenza cases were in winter.

With regard to the clinical findings, stridor was strikingly more common in other viruses probably PIV, because stridor is a prominent finding of PIV.

Leucopenia, lymphopenia, and neutropenia are the reported hematologic findings of respiratory viruses (27). We observed leucopenia and lymphopenia in all influenza cases and with some other viruses. The lowest neutrophil count ($100/\text{mm}^3$) was detected in RSV, and the lowest lymphocyte counts ($100/\text{mm}^3$) were in influenza and HPV. However, overall there was no significant statistical difference among the viruses in terms of hematologic findings or biochemical results.

Routine chest radiography is not necessary to confirm the diagnosis of pneumonia in children; radiographic findings are poor indicators of the etiologic diagnosis. All of our patients had chest X-rays because of hospitalization. The most common radiologic findings of respiratory viruses are multifocal or diffuse areas of consolidation, similar to the X-rays of our patients. RSV is reported to cause an airway-centric pattern of disease characterized by a combination of tree-in-bud opacities and peribronchiolar consolidation. Adenovirus causes multifocal pneumonia characterized by combinations of consolidation and ground-glass opacities. In the present study, no significant difference was found between the radiologic findings and viruses.

Our study had some limitations. First, the multiplex PCR kit used was able to identify only 15 respiratory tract pathogens. Second, the number of influenza cases was very small. Third, we only investigated hospitalized patients with lower RTIs, not patients who were admitted to the emergency services or outpatients' polyclinics. Finally, the treatment methods of patients were not specified in the study.

In conclusion, viruses are the main causative agents of RTIs in children. A definite differentiation cannot be made by the clinical and radiologic findings among the various types of viruses, though there are some differences. Timely and accurate diagnosis of viruses is necessary for point of view of public health because of their high socioeconomic burden.

Ethics Committee Approval: Ethics committee approval was received for this study from Cerrahpaşa Medical Faculty Ethic Committee (2017, No: 367965).

Informed Consent: Written informed consent was obtained from the parents.

Peer-review: Externally peer-reviewed.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ebeveynlerinden alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - D.A., H.Ç., Y.C.; Tasarım - D.A., H.Ç., Y.C.; Denetleme - H.Ç., Y.C.; Kaynaklar - M.K., K.M., Y.C.; Malzemeler - D.A., F.E., D.Ş.; Veri Toplanması ve/veya İşlenmesi - D.A., F.E., D.Ş., M.K., F.V.; Analiz ve/veya Yorum - D.A., F.E., D.Ş., M.K.; Literatür Taraması - D.A., M.K., Y.C.; Yazıyı Yazan - D.A., Y.C.; Eleştirel İnceleme - H.Ç., Y.C.; Diğer - D.A., H.Ç., Y.C., K.M.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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