Epidemiology and Acute Respiratory Distress Syndrome Propensity of Viral Respiratory Infections in Pediatric Intensive Care Units Prior to the Coronavirus Disease 2019 Pandemic

Gültaç Evren[1] Tolga Besci[2] Özgür Appak[3] Ayça Arzu Sayıner[3] Gazi Arslan[4] Murat Duman[5]

[1] Manisa City Hospital, Pediatric Intensive Care Unit, Manisa, Türkiye
[2] Izmir Buca Seyfi Demirsoy Training and Research Hospital, Pediatric Intensive Care Unit, Izmir, Türkiye
[3] Dokuz Eylul University Faculty of Medicine, Medical Microbiology, Izmir, Türkiye
[4] Dokuz Eylul University Faculty of Medicine, Pediatric Intensive Care Unit, Izmir, Türkiye
[5] Dokuz Eylul University Faculty of Medicine, Pediatric Emergency Care, Izmir, Türkiye,

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Address for correspondence Gultac Evren, MD, Pediatric Intensive Care Unit, Manisa City Hospital, Manisa, Türkiye (e-mail: gultacevren@gmail.com).

Abstract

Objective This study aimed to determine the epidemiology and acute respiratory distress syndrome (ARDS) propensity of common respiratory viruses in a tertiary pediatric intensive care unit (PICU) among hospitalized children who were tested for respiratory viruses by polymerase chain reaction (PCR) prior to the coronavirus disease 2019 (COVID-19) pandemic.

Methods Respiratory tract samples were collected from patients who were followed up in the Dokuz Eylul University Hospital pediatric intensive care unit between March 2015 and March 2020 and tested for viral pathogens. The results of 269 patients between 1 month and 18 years of age were evaluated retrospectively.

Results In the 5 years preceding the COVID-19 pandemic, 269 patients with a lower respiratory infection were admitted to the PICU. A positive viral PCR result was detected in 160 patients (59.5%). Human rhinovirus was the most common virus (40%), followed by respiratory syncytial virus (26.3%), human bocavirus (10%), and seasonal coronaviruses (10%). Five (33.3%) of the fifteen children who developed ARDS were infected with influenza A/B, while four (26.7%) were infected with human metapneumovirus (hMPV).

Conclusion Although rhinovirus was the most common viral agent in critically ill children, the incidence of ARDS was higher in children aged over 1 year who had influenza or hMPV infection.

Keywords
- virus
- respiratory infection
- pediatric intensive care
- epidemiology
- ARDS

Introduction

Viral infections are among the important causes of childhood morbidity and mortality worldwide. Viral infections are the primary cause of both upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) in children. Viral URTIs usually cause mild symptoms, but they spread readily in the community, and a small proportion of children with these infections required management in a pediatric intensive care unit (PICU).

Viruses are responsible for 30 to 70% of acute respiratory infections, influenza A virus (IAV), influenza B virus (IBV),

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respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), adenovirus (AdV), human metapneumovirus (hMPV), and rhinovirus (RV) are frequently reported viruses.[1–3] Among the viruses that cause LRTI, RSV accounts for 50 to 90% of cases.[4] It has been shown that in the preterm infant population, the most common agent associated with severe bronchiolitis is RV.[5]

The frequency of detection of viruses in acute respiratory infections depends on many factors such as patient selection criteria, the severity of the disease, the season of the year, and theiagnosis. Coinfection with more than one respiratory virus is common in children and has been reported in 10 to 40% of symptomatic patients.[6,7] Bacterial coinfections of the respiratory tract developed in at least 37.7% of the children with bronchiolitis requiring invasive ventilation.[8]

Pediatric acute respiratory distress syndrome (ARDS) was first defined as a syndrome that presents with hypoxemia, tachypnea, and decreased pulmonary compliance and has been defined according to Pediatric Acute Lung Injury Consensus Conference (PALICC)[9] criteria over the years. It constitutes approximately 1 to 4% of PICU admissions.[10] The most common causes are pneumonia, sepsis, and trauma. Viral infections are a major cause of pediatric ARDS. RSV and influenza A (H_1N_1) virus are the most commonly reported viruses to cause pediatric ARDS.[11]

It presents clinically with fever, leading to increased use of diagnostic tools and unnecessary antibiotic use. Therefore, accurate and timely identification of the responsible viral pathogen may reduce unnecessary antibiotic use and hospital stay.[12] Various risk factors, such as heart disease, chronic lung disease, and prematurity, which increase the severity of viral LRTI, have been identified and the underlying disease partially explains that some children have severe respiratory failure and require mechanical ventilation.[13] Although most viral infections are short-lived, some children are severely affected and require hospitalization.[14] Among these hospitalizations, a small percentage of children require PICU admission.[15]

Although there are epidemiological differences between the agents of the viral respiratory tract, young children are more likely to experience serious respiratory tract infections and to require PICU admission. This study aimed to determine the epidemiology and association with ARDS of the most prevalent respiratory viruses in children who were admitted to the PICU and tested for suspected viral infection by polymerase chain reaction (PCR) prior to COVID-19 pandemic.

Materials and Methods

The Institutional Ethical Committee of Dokuz Eylul University, Türkiye, approved this retrospective, single-center study (approval number: 5580-GOA).

The study included 269 children aged 1 month to 18 years who were admitted to the PICU at Dokuz Eylul University between March 2015 and March 2020 and tested for respiratory viral infection by PCR. Respiratory tract samples from intubated patients were obtained from bronchoalveolar lavage fluids, while samples from nonintubated patients were obtained from nasopharyngeal swabs within the first hour of admission to the PICU.

Demographic data for each patient, comorbidities (respiratory, cardiac, neurological, and 'immunologic diseases), history of prematurity (gestational age <37 weeks), specific viruses detected by PCR, need for invasive and noninvasive ventilation, postdiagnosis treatments (vasoactive infusions, antibiotics, and adjuvant treatments), development of ARDS, length of PICU stay, and mortality were recorded. Data for the Pediatric Index of Mortality-3 score and pediatric risk of mortality score-4 were calculated at admission to PICU.

Patients with respiratory failure due to LRTI were taken to noninvasive mechanical ventilation, and patients with GCS <8, hemodynamic instability, and no airway protective reflex were intubated. Antibiotics were started in patients with fever, elevated C-reactive protein and leukocyte levels, and infiltration on chest X-ray, and clinically crepitant rales in lung sounds until viral PCR results were obtained.

Multiple organ dysfunction syndrome (MODS) was defined by the simultaneous presence of two or more organ dysfunctions. MODS criteria constitute the following: cardiovascular (hypotension and vasopressor requirement); respiratory (PaO2/FiO2 ratio, PaCO2 count, intubation requirement); hematology (platelet count, INR); liver (serum bilirubin, alanine aminotransferase); renal (serum creatinine or urine output); and neurological (Glasgow coma score).[16]

The participants were screened for ARDS using the International PALICC criteria as follows: (1) patients with perinatal lung disease are excluded, and pARDS criteria must be met within 7 days of a clinical insult; (2) the cause of respiratory failure must not be explained by heart failure or fluid overload and must be evidenced by new pulmonary infiltrates on chest radiograph consistent with the parenchymal disease;' and (3) the use of oxygenation criteria is preferred over the PaO2/FiO2 or SaO2/FiO2 ratio in determining pARDS in mechanically ventilated or noninvasive ventilation patients.[9]

Patients aged 29 days to 18 years who were admitted to the PICU with LRTI and tested for viral PCR were included in the study. Viral PCR tests were conducted on the day of admission. Minibronchoalveolar lavage samples were taken from intubated patients, and nasopharyngeal swab samples were collected from nonintubated patients.

The AusDiagnostics test is based on the multiplex tandem PCR method and identifies IAV, IBV, hMPV, PIV1, 2, 3, RSV, AdV, RV/enterovirus (RV/EV), and *Bordetella* spp. The FTD 21 test, using different primers and probes, detects 20 agents in five reaction tubes by multiplex PCR. These agents are IAV, IAV subtype H1N1 (pandemic H1N1), IBV, human RV, human coronaviruses NL63 (HCoVNL63), 229E (HCoV 229E), OC43 (HCoV OC43) and HKU1 (HCoV HKU1), PIV 1, 2, 3, and 4, *Mycoplasma pneumoniae*, human bocavirus (HBoV), hMPV A/B, RSV A/B, AdV, EV, and human parechovirus.

Both assays include internal control and negative and positive run controls. EZ1 Virus Mini Kit V 2.0 (QIAGEN, Hamburg, Germany) was used for nucleic acid extraction

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which was performed on the EZ1 Advanced XL (QIAGEN) device according to the manufacturer's instructions.

Statistical analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL) for Windows. The independent sample *t*-test was used to compare continuous, normally distributed data expressed as mean standard deviation; the Mann–Whitney U test was used to compare nonnormally distributed data expressed as median (interquartile range). The Shapiro–Wilk test was used to evaluate the normal distribution of the variables. The count data were expressed in terms of numbers (percentage). To compare categorical data, either Pearson's chi-squared or Fishers exact tests were used. All tests were two-tailed, and statistical significance was defined as a *p*-value less than 0.05.

Results

In the 5-year period before COVID-19, 269 patients were admitted to PICU with lower a diagnosis of respiratory tract infection. A positive viral PCR result was identified in 160 (59.5%) patients. The mean age of the patients who were positive for viral PCR was 12 months, and 97 (60.6%) were male. Prematurity was commoner in patients with a positive PCR compared with those who were PCR negative (18.1%, 9.2%). PCR positivity was highest in the winter and spring months. A cardiovascular condition was the most common comorbidity (18.8%) in PCR-positive patients (►**Table 1**).

Human rhinoviruses (HRV) was the most common virus (40%), followed by RSV (26.3%), HBoV (10%), and seasonal

Table 1 Patients characteristics and outcomes

Outcomes	PCR positive $n = 160$	PCR negative $n = 109$	*p*-Value
Age (month) and median (IQR)	12 (5.5–36)	12 (9–108)	<**0.001**
Age categories			**0.024**
Infant (1–12 mo)	109 (68.1)	57 (52.3)	
Toddler (12–24 mo)	10 (6.3)	5 (4.6)	
Preschooler (24–72 mo)	20 (12.5)	16 (14.7)	
School (72–144 mo)	14 (8.8)	19 (17.4)	
Adolescent (144–216 mo)	7 (4.4)	12 (11)	
Sex, *n* (%)			0.227
Female	63 (39.4)	51(46.8)	
Male	97 (60.6)	58 (53.2)	
Prematurity, *n* (%)	29 (18.1)	10 (9.2)	**0.041**
PICU admission season, *n* (%)			**0.001**
Winter	62 (38.8)	36 (33)	
Spring	59 (36.9)	36 (33)	
Autumn	17 (10.6)	4 (3.7)	
Summer	22 (13.8)	33 (30.3)	
Comorbidities, *n* (%)	92 (57.5)	82 (75.2)	**0.003**
Respiratory	17 (10.6)	14 (12.8)	0.576
Neuromuscular	29 (18.1)	24 (22)	0.431
Cardiovascular	30 (18.8)	22 (20.2)	0.770
Immunologic and cancer	18 (11.3)	22 (20.2)	**0.043**
PIM 3 score, median (IQR)	4.4 (1–10.7)	5 (1.8–11.5)	0.304
PRISM 4 score, median (IQR)	1 (0.8–5)	2 (0.8–4.2)	0.680
Duration of invasive mechanical ventilation, median (IQR)	7 (4–15.5)	8 (4.5–15.5)	0.750
Duration of HFNC (days), median (IQR)	3 (2–5)	5 (3–6)	**0.011**
Duration of BİPAP (days), median (IQR)	2 (2–5)	5 (2–6.25)	0.071
Length of PICU stay (days), median (IQR)	5 (4–14.7)	9.5 (6–19)	**0.013**
Length of hospital stay (days), median (IQR)	15,5 (9–27.7)	20 (12.3–31.8)	**0.003**
Mortality, *n* (%)	16 (10)	6 (5.5)	0.187

Abbreviations: BİPAP, bilevel positive airway pressure; IQR, interquartile range; HFNC, high-flow nasal cannula; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PIM-3, Pediatric Index of Mortality-3; PRISM-4, Pediatric Risk of Mortality.
Note: Data are presented as median (interquartile range). PIM-3 was measured at time of PICU admission.

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Table 2 Frequency of respiratory viruses and coinfections

Variables	Values
Viral etiology, *n* (%)	
Human rhinovirus	64 (40.0)
Respiratory syncytial virus	42 (26.3)
Human bocavirus	17 (10.6)
Human coronavirus	16 (10.0)
Human metapneumovirus	13 (8.1)
Influenza virus (flu A/B)	12 (7.5)
Adenovirus	12 (7.5)
Parainfluenza virus	11 (6.9)
Human enterovirus	9 (5.6)
Mycoplasma pneumoniae	2 (1.3)
Bordetella pertussis	1 (0.6)
Viral infection type, *n* (%)	
Single viral infection	87 (54)
Multiple viral infections	73 (45.6)
Bacterial coinfection, *n* (%)	
Pseudomonas aeruginosa	4 (1.5)
Escherichia coli	1 (0.4)
Staphylococcus aureus	2 (0.7)
Candida albicans	1 (0.4)

coronaviruses (10%). A single viral pathogen was detected in 87 (54.4%) children, and at least two viruses were detected in 73 (45.6%) children. Nonbronchoscopic bronchoalveolar lavage cultures were obtained from patients receiving invasive mechanical ventilation who had suspected bacterial coinfections; eight children had positive cultures, comprising *Pseudomonas aeruginosa* (1.5%), *Staphylococcus aureus* (0.7%), *Escherichia coli* (0.4%), and *Candida albicans* (0.4%; ►**Table 2**).

Children who developed ARDS after viral infection were older ($p = 0.006$). ARDS developed in 5 out of 15 (33.3%) patients with influenza A/B and in 4 out of 15 (26.7%) patients with hMPV. The PICU stay of patients with ARDS was significantly longer than those without ARDS, but there was no difference in hospitalization periods. Patients with ARDS also required mechanical ventilation for longer ($p = 0.028$). The mortality rate was higher in patients with ARDS (26.7%) compared to patients without ARDS (8.3%, ►**Table 3**).

Table 3 Demographic of acute respiratory distress syndrome development in patients with specific virus positive

Variables	ARDS positive *n* = 15	ARDS negative *n* = 145	*p*-Value
Age (month), median (IQR)	36 (12–156)	11 (5.5–24)	**0.006**
Female (%)	6 (40)	57 (39.3)	0.958
Prematurity (%)	3 (20)	26 (17.9)	0.843
Specific virus, *n* (%)			**<0.001**
Influenza A/B	5 (33.3)	7 (4.8)	
Coronavirus	2 (13.3)	14 (9.7)	
Bocavirus	4 (26.7)	13 (9)	
Human metapneumovirus	4 (26.7)	9 (6.2)	
Other	0	102 (70.4)	
Length of PICU stay (day)	16 (4–83)	7 (2–69)	**0.008**
Length of hospital stay	22 (4–166)	15 (3–101)	0.119
Invasive mechanical ventilation (day)	12.5 (4–75)	7 (1–69)	**0.028**
Need for inotrope (%)	8 (53.3)	27 (18.6)	**0.002**
Tracheostomy	3 (20)	11 (7.6)	0.105
Chronic lung disease	5 (33.3)	3 (2.1)	**0.000**
Multiple organ dysfunction syndrome	3 (20)	9 (6.2)	0.054
Nosocomial infection	4 (26.7)	15 (10.3)	0.063
Mortality	4 (26.7)	12 (8.3)	**0.024**

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range.

Discussion

In our study, we retrospectively evaluated the respiratory tract viruses detected in children aged 0 to 18 years who were hospitalized in the PICU between 2015 and 2020. Respiratory tract virus testing was positive in 160 of 269 patients who underwent PCR at admission to the PICU. We believe that this is the first study in Türkiye to examine the trend of viral epidemiology and ARDS in the PICU before the COVID-19 pandemic. Both because of the milder clinical course of COVID-19 in children and the decline in the global SARS-CoV-2 from 20 to 5%, we expect other viral pathogens causing LRTIs in children to gain prominence again.

Outside the pandemic period RVs are reported to be the most common viral cause of lower respiratory infections globally.[13,17] Viruses can appear in different seasons due to geographical differences. HBoV was mostly detected in spring/winter in Lanzhou,[18] hMPV in spring/summer in Hong Kong,[19] and RSV infection in tropical regions in winter.[20] In our study, the occurrence of positive results in respiratory virus panel tests was statistically significantly higher in winter and spring. The most common pathogen was

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HRV (40.8%), and in our country, which has a temperate climate, positivity was highest in the spring months.

In a previous study of children with acute respiratory tract infections, prematurity was a risk factor for hospitalization especially for RSV infection.[21] In our study, there was a positive correlation between premature birth and PCR positivity. In a Chinese study, RSV was the most common virus and 58.3% of the patients requiring PICU care had underlying comorbidities.[22] In our study, 57.5% of patients had comorbidities. In a study evaluating the hospitalization of patients who were positive for influenza, RSV, and PIV, patients aged under 1 year were more frequently hospitalized, those aged over 5 years of age were mainly treated as outpatients.[23] In our study, the patients with PCR positivity were younger, suggesting that respiratory viral infections in older patients cause milder disease that less often requires PICU admission. The length of stay in the PICU and hospital was significantly longer in viral PCR-positive patients. A total of 110 of the PCR-positive patients underwent invasive ventilation, 90 patients underwent high-flow nasal cannula (HFNC), and 43 patients underwent bilevel positive airway pressure. Although the duration of invasive mechanical ventilation of these patients was not significantly different between viral PCR positive and negative patients, the duration of HFNC was shorter in patients with positive viral PCR. In 40 of the patients who underwent HFNC, it was used as a rescue treatment in postextubation after invasive mechanical ventilation. This was a factor in the shorter duration of HFNC.

Patients with ARDS account for 10% of all PICU hospitalizations.[24] In a study conducted in the United States, the most common viral agents detected in patients who developed ARDS were RV/EV (43%), followed by RSV (24%), hMPV (17%), AdV (14%), and influenza (13%).[25] In an adult study, 19 (14.8%) of patients hospitalized with hMPV progressed to ARDS.[26] In the study of Ghazaly et al, RSV was found to be the most common factor in ARDS patients younger than 1 year old.[27] In our study, contrary to other studies, the most common factors in the development of ARDS were found to be influenza A/B, HBoV, and hMPV. The risk of developing ARDS was lower in patients younger than 1 year old. This suggested that the higher incidence of RSV and RV infections in patients fewer than 1 year of age may result in a lower incidence of ARDS; the viruses that were associated with ARDS development (influenza A/B, bocavirus, and hMPV) were more common in older children.

In a study conducted in Türkiye, RSV, PIV and HRV, preschool HRV and multiple infections, and HRV in school age were the most common viral factors detected during the infant period.[28] In another study conducted in Türkiye again, RSV (42.8%), HRV (34.7%), and HBoV (10.0%) were detected in children less than 5 years of age with severe LRTIs.[29] ARDS developed in 28.6% of the patients hospitalized in the PICU with a diagnosis of viral LRTI, and it was the most common complication among the patients hospitalized with viral infection.[30] In our study, the ratio of ARDS development was 9.4% in PCR-positive patients hospitalized in PICU with LRTIs.

The main limitation of this study is its retrospective design. To minimize bias, a standard data form was developed for data collection, only patients with medical record information were included and the same clinician performed the entire data collection. Since the number of patients in each subgroup was very low, larger patient populations are needed to evaluate the differences in terms of ARDS rates and etiology. Also, after the pandemic, we were unable to test for coronavirus antibodies and antigens in our hospital, so there was no follow-up testing to rule out any possible coronavirus effects.

In a study conducted in Shanghai, in which 10 years of data were collected, viral pathogens that cause LRTIs in children were studied, and a very marked decrease in viral pathogens was detected during the quarantine period after the emergence of COVID-19. Following the COVID-19 pandemic, the incidence of viral pathogens decreased, likely due to mask wearing, improved hand hygiene, and compliance with social distancing rules.[31] However, as the COVID-19 pandemic precautions began to be eased in Australia, an RSV outbreak was seen in the summer months and the age of incidence was higher than in previous seasons. As we emerge from COVID-19-related lockdowns, it has been reported that respiratory viruses may show differences from the usual seasonality in coming years.[32] It must not be forgotten that as the COVID-19 pandemic comes to an end our struggle in PICUs will once again be with "conventional" agents of viral respiratory infections.

Conclusion

This study showed the etiology of respiratory viruses and risk factors for ARDS development in PICU patients with a diagnosis of LRTI before the COVID-19 pandemic. Respiratory tract viruses were a major etiological burden in patients hospitalized before the pandemic, and although RV was the most common viral agent in critically ill children, ARDS was more common in children aged over 1 year with influenza, HBoV or hMPV.

Conflict of Interest
None declared.

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