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Characteristics of Human Metapneumovirus-Related Acute Respiratory Infections in Children - A Four-Year Single Center Retrospective Study

Metapneumovirus Infection in Children

Keywords: metapneumovirus; children; respiratory; infections

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ABSTRACT

This study aimed to increase the data on characteristics and predictors of pediatric hMPV infection severity. Children admitted with ARI symptoms between 2021 and 2025 and diagnosed with hMPV by molecular testing were included. Seventy-eight children were included, of whom 48.7% were female. Most admissions occurred during winter and spring (92.3%). The median age was 14.9 months (IQR, 7.5–54.7), and 84.6% were younger than 5 years. At least one underlying comorbidity was present in 41% of patients, most commonly chronic lung disease. Major symptoms were cough (83.1%), rhinorrhea (61%), fever (59.2%), and stridor (41.6%), and tachypnea/dyspnea was observed in 31.2%. Median leukocyte count was 10,020/mm³ (IQR, 6,200–13,860), and median C-reactive protein level was 7.5 mg/dL (IQR, 1.1–26). Infiltration on chest radiographic (58.7%) were predominantly reticulonodular. About half of the patients (55.1%) required hospitalization; 21.8% needed respiratory support, and 6.4% were admitted to the pediatric intensive care unit. The need for respiratory support was significantly higher in children with comorbidities ($p = 0.025$), mortality was 2.6%. HMPV is a significant cause of ARIs in small children, particularly during winter and spring. Underlying comorbidities are associated with increased disease severity.

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INTRODUCTION

Human metapneumovirus (hMPV) is an RNA virus classified within the *Pneumoviridae* family, alongside respiratory syncytial virus (RSV). It was first identified in 2001 as a new virus causing respiratory infections in young children and the elderly (1). Two major genetic subgroups, A and B, and two classes within each of these subgroups (termed A1, A2, B1, and B2) were identified, which often circulate concurrently (2). It was demonstrated that hMPV infections exhibit a clear seasonal pattern. The study conducted by Castellana et al. reported that the timing of the epidemic was found to be compatible with geographical latitude; the peak occurred in June-September in the Southern Hemisphere and February-April in the Northern Hemisphere, while timing was variable in the intertropical zone (1,3,4).

Globally, hMPV represents a substantial burden of pediatric respiratory disease. It was estimated to cause approximately 14.2 million acute respiratory infections (ARIs) in children younger than five years of age worldwide in 2018 (5). Seroprevalence studies indicate that primary infection typically occurs early in life (1). Similarly, van den Hoogen et al. reported that 5 to 7% of ARIs in hospitalized children under five years of age worldwide were attributable to hMPV infection, and this contributed to 64.3 thousand hospitalizations and 7700 hMPV-related in-hospital deaths (1,5). During the COVID-19 pandemic, with increased use of moleculer testing, hMPV-related ARIs were identified more frequently in clinical practice, highlighting that these infections remain underrecognized.

The data describing the clinical spectrum of hMPV-related ARIs in children remains limited, particularly from middle-income countries. It most commonly causes mild upper respiratory tract infection; however, it can cause lower respiratory tract infections and severe fatal disease (6,7). Clinical manifestations in hospitalized patients vary from bronchiolitis or asthma exacerbations to severe pneumonia and, in some cases, acute respiratory distress syndrome (8-

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10). Proposed pathophysiological mechanisms involve airway obstruction resulting from excessive mucus production and hyperplasia of the respiratory epithelium.

Despite this general knowledge, information to guide risk stratification, clinical management, and identification of serious disease is still scarce. Additionally, regional data on hMPV epidemiology, seasonality, and consequences are limited in Türkiye. Therefore, this study was conducted to further define the clinical, laboratory, and radiological features of hMPV-related ARIs in children, support early diagnosis and clinical management, and identify factors associated with severe disease.

MATERIAL AND METHODS

Study design and clinical sample collection

This study employed a retrospective observational design and was conducted at Marmara University Pendik Training and Research Hospital in Istanbul. Children aged 1 month to 18 years, admitted with symptoms of ARIs between December 1, 2021, and November 30, 2025, and had hMPV detected in nasopharyngeal swab samples by reverse transcription quantitative polymerase chain reaction (RT-qPCR) were included in the study.

Acute respiratory infections were defined as the presence of recent respiratory symptoms such as rhinorrhea, nasal congestion, stridor, cough, dyspnea, and tachypnea; wheezing, rale, and rhonchi heard on auscultation; and the presence of infiltrates, atelectasis, hyperinflation, and effusion on chest imaging with/or without fever.

Molecular diagnosis of respiratory tract infections was performed as part of routine laboratory workflow using the Bio-Speedy Respiratory Tract RT-qPCR MX-24S Panel (Bioeksen R&D Technologies, Istanbul, Turkey). Nasopharyngeal swab samples were collected from the upper respiratory tract of patients. The collected samples were transported to the laboratory in vNAT sample transfer tubes (Bioeksen R&D Technologies, Istanbul, Turkey) containing 2 mL of fluid and processed according to the manufacturer's recommendations before analysis. For multiplex

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RT-qPCR analysis, 90 µL of patient sample from the vNAT tube was mixed with 90 µL of 2× Prime Master Mix in equal volumes to create a total reaction volume of 180 µL. Amplification was performed using the CFX96 Real-Time PCR System (Bio-Rad, USA) according to the manufacturer's recommended thermal cycling protocol. The respiratory tract pathogens qualitatively sought using this method are: Viral agents: SARS-CoV-2, Influenza A, Influenza B, Human Coronavirus 229E, Human Coronavirus OC43, Human Coronavirus NL63, Human Coronavirus HKU1, Human Parainfluenza virus 1–4, Human Metapneumovirus, Adenovirus, Human Bocavirus, Human Enterovirus, Human Rhinovirus, Human Parechovirus, and Respiratory Syncytial Virus (RSV A/B). Bacterial agents: *Streptococcus pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, Haemophilus influenzae, and Bordetella pertussis.*

Patients were divided into two groups according to the need for advanced respiratory support: those who did not require advanced respiratory support were classified into the mild ARIs group, whereas those who required high flow nasal cannula (HFNC), noninvasive ventilation (NIV), or invasive mechanical ventilation (IMV) were classified into the moderate-to-severe ARIs group. The two groups were compared in terms of demographic, clinical, laboratory, and radiological characteristics and clinical course, outcome to identify factors associated with disease severity.

This study was approved by the Ethics Committee for Non-Drug and Medical Device Research of the Marmara University Faculty of Medicine (July 18, 2025; 09.2025.25-0642).

In accordance with the decision of the institutional ethics committee, informed consent was not obtained due to the retrospective design of the study. All patient data was fully anonymized prior to analysis and data was processed in compliance with institutional and ethical regulations to ensure that no patient could be identified.

Statistical Analysis

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Statistical analyses were performed using IBM SPSS Statistics for MacOS, version 30.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages [n (%)], and comparisons between groups were performed using the Pearson chi-square test. Fisher's exact test was applied when more than 20% of the expected cell counts were less than 5 or when any expected cell count was less than 1. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables showing normal distribution were expressed as mean ± standard deviation. For comparisons between groups, the Student's t-test was used when the assumption of variance homogeneity was met, whereas the Welch t-test was applied when this assumption was violated. Continuous variables that did not follow a normal distribution were presented as median (interquartile range, IQR), and group comparisons were performed using the Mann–Whitney U test. To evaluate factors associated with the need for advanced respiratory support, univariate logistic regression analysis was performed. The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant.

RESULTS

During the four-year study period, between 2021 and 2025, a total of 78 children admitted with hMPV related ARIs were included in the study. Of these patients, 17 (21.8%) required advanced respiratory support, while 61 (78.2%) did not. Admissions occurred predominantly during the winter and spring seasons (92.3%) (Figure 1). No significant association was observed between season of admission and the severity of disease ($p = 0.56$).

The median age of the cohort was 14.9 months (interquartile range [IQR], 7.5-54.7 months). Children younger than five years of age constituted the majority of cases (84.6%). There was no statistically significant difference in age and sex distribution between mild to moderate-to-severe groups.

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The most common presenting symptoms were cough, rhinorrhea or nasal congestion, fever, and stridor (Table 1). On physical examination, tachypnea/dyspnea, rales, rhonchi, and wheezing were frequently observed**;** these physical signs were significantly more common among patients requiring advanced respiratory support compared with those who did not ($p<0.01$, $p=0.01$, $p=0.02$, $p=0.003$)

Underlying comorbidities were present in 32 patients (41%), including chronic lung disease, malignancy, metabolic disorders, chronic neurological diseases, and primary immunodeficiencies (Table 1). The need for advanced respiratory support was significantly higher among children with comorbidities compared with those without underlying diseases ($p=0.011$).

Laboratory evaluation revealed a median white blood cell count of 10,020/mm³ (IQR, 6,200–13,860), with neutrophil and lymphocyte counts within the normal range for age. Median C-reactive protein level was 7.6 mg/dL (IQR, 1.1–26). No significant differences were observed in laboratory parameters between the severity groups.

Chest radiography was performed in the 75 patients, and abnormal findings were detected in 58.7%, mainly reticulonodular infiltrates. The presence of infiltration on chest-X-ray was significantly higher in the moderate-to-severe group associated with the need for advanced respiratory support ($p=0.024$)**.**

Viral coinfection was detected in 29.5% of patients based on multiplex RT-qPCR analysis of nasal samples, while bacterial coinfection was identified in 17.9% of patients. However, no significant association was observed between coinfection and disease severity.

Forty-three patients (55.1%) were hospitalized. Of these, 23 patients did not require oxygen therapy; 3 required oxygen via face mask only, and 17 (21.8%) required advanced respiratory support. Five patients (6.4%) were admitted to the pediatric intensive care unit (PICU). The need for respiratory support was significantly higher in children with comorbidities ($p = 0.011$).

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The median length of hospital stay was 7 days (IQR, 5–11). Two patients (2.6%) died during hospitalization.

Univariate logistic regression analysis demonstrated that the presence of an underlying disease was significantly associated with the need for advanced respiratory support (OR:3.49, p=0.030). Radiologic infiltration showed a trend toward association; however, this did not reach statistical significance (OR:2.83, p=0.098). Immunodeficiency and age were not significantly associated with advanced respiratory support (Table 2).

DISCUSSION

In this study, clinical manifestations of hMPV related ARIs in children were evaluated to better define disease characteristics and identify predictors of severe disease.

Our findings demonstrate a seasonal pattern, with infection occurring predominantly during winter and spring months in Türkiye. This observation is consistent with previous studies reporting peak hMPV activity in late winter and early spring in the United States, the United Kingdom, the Netherlands, Finland, and Norway, while a different seasonal distribution, late spring and summer, has been reported in Hong Kong (1,3,4). Nevertheless, sporadic outbreaks outside the typical seasonal period have also been described, suggesting that hMPV circulation may vary depending on local epidemiological factors (11). Two major genetic subgroups, A and B, often circulate concurrently (2). There are conflicting reports regarding the association between hMPV genotype and disease severity, but genotyping was not performed in our study; therefore, we were unable to evaluate this relationship (12,13).

Human metapneumovirus-related ARIs predominantly affect young children, particularly those under five years of age. Primary infection usually occurs early in life, with many children infected during infancy (1,4,14,15). Global modeling studies estimate that hMPV accounts for approximately 14.2 million acute lower respiratory infections annually among children under five (5). Consistent with these data, the median age of patients in our cohort was 14.9 months,

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and 84.6% were younger than five years, underscoring the importance of hMPV as a respiratory pathogen in early childhood. A study comparing hMPV- and RSV-related ARIs in children reported mean ages of 16 and 10 months, respectively (16). However, due to the retrospective design of our study, the total number of ARI-related admissions during the study period could not be determined, limiting our ability to contextualize the burden of hMPV within the broader ARI population.

The most common symptoms in our patients were cough, rhinorrhea or nasal congestion, and fever, which is consistent with previous reports describing cough in 68%-90%, rhinitis in 44%-77%, fever in 52%-86%, and wheezing in 51%-56% of cases (4,14,15). However, in our cohort, wheezing was observed less frequently than expected; this may be attributable to the retrospective design of the study and potential underreporting in medical records. Previous studies have reported a higher prevalence of hMPV (8.9% versus 1.3%) among children younger than three years of age who were hospitalized for wheezing, compared with non-wheezing controls, but they also emphasized that hMPV plays a limited role in wheezing diseases among children older than three years of age (4). On the other hand, as expected, respiratory distress at admission and the presence of wheezing, rhonchi, and rales on examination were found to be associated with severe disease and the need for advanced respiratory support. Pathophysiologically, hMPV infection has been shown to cause excessive mucus production and respiratory epithelial hyperplasia, resulting in airway obstruction and enhanced airway hyperresponsiveness, which may contribute to disease severity (17). Veronese et al. reported that hearing wheezing on lung auscultation is an important determinant of severe hMPV lower respiratory tract infections and that the probability of experiencing hypoxemia is ten times higher (18). Despite these findings, no specific clinical features that reliably distinguish hMPV infection from other viral etiologies of bronchiolitis or pneumonia were found in this study.

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Laboratory findings in our patients were consistent with a typical viral infection pattern, with normal or mildly elevated leukocyte counts and low-to-moderate C-reactive protein levels. Similarly, chest radiographs most commonly demonstrated reticulonodular infiltrates, which are characteristic of viral pneumonia and may help differentiate hMPV infection from bacterial etiologies (19,20). Al-Hamoud et al. examined radiological images in immunocompromised adults with metapneumovirus infection; they found that the most frequent radiological patterns have findings compatible with bronchopneumonia, bronchiolitis, and bronchitis (84.2%) (21). Lobar pneumonia in hMPV infection is rare and has primarily been in isolated case reports (22). It was also observed in a small number of patients in our cohort.

Viral co-infection was identified in approximately one-third of our patients. Previous studies have reported co-infections with RSV, rhinovirus, and adenovirus, with some suggesting an association with more severe disease (23-27). Hassan Shah et al. conducted a review of the literature on hMPV coinfection and suggested that coinfections can synergistically contribute to severe inflammation, immune dysregulation, and clinical deterioration in high-risk groups, although the magnitude of this effect differs according to pathogen and host characteristics (28). However, consistent with other reports, we did not find a significant association between coinfection and disease severity (9, 22-31). These findings support the hypothesis that coinfecting viruses establishing dominance and suppressing the replication of subsequent viruses. Nevertheless, the relatively small sample size of our study may also account for the lack of a significant association.

Severe hMPV infection has been well documented in infants and the elderly (10,32). However, risk factors for severe disease are not yet fully defined. Congestive heart failure (25%), profound immunosuppression (20%), and severe chronic obstructive pulmonary disease (20%) have been identified as the leading risk factors (33). In contrast, in children, the impact of comorbidities such as chronic pulmonary disease, metabolic disorders, and chronic

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neurological diseases has been less clearly characterized. Prematurity has also been reported as a risk factor for hospitalization due to hMPV infection (34). A major finding of the present study is a significantly increased need for advanced respiratory support among children with underlying diseases. These results indicate that children with comorbid conditions are at higher risk for severe hMPV infection and therefore require close clinical monitoring. However, due to small number of patients in each category, individual underlying disease could not be analyzed separately.

Treatment remains supportive, as no specific antiviral agents or vaccines for hMPV are currently available. Intravenous antibiotics, corticosteroids, and inhaled bronchodilators were used more frequently in patients with severe disease. This likely reflects clinical attempts to manage disease severity and potential complications, rather than evidence-based treatment. At present, the development of vaccines and monoclonal antibodies targeting hMPV is ongoing. The findings of this study suggest that children with underlying chronic conditions may represent priority candidates for future vaccination or passive immunization strategies.

In this study, although only a small proportion of patients required PICU admission and overall mortality was low, fatal outcomes were observed. This is consistent with previous reports indicating that, while mortality rates associated with hMPV infection are generally low, the disease can be fatal, particularly in patients with immunodeficiencies (35). Likewise, Macroni et al. reported that, in addition to influenza viruses, *Pneumoviridae*, including RSV and hMPV, remain among the main viral pathogens associated with severe outcomes, especially acute respiratory failure and mortality (36). Together, these findings emphasize that hMPV should not be considered a benign pathogen.

This study has several limitations. The retrospective, single-center design and the relatively small sample size limit the generalizability of the findings. Additionally, incomplete clinical

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documentation and variability in treatment approaches may have affected the assessment of disease severity and outcomes.

In conclusion, hMPV is an important viral pathogen capable of causing severe respiratory infections, particularly in young children and those with underlying diseases. Awareness of risk factors and early recognition are essential for optimal clinical management and improved outcomes.

Conflicts of interest: None to declare.

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Figure Legends

Figure 1. Seasonal distrubution of human metapneumovirus acute respiratory tract infections in Children

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Table 1. Characteristics of children with human metapneumovirus–related acute respiratory infections in mild and moderate-to-severe groups

Variables (unit)		Mild (n=61)	Moderate-Severe (n=17)	p-value
		[*n* (%)] or Median (IQR)	[*n* (%)] or Median (IQR)	
Age (months)	14.4 (7.3-60)	14.9 (7.3-54.7)	22.4 (8.4-53.8)	0.861
Sex				0.482
Male	40 (51.3)	30 (49.2)	10 (58.8)	
Female	38 (48.7)	31 (50.8)	7 (41.2)	
Symptoms				
Duration of symptoms before admission (day)	2 (1-4)	3 (1-4)	2 (1-3)	0.051
Fever	45 (59.2)	32 (54.2)	13 (76.5)	0.100
Duration of fever (day)	2.7±1.8	3±1.9	2.2±1.7	0.186
Cough	64 (83.1)	48 (80.0)	16 (94.1)	0.276
Rhinorrhea/nasal congestion	47 (61)	40 (66.7)	7 (41.2)	0.057
Stridor	32 (41.6)	22 (36.7)	10 (58.8)	0.102
Vomiting	12 (15.6)	8 (13.3)	4 (23.5)	0.447
Diarrhea	9 (11.7)	7 (11.7)	2 (11.8)	1.000
Convulsion	5 (6.5)	3 (5)	2 (11.8)	0.304
Underlying disease	32 (41)	**21 (34.4)**	**11 (64.7)**	**0.025**
Primary immune deficiency	3 (9.4)	1 (4.8)	2 (18.2)	0.541
Chronic lung disease/asthma	11 (34.4)	8 (38.1)	3 (27.3)	
Malnutrition	1 (3.1)	1 (4.8)	0 (0)	
Prematurity history	2 (6.3)	1 (4.8)	1 (9.1)	
Malignancy/chemotherapy	5 (15.6)	4 (19)	1 (9.1)	
Metabolic disorder	4 (12.5)	3 (14.3)	1 (9.1)	
Chronic neurological disease	4 (12.5)	1 (4.8)	3 (27.3)	
Chronic renal disease	1 (3.1)	1 (4.8)	0 (0)	
Chronic liver disease	1 (3.1)	1 (4.8)	0 (0)	
Physical examination				
Alteration of consciousness	3 (3.9)	1 (1.7)	2 (11.8)	0.121
Dyspnea /tachypnea	24 (31.2)	11 (18.3)	13 (76.5)	**<0.001**
Stridor	5 (6.6)	1 (1.7)	4 (23.5)	**0.008**
Wheezing	8 (10.4)	2 (3.3)	6 (35.3)	**0.001**
Rhonchus	18 (23.4)	9 (15)	9 (52.9)	**0.003**
Rale	24 (31.2)	13 (21.7)	11 (64.7)	**<0.001**
Laboratory				
WBC (/μL)	10,020 (6,200-13,860)	10,100 (6,200-14,000)	8,300 (7,500-13,860)	0.775

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Neutrophil (/μL)	5,079±3,922	4,842±3,714	5,762±4,520	0.409
Lymphocyte (/μL)	4,022±2,813	4,026±2,671	4,009±3,277	0.983
Hg (g/dL)	11 (10.4-12.1)	10.9 (10.4-11.9)	11.5 (10.5-12.4)	0.355
PLT (/μL)	309,666±122,678	315,061±122,435	294,117±125,790	0.548
AST (U/L)	35 (28-57)	35 (28-59.5)	37 (26-48)	0.649
ALT (U/L)	19 (12-35.5)	19 (13-38.2)	15 (9-31)	0.151
LDH (U/L)	300 (260-391)	316 (279-361)	265 (204.5-424)	0.081
CRP mg/L	7.6 (1.1-26)	7.1 (1.1-20)	18 (3.4-26.4)	0.233
Radiological findings (Chest X-ray)	44 (58.7)	31 (53.4)	13 (76.5)	0.090
Reticulonodular infiltration	41 (93.2)	29 (93.5)	12 (92.3)	1.000
Lobar infiltration	3 (6.8)	2 (6.5)	1 (7.7)	
m-PCR				
Patients with co-detected viruses (n)	23 (29.5)	20 (32.8)	3 (17.6)	0.226
Adenovirus	8 (32)	7 (31.8)	1 (33.3)	0.611
Bocavirus	7 (28)	5 (22.7)	2 (66.7)	
Rhinovirus	5 (20)	5 (22.7)	0 (0)	
Influenza	3 (12)	3 (13.6)	0 (0)	
RSV	1 (4)	1 (4.5)	0 (0)	
Parainfluenza	1 (4)	1 (4.5)	0 (0)	
Patients with co-detected bacteria (n)	14 (17.9)	11 (18)	3 (17.6)	0.64
S. pneumoniae	5 (6.4)	3 (4.9)	2 (11.8)	0.454
H. influenzae	4 (5.1)	3 (4.9)	1(5.9)	
S. pneumoniae+ H. influenzae	5 (6.4)	5 (8.2)	0	
Treatment				
Antibiotic treatment	52 (68.4)	38 (64.4)	14 (82.4)	0.161
Oral	13 (25)	**13 (34.2)**	**0 (0)**	**0.011**
Intravenous	39 (75)	**25 (65.8)**	**14 (100)**	
Bronchodilator	36 (47.4)	**21 (35.6)**	**15 (88.2)**	**<0.001**
Steroid (inhaler/intravenous)	15 (19.7)	**8 (13.6)**	**7 (41.2)**	**0.033**
Respiratory support (day)	6 (3.5-10)	-	6 (3.5-10)	-
Hospitalization	43 (55.1)	**26 (42.6)**	**17 (100)**	**<0.001**
PICU admission (n)	5 (6.4)	**1 (1.6)**	**4 (23.5)**	**0.007**
Hospitalization time in PICU (day)	3 (0-26)	10.5 (0-21)	3 (2-26)	0.571
Total hospitalization time (day)	7 (5-11)	7 (3-11)	8 (6-14)	0.124
Complications	33 (42.3)	**21 (34.4)**	**12 (70.6)**	**0.010**
Pneumonia	27 (81.8)	16 (76.2)	11 (91.7)	0.123
Pneumothorax	1 (3.0)	0 (0)	1 (8.3)	
Bronchitis	4 (12.1)	4 (19.1)	0 (0)	
Bacteriemia	1 (3.0)	1(4.8)	0 (0)	
Mortality	2 (2.6)	**0 (0)**	**2 (11.8)**	**<0.01**

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Categorical variables were presented as number and percentage [n (%)], continous variables with normal distribution were expressed as mean ± standard deviation, whereas continous variables without the a normal distrubution were reported as median (interquartile range, IQR).

WBC: White blood cell, Hg: Hemoglobin, PLT: Platelet, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Laktat dehidrogenaz, CRP: C-reactive protein, m-PCR: Multiplex polymerase chain reaction, RSV: respiratory syncytial virus, URI: Upper respiratory infection, LRI: Lower respiratory infection, PICU: Pediatric intensive care unit

Table 2. Clinical Characteristics Associated with Advanced Respiratory Support in Children with hMPV Infection

Variables	OR (%95 CI)	p-value
Age	0.999 (0.987-1.012)	0.886
Underlying disease	**3.492 (1.132-10.770)**	**0.030**
Immunodeficiency	4.444 (0.355-55.575)	0.247
Radiologic infiltration	2.831 (0.824-9.720)	0.098

Univariate logistic regression analysis demonstrated that the presence of an underlying disease was significantly associated with the need for advanced respiratory support (OR:3.49, p=0.030). Radiologic infiltration showed a trend toward association; however, this did not reach statistical significance (OR:2.83, p=0.098). Immunodeficiency and age were not significantly associated with advanced respiratory support.

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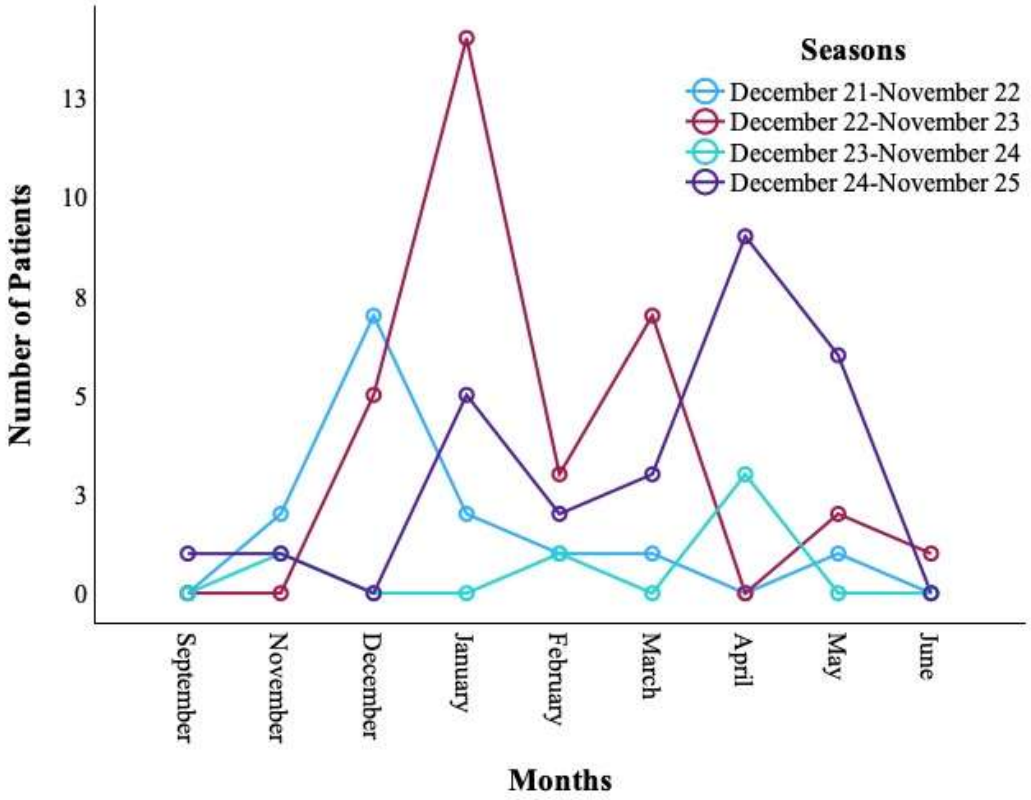

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