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Incidence and Clinical Profile of Respiratory Syncytial Virus Infection in Infants Admitted with Diagnosis of Lower Respiratory Tract Infection

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What is known on this subject?

Respiratory syncytial virus (RSV) infection exhibits a higher prevalence among males, and a notable association was identified between RSV infection and patients younger than 6 months. Seasonal variations in RSV incidence were evident, with peak infections observed in December, January, and March. Statistically, a negative association was found between the duration of breastfeeding and RSV infection. RSV positivity was significantly correlated with meteorological parameters such as temperature and relative humidity. A significant association was noted between clinically diagnosed otitis media and chest retraction due to RSV infection.

What this study adds?

The study highlights that the age of patients younger than 6 months, breastfeeding practices, and environmental factors such as air temperature and humidity appear to have a significant impact on the development of RSV infection.

ABSTRACT

Objective: Lower respiratory tract infections of predominantly viral origin disproportionately affect infants and children, and respiratory syncytial virus (RSV) is a primary pathogen in this age group. This study employed rapid testing methodologies to detect RSV infection among hospitalized pediatric patients, providing insights into its prevalence, epidemiological, and clinical characteristics, and impact on mortality and morbidity.

Material and Methods: This study, conducted between September 1, 2009 and April 30, 2011, targeted infants aged 0-24 months who were hospitalized with lower respiratory infections at the Pediatric Clinic of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Hospital. Upon admission, each patient underwent a comprehensive medical history evaluation, which included assessments for prematurity, congenital heart disease, recurrent infectious diseases, reactive respiratory system disease, and immune system disorders. Additionally, physical examination, routine tests, and nasopharyngeal swab samples were collected. RSV detection was performed using the Respi-Strip kit.

Results: Among the 311 patients included in the study, 182 (58%) were male, and RSV was detected in 110 (35%) patients. Of those who tested positive for RSV, 72 (65%) were male. A significant prevalence of RSV infection was observed among patients aged 6 months. The incidence of RSV was notably higher in December, January, and March. A statistically significant negative correlation was found between the duration of breastfeeding and the likelihood of RSV infection. RSV positivity was significantly associated

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ABSTRACT

with temperatures below 10 °C and relative humidity levels exceeding 60%. Additionally, a significant association was noted between RSV infection, the presence of clinically diagnosed otitis media, and chest retraction.

Conclusion: Regular screening for RSV is essential for early diagnosis, enabling targeted therapy, and improving patient outcomes. This proactive strategy may reduce morbidity, mortality, and economic impacts. Further epidemiological and clinical research on RSV transmission is crucial for protecting populations at risk, enhancing disease prevention measures, optimizing isolation protocols, and developing novel treatment options.

Keywords: Lower respiratory tract infection, infant period, respiratory syncytial virus

Introduction

According to the World Health Organization's 2020 data, lower respiratory infections (LRIs) are the fourth leading cause of death globally and a major contributor to child mortality among infectious diseases. It is estimated that one in seven deaths in children under the age of 5 is attributed to LRIs (1,2).

The predominant cause of LRIs are viruses, with infants and young children particularly being susceptible. Key viral pathogens responsible for lower respiratory tract infections in the pediatric population include respiratory syncytial virus (RSV), human rhinovirus, human metapneumovirus, parainfluenza viruses, influenza A-B and adenoviruses (3). According to 2022 data from the Turkish Statistical Institute, LRIs accounted for 8.2% of deaths in children aged 1-4 years in Turkey. The Turkey Burden of Disease Study reported that respiratory infections were the second cause of death in the 0-4 age group, representing 13.4% and 6.5% in the 5-14 age group. These infections account for 14% of all deaths in the 0-14 age group (4,5). This data highlights that LRIs pose a significant public health concern in children under 2 years old in the country.

RSV is a common cause of bronchiolitis and pneumonia during infancy. Although RSV typically causes flu-like symptoms in adults, it can cause severe lower respiratory tract infections in approximately 40% of infected infants and young children within 2 to 5 days. Approximately 50-70% of infants are infected with RSV in the first year and 95% by the age of 2 despite the presence of serum antibodies. Re-infections with RSV can occur even with existing antibodies in subsequent years. Primary RSV infection can have a severe course in infants aged 2 months with high levels of maternal antibodies. Severe primary RSV infections are particularly problematic in infants aged 2 months with high maternal antibody levels and in those with chronic lung or congenital heart disease, leading to frequent severe respiratory infections and increased mortality. Rapid and accurate diagnosis of the viruses responsible for LRI is critical for initiating timely and appropriate treatment, avoiding unnecessary antibiotic use, implementing appropriate isolation measures, and preventing hospital-acquired infections caused by these viruses. Methods such as viral isolation via cell culture and serological assays are expensive and may take weeks to yield results from the onset of viral infection. To facilitate an early diagnosis, tests such as electron microscopy, enzyme immunoassay, radioimmunoassay, and latex agglutination have been developed. Additionally, using nasopharyngeal swab samples, the RSV Respi-Strip kit, which employs the strip method with monoclonal antibodies to determine the RSV F protein, enables rapid bedside diagnosis (6,7).

The aim of this study was to determine the role of RSV as a causative agent of lower respiratory tract infections in children aged 0-24 months. The study was conducted on patients admitted to the Pediatric Clinic of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital within the specified age range.

In particular, during winter months, a significant proportion of children admitted to our clinic present with LRIs. The purpose of this study was to detect RSV infection using a rapid testing method among children aged 0-24 months admitted to our hospital due to LRI. The objectives of this study were to determine the prevalence of RSV infection, analyze its epidemiological and clinical characteristics, and evaluate its impact on mortality and morbidity.

Material and Methods

This study was conducted from September 1, 2009, to April 30, 2011, and included patients aged 0-24 months who presented to the General Pediatric Outpatient Clinic and Pediatric Emergency Department of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital with a diagnosis of LRI and were deemed suitable for hospitalization. Only patients who could not be managed on an outpatient basis and were eligible for admission to the pediatric clinic were selected for the study. Prior to inclusion, parents were notified about the study, and informed consent was obtained before the inclusion of any children. The

study protocol was approved by the Ethics Committee of the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital (no: 78113307/1005/168, decision no: 7, date: 23.09.2009). Upon admission, patients' medical histories, physical examinations, and diagnostic tests, such as chest X-ray, complete blood count, biochemistry, blood gas analysis, and C-reactive protein levels, were evaluated. Comprehensive data were recorded, including patient age, sex, admission month, admission season, parental educational level, family income level, maternal age, family smoking habits, exposure to air pollution, number of rooms in the household, household size, birth order, duration of hospitalization, history of previous infections, gestational age by weeks, mode of delivery, and duration of breastfeeding.

The clinical findings at admission included fever, cough, runny nose, tachypnea, dyspnea, stridor, wheezing, apnea, acute otitis media (AOM), chest retraction, and pulse oximetry values.

Patients included in the study underwent routine tests upon admission, which included the collection of nasopharyngeal swab samples. The collection procedure involved positioning the patient's neck appropriately and using a sterile cotton swab to obtain the sample. The samples were tested with the Abbott RSV Respi-Strip (Rapid Diagnostic Test for Syncytial Virus Detection in nasopharyngeal Specimens, Gembloux-Belgium). The procedure involved placing the swabs in tubes containing approximately 0.5 cc of test matrix, transferring them into a liquid medium, and inserting a strip into the prepared sample. After a 15 min incubation period, the results were interpreted. The appearance of a double red line in the indicator carrying monoclonal antibodies against the fusion (F) protein of RSV was considered positive, whereas a single red line was considered negative. The absence of a line was considered an invalid sample. The entire evaluation process (from sample collection to interpretation) took approximately 20 minutes.

On the same day that RSV nasopharyngeal swabs were collected, meteorological data on temperature, humidity, and atmospheric pressure were obtained from daily records of the General Directorate of Meteorology.

Data regarding supportive respiratory care interventions administered to patients included the use of bronchodilators, duration and types of use, oxygen inhalation (duration and dosage),and antibiotic use.

For patients requiring intensive care, information was documented on the use of mechanical ventilators, duration of intensive care admission, and clinical course of the patients during the intensive care monitoring period.

Statistical Analysis

Statistical analysis of the study data was performed using the SPSS (Statistical Package for the Social Sciences) for Windows. Descriptive statistical methods, including mean, standard deviation, and frequency distributions, were employed to evaluate the study data. To compare quantitative variables between groups, the Student's t-test was used for normally distributed data, whereas the Mann-Whitney U test was applied for non-normally distributed data. For the comparison of qualitative data, the Pearson chi-squared test and Fisher's exact test were used. Statistical significance was determined at a threshold of $p<0.05$, with a confidence interval of 95%.

Results

Between September 1, 2009, and April 30, 2011, a total of 311 patients aged 0-24 months who presented with LRIs at the Pediatric Clinic of University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital were included in the study. Patients who were deemed suitable for hospitalization after failure of outpatient treatment provided informed consent prior to participation.

Of 1.809 patients admitted to the 1st pediatric clinic during the study period, 311 (17.2%) were enrolled in this study. The cohort comprised 129 (41.5%) women and 182 (58.5%) men. RSV was detected in 110 (35.4%) patients, whereas 201 (64.6%) tested negative for RSV. Among the RSV-positive patients in our study, 72 (65.5%) were male, and 38 (34.5%) were female, resulting in a male-to-female ratio of 1.89 (Figure 1).

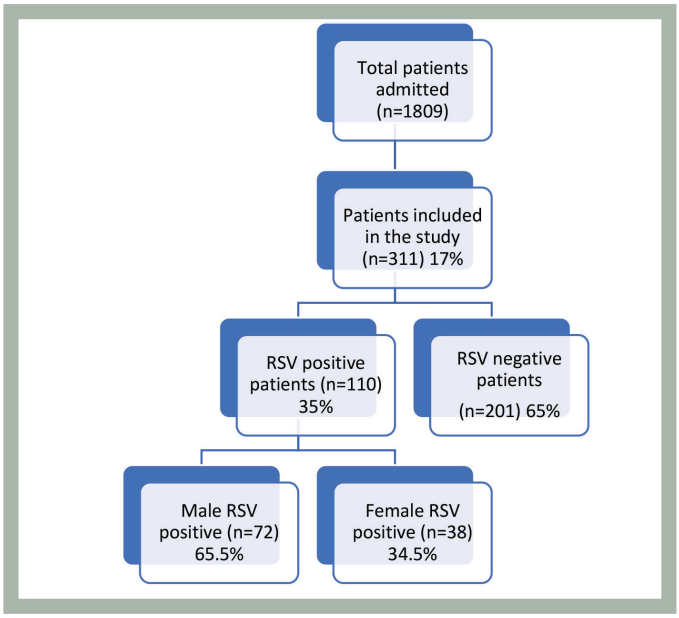

Figure 1. General characteristics of patients
RSV: Respiratory syncytial virus

Patients were categorized by age into the following groups 0-1 months, 1-6 months, 6-12 months and 12-24 months. RSV positivity was significantly higher in patients aged 6 months (p=0.01), with a mean age of this group was 5.8±5.2 months in this group. The mean ages were 3.5±3.2 months for RSV (+) patients and 6.8±5.6 months for RSV (-) patients (Table 1). The median length of hospitalization was similar between RSV-positive and -negative patients at 7 days. Seasonal analysis of RSV-positive cases among the 110 patients identified as RSV-positive revealed that 64 (58%) were admitted during winter months (December, January, February), 36 (33%) during spring months (March, April, May), and 10 (9%) during autumn months (September, October, November). The incidence of RSV was significantly higher in December, January, and March (Table 2). Breastfeeding duration was classified as 3 months, 4-6 months, 7-9 months, 10-12 months, and >12 months. It was observed that 76 (69%) of the patients with RSV infection had been breastfed for less than 3 months, and none of the 5 patients who had been breastfed for more than 12 months had RSV infection (Table 3). Analysis of meteorological data indicated a significant relationship between RSV infection rates and temperatures below 10 °C as well as relative humidity levels above 60% (Table 4). Clinical findings at admission showed that patients with chest retraction and AOM had a significantly higher incidence of RSV infection. The severity of

Table 1. Demographic characteristics and risk factors of children with RSV-positive and RSV-negative LRTI

Variables	RSV (-) (n=201)	RSV(+) (n=110)
Male	110 (61%)	72 (65%)
Female	91 (39%)	38 (35%)
Age (months)	6.8±5.6	3.5±3.2
Age groups		
0-1 months	13 (6%)	22 (20%)
>1-6 months	117 (58%)	70 (64%)
>6-12 months	46 (23%)	16 (14%)
>12-24 months	26 (13%)	2 (2%)
Birth characteristics		
Preterm	28	14
Term	173	96
Delivery method		
Spontaneous vaginal	96	59
Cesarean section	105	51
Socio-economic status		
Low	63 (31%)	54 (49%)
Middle	125 (62%)	51 (47%)
High	13 (6%)	5 (4%)
Smoking exposure		
Yes	107 (53%)	64 (58%)
No	94 (47%)	46 (42%)
Maternal education		
No education	56 (28%)	29 (27%)
Primary education	131 (65%)	71 (64%)
High school and university courses	14 (7%)	10 (9%)
Paternal education		
No education	12 (6%)	5 (4%)
Primary education	120 (60%)	62 (56%)
High school and university courses	69 (34%)	43 (40%)

RSV: Respiratory syncytial virus, LRTI: Lower respiratory tract infection

Table 2. Significant associations between RSV infection and months

Conditions	n	p value
Months		
December	28 (25%)	**0.001**
January	24 (22%)	**0.001**
March	20 (18%)	**0.001**
Seasons		
December, January, and February	64 (58%)	
March-May	36 (33%)	
September-November	10 (9%)	

RSV: Respiratory syncytial virus

Table 3. Relationship between breastfeeding and RSV infection

Condition	n	p value
Breastfeeding for 3 months (positive correlation with RSV infection)	76 (69%)	**0.016**
Breastfeeding 4-6 months	20	
Breastfeeding 7-9 months	10	
Breastfeeding 10-12 months	4	
Breastfeeding for more than 12 months	0	
Breastfeeding >12 months (no RSV infection in any of them)	5 (4.5%)	**0.016**

RSV: Respiratory syncytial virus

Table 4. RSV infection and meteorological conditions

Conditions	p value
Temperature below 10 °C	**0.019**
Humidity ≥60%	**0.013**
Air pressure	0.717

RSV: Respiratory syncytial virus

Table 5. Significant associations between RSV infection and patient age and clinic experience

Conditions	p value
<6 months of age	**0.001**
Otitis media	**0.023**
Chest retraction detection	**0.030**
Worsening in the LRI clinic	**0.008**

RSV: Respiratory syncytial virus, LRI: Lower respiratory infection

LRI symptoms was classified as mild, moderate, and severe , with RSV-positive patients exhibiting more severe symptoms (Table 5).

No significant findings were observed in the other statistical evaluations (Table 6).

Discussion

LRIs are primarily caused by bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, as well as viruses such as influenza and RSV. Globally, LRIs are the leading cause of death, accounting for over 2 million deaths annually. They are particularly deadly for children under 5 years old, with approximately 0.67 million deaths recorded in this age group worldwide in 2019 (8).

Acute viral pneumonia is a recurring problem throughout childhood. Although RSV becomes less prominent as an etiologic agent after the first year , it still plays a causative role in approximately 40%-75% of hospitalized cases of bronchiolitis, 15%-40% of childhood pneumonia, and 6%-15% of croup. Bronchiolitis and pneumonia caused by RSV are more common in males than in females, with a ratio of approximately 1.5:1. In the United States, additional risk factors include having one or more siblings in the home, being of white race, residing in rural areas, maternal smoking, and maternal education < of less than 12 years. Medical factors in infants associated with the highest risk are prematurity chronic lung disease, congenital heart disease, immunodeficiency, and prematurity itself. However, approximately 80% of children under 2 years hospitalized for RSV infection do not have easily identifiable risk factors (9).

The prevalence of RSV infection, its rapid transmissibility, and potential to cause severe clinical manifestations in high-risk cases have been the subjects of numerous studies. For instance, Hacımustafaoğlu et al. (10), reported the rate of RSV in patients under 2 years of age admitted to the hospital due to LRI as 37.9%. Similarly, study conducted by Tayachew et al. (11) in Ethiopia between 2021-2022 , found that among 1.174 children under 2 years of age with diagnosis of LRI,

Table 6. Conditions not significantly associated with RSV infection

Conditions	p value
Maternal age	0.559
Method of birth	0.090
Birth order	0.598
Presence of sick siblings	0.657
Daycare attendance	0.442
Smoking in the family	0.644
Exposure to environmental smoke	0.499
Number of family members	0.995
Number of rooms in the house	0.136
Parental education level	0.315
Family income	0.103
Pulse oxygen saturation	0.210
Fever	0.855
Cough	0.510
Runny nose	0.705
Tachypnea	0.294
Nasal flaring	0.649
Stridor	0.115
Apnea	0.889
Shortness of breath	0.285
Bronchodilator use	0.405
Duration of bronchodilator use	0.202
The type of bronchodilator used	0.933
Oxygen intake times	0.520
Need for mechanical ventilation	0.420
Length of hospital stay	0.078
Need for intensive care	0.854
Length of stay in intensive care	0.469
Infiltration before and after lung X-rays	0.584
Exacerbations of LRI	0.232
Liver function impairment	0.057
Kidney function impairment	0.672
Blood gas analysis	0.382
Leukocytosis	0.059
Lymphocytosis	0.057
Anemia	0.157
Elevated CRP levels	0.605
Thrombocytopenia	0.231

LRI: Lower respiratory infection, CRP: C-reactive protein

278 (23.7%) tested positive for RSV. In the study of Di Carlo et al. (12) between November 2005 and May 2006, among 645 children under 2 years of age admitted to the hospital with LRI diagnosis, 335 were considered to have a viral disease, among these 178 (27.6% of all patients) were identified as RSV positive in the tests. Hatipoğlu et al. (13) found that, out of 80 patients under 2 years of age admitted to the hospital, 28 (35%) were identified as RSV positive. Pale et al. (14) detected RSV infection rate as 26.7% (113/424) of the participants with LRI in Mozambique. In our study, we focused on 311 patients aged 0-24 months diagnosed with LRI and admitted to the hospital and determined the frequency of RSV as 35.4%. Our findings are consistent with those of the existing literature. We also obtained results similar to those from studies conducted in our country.

A notable correlation exists between RSV hospitalizations and patient age, with younger patients experiencing higher hospitalization rates. Stein et al. (15) conducted a systematic literature review and meta-analysis involving 34 studies from 26 countries. The current study indicated that RSV infections are particularly severe in patients aged 1 year and those with a history of premature birth. According to the same study, the hospitalization rate for RSV patients in the under 5 years category was 4.37%, for those 1 year of age 19.19%, for those under 6 months 20.01%, and for premature infants under 1 year, it was 63.85% (15). According to our study, the mean age was 3.6±3.2 months for RSV (+) LRI and 6.8±5.6 months for RSV (-) LRI group (p=0.002). RSV positivity was significantly higher in patients aged 6 months (p=0.01).

RSV, a major cause of infant hospitalization. RSV is an enveloped negative-stranded RNA virus that has recently been reclassified in the Pneumoviridae family. Infection of respiratory cells occurs when two major surface glycoproteins (G and F) get into contact with the cell receptor CX3CR1 and mediate entry by F, respectively. Viral mRNA transcription, genomic RNA synthesis, and nucleocapsid formation occur in large cytoplasmic inclusion bodies to avoid recognition by the host innate immune response. Most progeny virions remain attached to the infected cell surface; and the F of infected cells with adjacent cells results in the formation of large multinucleated syncytes that eventually undergo apoptosis. Desquamated epithelial cells can form plugs, which, when combined with mucus and fibrin, may lead to obstructions in the lower airways (16). Severe RSV infections during infancy also increase the risk of asthma in children, which continues into adolescence (17). We noted more severe clinical symptoms in children with RSV, particularly an increased incidence of chest retractions, consistent with the literature.

Numerous studies have observed a positive correlation between RSV infection and male gender. Bourdeau et al. (18) found that of the 11,014 RSV-related hospitalized patients, 54.8% (5.488) were male. Biggs et al. (19), of the 1.129 RSV-positive cases, 665 (59%) were male. Our study is consistent with the literature, identifying 72 (65%) of the 110 RSV-positive cases as male.

RSV infections often present with both upper and lower respiratory symptoms, including coryza, fever, pharyngitis, and otitis media (AOM) (9). AOM is a known complication of RSV infection affecting as many as 50% of children under 5 years old with RSV. The incidence of RSV-associated AOM is significantly higher in children under 2 years of age than in older children. Sagai et al. (20) examined 230 children diagnosed with RSV infection using enzyme immunoassay. Among these children, 120 (52.2%) developed AOM. RSV antigen was detected in the middle ear fluid of 36 out of 52 patients with AOM (69.2%). Additionally, this study identified a significantly higher incidence rate of AOM amongst children under 2 years of age (73.1%) than among older children (29.7%) (20). In our study, we observed an increased frequency of otitis media in cases with RSV infection (p=0.023), consistent with the literature.

Globally, RSV follows a seasonal pattern. In temperate climates, RSV circulates throughout the winter season and peaks between December and January. In tropical regions, RSV outbreaks still occur during hot, humid, and rainy days in the summer season (21). In their study, Miyama et al. (22) described the RSV outbreaks in Japan between the years 2012 and 2019 and identified that during the 2012-2016 seasons, epidemic clusters were detected between September and December, whereas during 2017-2019, they were between July and October seasons. Constantopoulos et al. (23) found increased RSV infection in November, peaking in February. These cases decreased gradually until May in Greece. Rossi et al. (24) concluded that the frequency of RSV infection increased in February and March in Italy. In our study, we found that 58.2% of RSV-positive cases were observed in the winter months (December, January, February), 32.7% in the spring months (March, April, May), and 9.1% in the fall months (September, October, November). We identified that outbreaks peaked in December, January, and March. Our research yielded results similar to those reported in the literature. Some studies have described the epidemiological changes in RSV outbreaks following the coronavirus disease-2019 (COVID-19) pandemic. Ren et al. (25) demonstrated that, in 2020-2021, the RSV positivity rate in children hospitalized with LRI remained high, in all groups of patients <5 years

as compared to patients from 2018-2019 in central China. In contrast, Stamm et al. (26) described a parallel decline in RSV incidence in Germany in 2020. Mondal et al. (27) described that RSV activity had significantly declined since the pandemic outbreak and remained low until October 2021 in the USA. These studies indicated that the decrease in RSV frequency during the COVID-19 pandemic was influenced by isolation and contact restriction measures. Ren et al. (25) noted an increase in RSV cases, which was attributed to the virus's high resilience in external environments and ease of transmission. Although the frequency and outbreaks of RSV showed variance during and after the COVID-19 pandemic, a study conducted by Çağlar et al. (28) in our country covering the period from April 2018 to March 2023 demonstrated that RSV infection returned to its usual seasonality, beginning in the fall, peaking in winter, and ending in spring. There is a need for studies in our country to analyze the epidemiological changes in RSV following the COVID-19 pandemic.

The mechanism by which breastfeeding reduces the risk of infection is not entirely clear although the immunomodulatory content is known. In the early months of life, it is believed to be effective against respiratory infections through both mucosal and systemic protective mechanisms (29). In the systematic review by Mineva et al. (30), we found that non-breast feeding practices pose a significant risk of severe RSV-associated acute LRI and hospitalization. Exclusive breastfeeding for more than 4-6 months significantly reduced the rates of hospitalization, length of hospital stay, demand for supplemental oxygen, and admission to intensive care units (ICU) (30). In our study, we similarly observed a significant inverse correlation between the duration of breastfeeding and the incidence of RSV infection. This indicates that longer breastfeeding durations are associated with lower frequencies of RSV infection.

Numerous studies have been conducted to determine the relationship between RSV infection and meteorological conditions. Linssen et al. (31) conducted a 13-year study on pediatric intensive care unit (PICU) admissions for RSV bronchiolitis in the Netherlands. They identified maximum temperature and global radiation as weather variables with the strongest predictive effect on RSV-related PICU admission burden. Decreases in temperature and global radiation are directly proportional to RSV infection rates. Additionally, increases in relative humidity and cloud coverage contribute to higher infection rates (31). Wagatsuma et al. (32) demonstrated that low mean temperature and high relative humidity are positively correlated with RSV infection in Japan. In the data we obtained, we found a significant relationship between RSV infection and meteorological conditions. We observed a significant increase in RSV infections when air temperatures were below 10 °C. Additionally, relative humidity levels of 60% or higher were found to be a significant facilitating factor for the occurrence of RSV infection.

Conclusion

Based on the results of our study, proper isolation, prevention of infection spread, patient monitoring, and appropriate treatment planning can be more accurately implemented when RSV is detected in nasopharyngeal swab samples from patients. Among infectious diseases, respiratory tract infections rank first among serious problems, especially in developing countries. Periodic screening and detection of the causative microorganism in cases of lower respiratory tract infections will significantly reduce morbidity, mortality, and financial burden through patient isolation, implementation of appropriate treatment regimens, and follow-up. Societal risk can be reduced through socio-economic support and education programs for families with patient cases. Considering the transmission periods and clinical features of RSV infection identified in our study, more comprehensive research should prioritize preventive medicine practices for individuals at risk for RSV, followed by the identification of the causative agent, isolation, and use of newly developed treatment methods, to yield beneficial results in controlling the disease.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Training and Research Hospital (no: 78113307/1005/168, decision no: 7, date: 23.09.2009).

Informed Consent: Parents were informed of the study and provided informed consent before inclusion of any cases.

Authorship Contributions

Surgical and Medical Practices: P.A., Y.A., T.A., Concept: P.A., Y.A., T.A., Design: P.A., Y.A., H.Ç., Data Collection or Processing: P.A., H.Ç., Analysis or Interpretation: P.A., Y.A., T.A., Literature Search: P.A., T.A., H.Ç., Writing: P.A.

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