flora

RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2025;30(1):31-41 • doi: 10.5578/flora.2025011232

# Clinical Course of SARS-CoV-2, Influenza Virus and RSV Infections in Children During the Pandemic: Can ILI and SARI Definitions Predict Clinical Diagnosis?

## Pandemi Sürecinde Çocuklarda SARS-CoV-2, İnfluenza Virüs ve RSV İnfeksiyonlarının Klinik Seyri: ILI ve SARI Tanımları Klinik Tanıyı Öngörebilir mi?

Tuba KURUOĞLU[1](İD), Derya BAYIRLI TURAN[2](İD), Emine Hafize ERDENİZ[3](İD), Demet GÜR VURAL[4](İD), Ahmet Cenkay ORBAY[5](İD)

[1] Department of Infectious Diseases and Clinical Microbiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye
[2] Department of Infectious Diseases and Clinical Microbiology, Yeni Yüzyıl University Faculty of Medicine, İstanbul, Türkiye
[3] Department of Pediatric Infectious Diseases, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye
[4] Department of Medical Microbiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye
[5] Department of Biotechnology, Yeditepe University Institute of Natural & Applied Sciences, İstanbul, Türkiye

***Cite this article as:*** *Kuruoğlu T, Bayırlı Turan D, Erdeniz EH, Gür Vural D, Orbay AC. Clinical course of SARS-CoV-2, influenza virus and RSV infections in children during the pandemic: Can ILI and SARI definitions predict clinical diagnosis? FLORA 2025;30(1):31-41.*

### ABSTRACT

***Introduction:*** *In this study, we aimed to evaluate cases of respiratory tract infections caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), respiratory syncytial virus (RSV), and influenza viruses in children aged 2-5 years during the pandemic, and to assess the compatibility of these cases with the definitions of influenza-like illness (ILI) and severe acute respiratory infections (SARI).*

***Materials and Methods:*** *A total of 87 patients under the age of five, presented to pediatric outpatient clinics with respiratory tract infection complaints between December 15, 2022, and March 15, 2023, and underwent respiratory polymerase chain reaction (PCR) testing on nasopharyngeal swab samples, were included in the study. All data were retrieved from hospital records.*

***Results:*** *The mean age of the patients was 38.3 ± 10.4 months (range= 25-60 months), and 48 (55.2%) were male. Of the patients admitted with respiratory tract infection, 13 (14.9%) were found to be RSV positive, 18 (20.7%) were influenza virus positive, and 12 (13.8%) were SARS-CoV-2 PCR positive. The rate of patients with runny nose (94.4%) and conjunctivitis (27.8%) in the influenza virus positive group, and dyspnea (61.5%), retraction (53.8%), rhonchi (46%), pulmonary findings on radiography (69.2%) and reticular pattern (14%) in the RSV positive group were significantly higher than the other groups. The sensitivity and specificity of the ILI definition for detecting influenza positivity were determined to be 100% and 46.2%, respectively. However, these results indicate that the ILI and/or SARI definitions were not effective in identifying RSV infection or novel coronavirus diseases-2019 (COVID-19) in children.*

***Conclusion:*** *Our study demonstrated that RSV and influenza virus infections decreased in children during the pandemic. Notably, in the younger age group, respiratory symptoms were predominant in the diagnosis of RSV, while runny nose and conjunctivitis were key indicators for the diagnosis of influenza. However, no distinct distinguishing findings were found for COVID-19. Moreover, to the best of our knowledge, this study is the first in the literature to demonstrate that while the ILI definition is sufficient to identify influenza and similar infections, it is inadequate for identifying RSV infection and COVID-19.*

***Key Words:*** *Child; Influenza; RSV; SARS-CoV-2; ILI-SARI*

Received/Geliş Tarihi: 22/09/2024 - Accepted/Kabul Ediliş Tarihi: 28/11/2024





Available Online Date: 21.03.2025

## ÖZ

### Pandemi Sürecinde Çocuklarda SARS-CoV-2, İnfluenza Virüs ve RSV İnfeksiyonlarının Klinik Seyri: ILI ve SARI Tanımları Klinik Tanıyı Öngörebilir mi?



Tuba KURUOĞLU[1], Derya BAYIRLI TURAN[2], Emine Hafize ERDENİZ[3], Demet GÜR VURAL[4], Ahmet Cenkay ORBAY[5]

[1] Ondokuz Mayıs Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Samsun, Türkiye
[2] Yeni Yüzyıl Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, İstanbul, Türkiye
[3] Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Çocuk İnfeksiyon Hastalıkları Anabilim Dalı, Samsun, Türkiye
[4] Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, Samsun, Türkiye
[5] Yeditepe Üniversitesi Fen Bilimleri Enstitüsü, Biyoteknoloji Bölümü, İstanbul, Türkiye



***Giriş:*** *Bu çalışmada, pandemi döneminde 2-5 yaş arası çocuklarda şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2), respiratuvar sinsityal virüs (RSV) ve influenza virüslerinin neden olduğu solunum yolu infeksiyonu vakalarının değerlendirilmesi ve bu vakaların influenza benzeri hastalık (ILI) ve şiddetli akut solunum infeksiyonu (SARI) tanımlarına uygunluğunun araştırılması amaçlanmıştır.*

***Materyal ve Metod:*** *Çalışmaya 15 Aralık 2022 ile 15 Mart 2023 tarihleri arasında pediatri polikliniklerine solunum yolu infeksiyonu şikayetleriyle başvuran ve nazofarenks sürüntüsü örneklerine solunum yolu polimeraz zincir reaksiyonu (PZR) testi yapılan beş yaş altındaki toplam 87 hasta dahil edildi. Tüm veriler hastane kayıtlarından alındı.*

***Bulgular:*** *Hastaların ortalama yaşı 38.3 ± 10.4 ay idi (aralık= 25-60 ay) ve 48 (%55.2)'i erkekti. Solunum yolu infeksiyonuyla başvuran hastaların 13 (%14.9)'ünde RSV, 18 (%20.7)'inde influenza virüsü, 12 (%13.8)'sinde SARS CoV-2 PZR pozitif saptandı. İnfluenza virüs pozitif grupta burun akıntısı (%94.4) ve konjonktivit (%27.8) olan hasta oranları, RSV pozitif grupta ise nefes darlığı (%61.5), retraksiyon (%53.8), ronkus (%46.2), direkt grafide akciğer bulgusu varlığı (%69.2) ve retiküler görüntü (%14) saptanan hasta oranları diğer gruplara göre anlamlı yüksekti (her biri için p< 0.05). İnfluenza benzeri hastalık tanımının influenza pozitifliği için duyarlılığı ve özgüllüğü sırasıyla %100 ve %46.2 olarak belirlenmiştir. Ancak bu sonuçlar, ILI ve/veya SARI kapsamının çocuklarda RSV infeksiyonunu ve COVID-19'u tanımlayamadığını göstermiştir.*

***Sonuç:*** *Çalışma, pandemi döneminde çocuklarda RSV ve influenza infeksiyonlarının azaldığını, özellikle küçük yaş grubunda RSV tanısında solunum semptomlarının, influenza tanısında ise burun akıntısı ve konjonktivitin öne çıktığını göstermiştir. Ancak COVID-19 için belirgin bir ayırıcı bulgu bulunamamıştır. Ayrıca çalışma, ulaşılabildiği kadarıyla literatürde ilk kez olarak, ILI tanımının influenza ve benzeri infeksiyonları belirlemede yeterli olduğunu ancak RSV ve COVID-19'u tanımlamada yetersiz kaldığını göstermiştir.*



***Anahtar Kelimeler:*** *Çocuk; Influenza; RSV; SARS-CoV-2; ILI-SARI*


## INTRODUCTION

Novel coronavirus disease-2019 (COVID-19), caused by the acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, has caused a worldwide pandemic. SARS-CoV-2 is a virus that spreads rapidly among humans, with some variants having higher mortality rates. It has been reported that COVID-19 is much less common in children than in adults, is mostly milder, complications are rare, and morbidity and mortality rates are very low[1-3].

Respiratory syncytial virus (RSV) is one of the viruses that most commonly causes respiratory tract infections in children. RSV mostly affects the upper respiratory tract in children. RSV infections are mostly mild in children, and complications are rare in cases without an underlying cause, but they may cause lung infiltration[4,5].

Influenza virus frequently causes infection in children and usually causes a self-limiting disease. Complications are rare in cases of influenza in children. Death rates from influenza are lower in children than in adults. Types A and B of influenza viruses are mostly responsible for epidemics. In adults and older children, influenza A serological type H3N2, influenza B, and influenza A serological type H1N1 often cause severe disease[6-8].

The World Health Organization (WHO) has developed and updated the definitions of influenza-like illness (ILI) and severe

acute respiratory infection (SARI) in recent years. Accordingly, ILI is defined as a fever (≥38 °C) that began within the past 10 days, accompanied by a cough. SARI is defined as a clinical condition requiring hospitalization, with a history of fever within the past 10 days or a measured fever of ≥38 °C, along with a cough. The approach according to these definitions is recommended for pediatric patients presenting with a respiratory tract infection[9].

Significant changes in the epidemiological data on viral respiratory tract infections, such as influenza and RSV in children, have been reported during the COVID-19 pandemic. This decrease has been attributed to reduced person-to-person contact resulting from pandemic measures[10-14]. The present study aimed to evaluate cases of respiratory tract infections caused by SARS-CoV-2, RSV, and influenza viruses during the pandemic period in children aged 2-5 years and to investigate the compatibility of these cases with the definitions of ILI and SARI.

## MATERIALS and METHODS

This multicenter prospective study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (reference number: 2022/460).

### Patients and Tests

The study included patients who presented to the pediatric outpatient clinic between December 15, 2022, and March 15, 2023, with at least one symptom or sign of acute respiratory tract infection (such as rhinitis, nasal congestion, sore throat, or fever of undetermined origin, excluding urinary tract infection or acute gastroenteritis) and had nasopharyngeal swab samples collected. A total of 87 voluntary pediatric patients aged between 25 and 60 months who underwent respiratory PCR testing were included in the study. Patients born prematurely and those with severe congenital or chronic diseases (such as congenital heart disease, neuromuscular or chronic lung disease, immune deficiency, or chromosomal anomalies) were excluded from the study. Additionally, two patients with concurrent influenza and RSV PCR positivity were excluded from the study to prevent errors in the statistical analyses.

In this study, children infected with SARS-CoV-2, RSV, and influenza were compared based on their demographic characteristics, symptoms, clinical findings, laboratory and radiological results, parental history of respiratory tract infections, and history of COVID-19 and influenza vaccination.

PCR tests for the presence of RSV, influenza virus, and SARS-CoV-2 were performed on nasopharyngeal swab samples taken from children using a multiplex PCR kit (RT, Türkiye) in the microbiology research laboratory.

### Definitions

The definitions of ILI and SARI were as follows[9]:

ILI: Cough with fever (≥38 °C) that started in the last 10 days.

SARI: A history of fever that started in the last 10 days or a clinical picture requiring hospitalization with a measured fever of ≥38 °C and cough.

### Statistical Analysis

The sample size in the study was calculated by power analysis using G-Power (version 3.1.9.6, Franz Faul, Universitat Kiel, Germany). With an effect size of 0.48, a type 1 error rate of 0.05, and a test power of 0.95, the total required sample size was calculated to be at least 86 participants.

All statistical analyses in the study were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were presented as numbers and percentages. Comparisons between groups for categorical variables were conducted using Pearson's Chi-square test and Fisher's exact test. Whether continuous variables conformed to normal distribution was analyzed with the Kolmogorov-Smirnov test. Differences between two groups for non-normally distributed continuous variables were analyzed using the Mann-Whitney U test, while differences among multiple groups were analyzed using the Kruskal-Wallis test. The risk coefficients of the variables related to infections were determined using logistic regression analysis. The results were evaluated within a 95% confidence

interval, and p-values <0.05 were considered statistically significant. Bonferroni correction was applied where necessary.

Sensitivity, specificity, and accuracy calculations were made as follows:

Sensitivity= True positives / (True positives + False negatives)

Specificity= True negatives / (True negatives + False positives)

Accuracy= (True positives + True negatives) / All patients

## RESULTS

The mean age of the patients was 38.3 ± 10.4 months (range= 25-60 months), and 48 (55.2%) were male. The most common symptoms and findings were cough (82.8%), runny nose (70.1%) and fever (64.4%), respectively. The most common lung findings were rales (19.5%), retraction (14.9%), and rhonchi (14.9%). Although findings were detected on chest radiography in 31 (35.2%) of the cases, a reticular pattern was present in 16 (8.7%) of them (Table 1).

Of the patients admitted with respiratory tract infection, 13 (14.9%) were positive for RSV, 18 (20.7%) were positive for influenza virus, and 12 (13.8%) were positive for SARS-CoV-2. The cough rate in the PCR-negative group was found to be significantly lower than in the PCR-positive group (p= 0.012). The rates of other symptoms, findings, and medical histories were similar between the PCR-negative and PCR-positive groups (p> 0.05 for each) (Table 1).

The rate of patients with runny nose (94.4%) and conjunctivitis (27.8%) in the influenza-positive group, and shortness of breath (61.5%), retraction (53.8%), rhonchi (46%), pulmonary findings on radiography (69.2%) and reticular pattern presence (14%) were significantly higher than the other groups, and the rate of maternal

**Table 1. Comparison of the rates of various variables between groups**

| | General | | PCR negative | | p | RSV (+) | | Influenza (+) | | SARS-CoV-2 (+) | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | | n | % | n | % | n | % | |
| Total | 87 | 100 | 44 | 50.6 | | 13 | 14.9 | 18 | 20.7 | 12 | 13.8 | |
| Gender | | | | | .582 | | | | | | | .927 |
| Male | 48 | 55.2 | 23 | 52.3 | | 7 | 53.8 | 11 | 61.1 | 7 | 58.3 | |
| Symptoms and signs | | | | | | | | | | | | |
| Cough | 72 | 82.8 | 32 | 72.7 | **.012** | 13 | 100.0 | 16 | 88.9 | 11 | 91.7 | .073 |
| Runny nose | 61 | 70.1 | 30 | 68.2 | .69 | 9 | 69.2 | **17** | **94.4** | 5 | 41.7 | **.02** |
| Dyspnea | 24 | 27.6 | 9 | 20.5 | .132 | **8** | **61.5** | 4 | 22.2 | 3 | 25.0 | **.03** |
| Conjunctivitis | 8 | 9.2 | 3 | 6.8 | .438 | 0 | 0.0 | **5** | **27.8** | 0 | 0.0 | **.016** |
| Pulmonary findings | | | | | | | | | | | | |
| Retraction | 13 | 14.9 | 4 | 9.1 | .121 | **7** | **53.8** | 1 | 5.6 | 1 | 8.3 | **<.001** |
| Rhonchi | 13 | 14.9 | 5 | 11.4 | .344 | **6** | **46.2** | 2 | 11.1 | 0 | 0.0 | **.005** |
| Pulmonary radiography findings | | | | | .503 | | | | | | | **.008** |
| Present | 31 | 35.6 | 17 | 38.6 | | **6** | **69.2** | 6 | 11.1 | 44 | 23.1 | |
| Reticular pattern | 16 | 8.7 | 7 | 7.7 | | **6** | **14.0** | 2 | 5.4 | 1 | 7.7 | |
| History | | | | | | | | | | | | |
| Mother's vaccination (COVID-19) | 63 | 72.4 | 32 | 72.7 | .307 | **7** | 53.8 | 14 | 77.8 | 10 | 83.3 | **.04** |
| Treatment | | | | | | | | | | | | |
| Decongestant | 6 | 6.9 | 2 | 4.5 | .434 | 0 | 0.0 | **4** | **22.2** | 0 | 0.0 | **.032** |
| Hypertonic saline | 19 | 21.8 | 10 | 22.7 | .795 | **6** | **46.2** | 3 | 16.7 | 0 | 0.0 | **.044** |

Chi-square and Fisher's exact tests were used. PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, COVID-19: Coronavirus disease-2019, URTI: Upper respiratory tract infection.

COVID-19 vaccination was significantly lower in the RSV group (p< 0.05 for each). The groups were similar in terms of other symptoms and findings, chest radiography findings, and history distribution (p> 0.05 for each) (Table 1).

PCR-negative and PCR-positive groups were similar in terms of mean fever, fever duration, lymphocyte count, neutrophil count, neutrophil-lymphocyte ratio (NLR) value, and mean total number of COVID-19 vaccine doses administered to mother and father (p> 0.05 for each) (Table 2).

In the RSV group, the mean age was 29.6 months, significantly lower than the other groups, and the mean leukocyte count was significantly higher (p< 0.05 for both). The groups were similar in terms of mean fever, fever duration, lymphocyte count, neutrophil count, NLR value, and mean total number of COVID-19 vaccine doses administered to the mother and father (p> 0.05 for each) (Table 2).

Logistic regression analysis revealed that cough was an independent risk factor for the positivity of these three viral factors, increasing the risk by 5.0 times (95% CI= 1.3-19.3, p= 0.019). For RSV positivity, the following were identified as independent risk factors: age (p= 0.006), shortness of breath (p= 0.006), presence of retraction (p< 0.001), rhonchi (p= 0.002), presence of findings on chest X-ray (p= 0.01), presence of a reticular image on chest X-ray (p= 0.009), and lack of a COVID-19 vaccination history in the mother (p= 0.008). The presence of runny nose (p= 0.032) and conjunctivitis (p= 0.007) were independent risk factors for influenza virus positivity (Table 3).

SARS-CoV-2 PCR positivity rates were similar between patients with and without ILI or SARI (18.4% vs. 10.2%; p= 0.27). Accordingly, the sensitivity and specificity of ILI or SARI identification in terms of SARS-CoV-2 positivity were determined to be 58.3% and 41.3%, respectively. Accordingly, the sensitivity and specificity of SARI identification in terms of SARS-CoV-2 positivity were found to be 42.9% and 71.0%, respectively (Table 4).

The influenza virus PCR positivity rate among those meeting the ILI or SARI criteria was found to be significantly higher than among those who did not meet these criteria (31.6% vs. 12.2%; p= 0.027). Accordingly, the sensitivity and specificity of ILI or SARI identification in terms of influenza virus positivity were determined to be 66.7% and 37.7%, respectively. The influenza virus PCR positivity rate was significantly higher in patients diagnosed with ILI compared to those diagnosed with SARI (46.2% vs. 0%; p= 0.004). No influenza virus positivity was identified in patients classified as SARI. Accordingly, the sensitivity and specificity of the ILI definition for influenza positivity were determined to be 100% and 46.2%, respectively (Table 4).

RSV PCR positivity rates were found to be similar between patients with and without ILI or SARI (13.2% vs. 16.3%; p= 0.681). Accordingly, the sensitivity and specificity of ILI or SARI identification for RSV positivity were determined to be 38.5% and 44.6%, respectively. RSV PCR positivity rates were similar in patients identified as having ILI or SARI (11.5% vs. 16.7%; p= 0.643). Accordingly, the sensitivity and specificity of the ILI definition in terms of RSV positivity

**Table 2. Comparison of average values of various variables according to groups**

| | General | | PCR negative | | P* | RSV (+) | | Influenza (+) | | SARS-CoV-2 (+) | | P$^{Ý}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | Mean | SD | |
| Age (months) | 38.3 | 10.4 | 39.4 | 11.0 | .363 | 29.6 | 3.9 | 41.7 | 9.2 | 38.7 | 10.4 | .003 |
| Height (cm) | 88.1 | 19.0 | 90.5 | 17.3 | .374 | 72.0 | 15.9 | 96.1 | 19.7 | 86.0 | 18.5 | .011 |
| Weight (kg) | 13.2 | 4.9 | 13.7 | 4.5 | .472 | 9.6 | 4.3 | 14.0 | 5.0 | 14.4 | 5.7 | .048 |
| Leukocyte ($10^9$/mL) | 11.0 | 6.3 | 10.4 | 5.9 | .618 | 15.2 | 6.6 | 8.6 | 6.5 | 7.9 | 3.5 | .027 |

Kruskal Wallis test was used. *Comparisons between PCR negative and PCR positive groups. $^{Ý}$Comparisons between all groups. PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, Mean: Mean, SD: Standard deviation, NLR: Neutrophil leukocyte ratio.

**Table 3. Logistic regression analyses**

| | PCR positivity | RSV (+) | Influenza (+) | SARS-CoV-2 (+) | Exp (B) | 95% CI (lower-upper) |
|---|---|---|---|---|---|---|
| Total | p | p | p | p | | |
| Age (months) | | **0.006** | | | **0.8** | 0.7-0.9 |
| Symptoms and signs | | | | | | |
| Cough | **0.019** | | | | **5.0** | 1.3-19.3 |
| Runny nose | | | 0.032 | | **9.6** | 1.2-77.0 |
| Shortness of breath | | **0.006** | | | **5.8** | 1.7-20.2 |
| Conjunctivitis | | | **0.007** | | **8.5** | 1.8-39.9 |
| Lung findings | | | | | | |
| Retraction | | **<0.001** | | | **13.2** | 3.4-52.2 |
| Rhonchi | | **0.002** | | | **8.2** | 2.2-31.3 |
| Presence of chest radiography findings | | **0.01** | | | **5.3** | 1.5-19.1 |
| Reticular pattern | | **0.009** | | | **5.5** | 1.5-19.7 |
| History | | | | | | |
| Mother's vaccination | | **0.008** | | | **0.2** | 0.1-0.6 |

PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, Exp (B): Exponential B coefficient (odds ratio), CI: Confidence interval, COVID-19: Coronavirus disease- 2019, URTI: Upper respiratory tract infection.

**Table 4. Comparisons of PCR results according to ILI and/or SARI definitions**

| | Total | SARS-CoV-2 PCR (+) | | p | Sensitivity | Specificity | Accuracy |
|---|---|---|---|---|---|---|---|
| | n | n | % | | | | |
| All patients | | | | 0.27 | | | |
| ILI/SARI | 38 | 7 | 18.4 | | 58.3 | 41.3 | 58.6 |
| Covered in ILI/SARI | | | | 0.656 | | | |
| ILI | 26 | 4 | 15.4 | | 57.1 | 29.0 | 34.2 |
| SARI | 12 | 3 | 25.0 | | 42.9 | 71.0 | 65.8 |
| | **Total** | **Influenza PCR (+)** | | | | | |
| | n | n | % | | | | |
| All patients | | | | **0.027** | | | |
| ILI/SARI | 38 | 12 | 31.6 | | 66.7 | 37.7 | 63.2 |
| Covered in ILI/SARI | | | | **0.004** | | | |
| ILI | 26 | 12 | 46.2 | | 100.0 | 46.2 | 63.2 |
| SARI | 12 | 0 | 0.0 | | 0.0 | 53.8 | 36.8 |
| | **Total** | **RSV PCR (+)** | | | | | |
| | n | n | % | | | | |
| All patients | | | | 0.681 | | | |
| ILI/SARI | 38 | 5 | 13.2 | | 38.5 | 44.6 | 52.9 |
| Covered in ILI/SARI | | | | 0.643 | | | |
| ILI | 26 | 3 | 11.5 | | 60.0 | 30.3 | 34.2 |
| SARI | 12 | 2 | 16.7 | | 40.0 | 69.7 | 65.8 |

Chi-square test was used. ILI: Influenza-like illness, SARI: Severe acute respiratory infection, PCR: Polymerase chain reaction.

were determined to be 60.0% and 30.3%, respectively (Table 4).

## DISCUSSION

With the COVID-19 pandemic, significant epidemiological changes have been observed in respiratory tract infection factors in children. In addition, there are difficulties in making the differential diagnosis of viral respiratory tract infections, which are common in young children, without using molecular methods[10-12]. This study examined the differences in clinical findings among COVID-19, RSV, and influenza virus infections in children.

RSV is a virus that causes infection mostly in young children, is easily transmitted, and can infiltrate the lungs[4,5]. Some studies have reported that the RSV positivity rate in children during the pandemic decreased significantly compared to before the pandemic[4,10-17]. In the present study, RSV was detected in 14.9% of children who presented with respiratory tract infections during the pandemic. This finding suggests that pandemic practices and various measures implemented across society have contributed to reducing the prevalence of RSV in children. Kuchar et al. found that the risk of RSV in children was higher than SARS-CoV-2 during the pandemic[18]. The fact that the RSV rate was higher than SARS-CoV-2 in the present study supports this finding.

In the present study, the rates of shortness of breath, retraction, rhonchi, pulmonary findings on radiographs, and reticular pattern appearance were significantly higher in the RSV-positive group compared to the other groups. These findings were identified as independent risk factors for RSV positivity, increasing the likelihood of a positive RSV diagnosis by 5.3 to 13.2 times. These findings demonstrate that RSV can frequently cause lung infiltration in children under five years of age. Additionally, the presence of lung findings in pediatric patients presenting with respiratory tract infection complaints strongly suggests RSV as the diagnosis, compared to influenza and COVID-19. Hedberg et al. found that RSV positivity was significantly higher at younger ages in children with respiratory tract infections compared to influenza and SARS-CoV-2[19]. In the study, the mean age of the RSV group was found to be significantly lower than that of the other groups. Age was identified as an independent risk factor for RSV positivity, with each additional month of age reducing the risk of RSV by 0.1 times. This finding indicates that RSV tends to cause infections in younger children compared to influenza and COVID-19. The average leukocyte count was found to be significantly higher in children with RSV. This finding may indicate that the leukocyte response to RSV is more pronounced and that RSV is more likely than the other two viruses in the diagnosis of viral upper respiratory tract infection (URTI) associated with a high leukocyte count. The rate of maternal COVID-19 vaccination was found to be significantly lower in the RSV-positive group, and the absence of a vaccination history in the mother was found to be an independent risk factor for RSV positivity. This may be attributed to vaccinated mothers being more cautious in protecting their children from external contacts.

Influenza virus infection is a common illness in children, typically presenting with symptoms such as high fever, cough, runny nose, and conjunctivitis[6-8]. Some studies have shown that the influenza virus positivity rate in children during the pandemic decreased significantly compared to before the pandemic[4,9-17,20-25]. In the present study, influenza virus was detected in 20.7% of the patients who presented with respiratory tract infections during the pandemic. Kuchar et al. found that the risk of influenza virus infection was higher in children during the pandemic than SARS-CoV-2[18]. The fact that the rate of influenza was higher than SARS-CoV-2 in the present study supports this finding.

In the present study, the rates of patients with runny nose (94.4%) and conjunctivitis (27.8%) in the influenza virus-positive group were found to be significantly higher than the other groups. The presence of runny nose and conjunctivitis were identified as independent risk factors for influenza virus positivity. The risk was found to be 13.2 times higher with runny nose and 8.5 times higher with conjunctivitis. These findings

demonstrate that the influenza virus, as expected, more frequently causes typical symptoms such as runny nose and conjunctivitis. The presence of these symptoms in children under the age of five presenting with URTI complaints strongly supports a diagnosis of influenza.

COVID-19 infection is less common in children than in adults, and the clinical picture is generally milder[1-3]. Kuchar et al. found that the positivity rate for SARS-CoV-2 was lower in children with URTI symptoms compared to RSV and Influenza viruses. They concluded that COVID-19 should not be considered a primary diagnosis in young children with such symptoms[18]. In the present study, SARS-CoV-2 was detected in 13.8% of children presenting with URTI complaints, a rate lower than that observed for RSV and influenza virus.

Hedberg et al. reported that the SARS-CoV-2 positivity rate in children was higher in older children[4,19]. In the present study, the average age in the SARS-CoV-2 group was found to be significantly higher than in the RSV-positive group. This finding may suggest that as the age of children decreases, the likelihood of COVID-19 diagnosis diminishes.

Prozan et al. reported that the presence of fever and the NLR value could be used to differentiate COVID-19 from influenza and RSV infections in adults[26]. However, in the present study conducted in children, the rates of any of the symptoms, signs, and medical histories were not found to be significantly higher in SARS-CoV-2-positive patients. Additionally, none of these variables were identified as independent risk factors for SARS-CoV-2 positivity. These findings show that symptoms, clinical findings, or medical history do not provide specific diagnostic information for COVID-19 in children under five years of age presenting with URTI complaints.

In the present study, the cough rate in the PCR-positive group for the three viruses was found to be significantly higher than in the PCR-negative group. This finding suggests that the presence of a cough may indicate the likelihood of RSV, influenza, or COVID-19 but cannot differentiate between these infections. Except for cough, symptoms, signs, and chest radiography findings were found to be similar between the PCR-positive and PCR-negative groups. In logistic regression analyses, it was determined that cough was an independent risk factor for PCR positivity and increased the risk of PCR positivity by five times. This indicates that other respiratory tract infection symptoms and signs cannot specifically support or rule out the diagnosis of any of these three infections. The study also found that factors such as a history of COVID-19 in the patient or their household, a recent or current URTI in the household, the patient or their sibling attending school or nursery, the number of people in the household, and the parents' COVID-19 vaccination history neither support nor rule out the diagnosis of any of these three infections.

WHO introduced a new definition of ILI in 2011 and subsequently updated it in 2018[9]. In some studies conducted after the onset of the COVID-19 pandemic, the ILI definition was applied to all general respiratory infections, with less emphasis on the criteria of fever and cough. Accordingly, patients with respiratory tract infections were classified as having either COVID-19 or influenza, and comparisons were made among these patient groups[27-29]. In one study, an epidemiological comparison of ILI and COVID-19 was made[6,30]. To the best of our knowledge, no study has evaluated influenza, COVID-19, and RSV positivity rates based on whether they meet the ILI and/or SARI criteria. In the present study, SARS-CoV-2 PCR positivity rates were found to be similar between patients who met and did not meet the ILI or SARI criteria (18.4% vs. 10.2%). Accordingly, the sensitivity and specificity of ILI or SARI identification for SARS-CoV-2 positivity were determined to be 53.8% and 41.3%, respectively. Additionally, SARS-CoV-2 PCR positivity rates were found to be similar in patients identified as meeting ILI or SARI criteria (15.4% vs. 25.0%). Accordingly, the sensitivity and specificity of SARI identification for SARS-CoV-2 positivity were determined to be 42.9% and 71.0%, respectively. All of these findings indicate that the scope of ILI and/or SARI, as defined before COVID-19, is highly inadequate for accurately identifying COVID-19 in children.

In the present study, the influenza PCR positivity rate among those meeting the ILI or SARI criteria was found to be significantly higher than among those not meeting these criteria (31.6% vs. 12.2%). Accordingly, the sensitivity and specificity of ILI or SARI identification for influenza virus positivity were determined to be 66.7% and 37.7%, respectively. In addition, the influenza PCR positivity rate in patients diagnosed with ILI was found to be significantly higher than in those diagnosed with SARI (46.2% vs. 0%). Accordingly, the sensitivity and specificity of the ILI definition for influenza positivity were determined to be 100% and 53.8%, respectively. All these findings show that ILI identification is highly successful in detecting children with influenza. The low specificity observed indicates that the ILI criteria, as expected, also encompass some other influenza-like respiratory infections. Influenza virus positivity was not detected in those identified as SARI in the study. This finding suggests that the diagnosis in children meeting the SARI criteria should focus on respiratory tract infections other than influenza.

In the present study, RSV PCR positivity rates were found to be similar in patients with and without ILI or SARI (13.2% vs. 16.3%). Accordingly, the sensitivity and specificity of ILI or SARI identification for RSV positivity were determined to be 38.5% and 44.6%, respectively. Additionally, RSV PCR positivity rates were found to be similar in patients defined as ILI or SARI (11.5% vs. 16.7%). Accordingly, the sensitivity and specificity of the ILI definition for RSV positivity were determined to be 60.0% and 30.3%, respectively. All of these findings indicate that ILI and/or SARI criteria are insufficient for identifying RSV in children.

The relatively small number of patients who underwent PCR testing in the present study may have negatively impacted the significance values in the statistical analyses. In addition, the absence of pre-pandemic data in the study prevented a clear comparison of positivity rates before and during the pandemic. The fact that panels for all upper respiratory tract viruses were not used in the study is also a limitation; however, the detection of at least one of the three viruses within the scope of the study in more than half of the cases may have prevented the analyses regarding these infections from being weak.

The findings obtained from the present study show that the frequency of RSV and influenza virus-related infections decreased in children during the pandemic. The diagnosis of RSV is more prominent, especially in young children and those presenting with shortness of breath, retraction, rhonchi, leukocytosis, and a reticular appearance in the lungs. Conversely, the diagnosis of influenza is more prominent in children with runny nose and conjunctivitis. However, no distinctive specific finding was identified for COVID-19. The present study also showed, to the best of our knowledge, for the first time in the literature, that the definition of ILI is sufficient for diagnosing Influenza and similar infections, but that the definitions of ILI and/or SARI are insufficient to define the clinical picture of RSV and COVID-19.

## ETHICS COMMITTEE APPROVAL

This study approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (Decision no: 2022/460, Date: 26.10.2022).

## CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

## AUTHORSHIP CONTRIBUTIONS

Concept and Design: TK, DBT

Analysis/Interpretation: TK, DBT

Data Collection or Processing: EHE, DGV

Writing: TK

Review and Correction: TK, DBT

Final Approval: TK, DBT

## REFERENCES

1. *Nikolopoulou GB, Maltezou HC. COVID-19 in Children: Where do we stand? Arch Med Res 2022;53:1-8. https://doi.org/10.1016/j.arcmed.2021.07.002*
2. *Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol 2021;93:1057-69. https://doi.org/10.1002/jmv.26398*

3. *Zhang P, Wei M, Jing P, Li Z, Li J, Zhu F. COVID-19 in children: Epidemic issues and candidate vaccines. Chin Med J (Engl) 2022;135:1314-24. https://doi.org/10.1097/CM9.0000000000002169*
4. *Stacevičienė I, Ivas˘kevičienė I, Burokienė S, Steponavičienė A, Vaičiūnienė D, Tarutytė G, Jankauskienė A. Epidemiological changes of acute respiratory infections in children: A single-center experience after COVID-19 lockdown. PLOS ONE 5:2024. https://doi.org/10.1371/journal.pone.0300877*
5. *Haddadin Z, Beveridge S, Fernandez K, Rankin DA, Probst V, Spieker AJ, et al. Respiratory syncytial virus disease severity in young children. Clin Infect Dis 2021;73:e4384-e91. https://doi.org/10.1093/cid/ciaa1612*
6. *Potdar V, Vijay N, Mukhopadhyay L, Aggarwal N, Bhardwaj SD, Choudhary ML. Pan-India influenza-like illness (ILI) and Severe acute respiratory infection (SARI) surveillance: Epidemiological, clinical and genomic analysis. Front Public Health 2023:11:1218292. https://doi.org/10.3389/fpubh.2023.1218292*
7. *Nayak J, Hoy G, Gordon A. Influenza in children. Cold Spring Harb Perspect Med 2021;11:a038430. https://doi.org/10.1101/cshperspect.a038430*
8. *UK Health Security Agency. National influenza and COVID-19 surveillance report Week 27 report (up to week 26 2024 data). 2024;5.*
9. *Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, et al. Revision of clinical case definitions: Influenza-like illness and severe acute respiratory infection. Bull World Health Organ 2018;96:122-8. https://doi.org/10.2471/BLT.17.194514*
10. *Redlberger-Fritz M, Kundi M, Aberle SW, Puchhammer-Stöckl E. Significant impact of nationwide SARS-CoV-2 lockdown measures on the circulation of other respiratory virus infections in Austria. J Clin Virol 2021;137:104795. https://doi.org/10.1016/j.jcv.2021.104795*
11. *Huang QS, Wood T, Jelley L, Jennings T, Jefferies S, Daniells K, et al. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. Nat Commun 2021;12:1001. https://doi.org/10.1038/s41467-021-21157-9*
12. *Haddadin Z, Schuster JE, Spieker AJ, Rahman H, Blozinski A, Stewart L, et al. Acute respiratory illnesses in children in the SARS-CoV-2 pandemic: Prospective multicenter study. Pediatrics 2021;148:e2021051462. https://doi.org/10.1542/peds.2021-051462*
13. *Stamm P, Sagoschen I, Weise K, Plachter B, Münzel T, Gori T, et al. Influenza and RSV incidence during COVID-19 pandemic-an observational study from in-hospital point-of-care testing. Med Microbiol Immunol 2021;210:277-82. https://doi.org/10.1007/s00430-021-00720-7*
14. *Tempia S, Walaza S, Bhiman JN, McMorrow ML, Moyes J, Mkhencele T, et al. Decline of influenza and respiratory syncytial virus detection in facility-based surveillance during the COVID-19 pandemic, South Africa, January to October 2020. Euro Surveill 2021;26:2001600. https://doi.org/10.2807/1560-7917.ES.2021.26.29.2001600*
15. *Varela FH, Scotta MC, Polese-Bonatto M, Sartor ITS, Ferreira CF, Fernandes IR, et al. Absence of detection of RSV and influenza during the COVID-19 pandemic in a Brazilian cohort: Likely role of lower transmission in the community. J Glob Health 2021;11:05007. https://doi.org/10.7189/jogh.11.05007*
16. *Foley DA, Yeoh DK, Minney-Smith CA, Martin AC, Mace AO, Sikazwe CT, et al. The interseasonal resurgence of respiratory syncytial virus in Australian children following the reduction of coronavirus disease 2019-related public health measures. Clin Infect Dis 2021;73:e2829-30. https://doi.org/10.1093/cid/ciaa1906*
17. *Vittucci AC, Piccioni L, Coltella L, Ciarlitto C, Antilici L, Bozzola E, et al. The disappearance of respiratory viruses in children during the COVID-19 pandemic. Int J Environ Res Public Health 2021;18:9550. https://doi.org/10.3390/ijerph18189550*
18. *Kuchar E, Załęski A, Wronowski M, Krankowska D, Podsiadły E, Brodaczewska K, et al. Children were less frequently infected with SARS-CoV-2 than adults during 2020 COVID-19 pandemic in Warsaw, Poland. Eur J Clin Microbiol Infect Dis 2021;40:541-7. https://doi.org/10.1007/s10096-020-04038-9*
19. *Hedberg P, Karlsson Valik J, van der Werff S, Tanushi H, Requena Mendez A, Granath F, et al. Clinical phenotypes and outcomes of SARS-CoV-2, influenza, RSV and seven other respiratory viruses: A retrospective study using complete hospital data. Thorax 2022;77:154-63. https://doi.org/10.1136/thoraxjnl-2021-216949*
20. *Mott JA, Fry AM, Kondor R, Wentworth DE, Olsen SJ. Re-emergence of influenza virus circulation during 2020 in parts of tropical Asia: Implications for other countries. Influenza Other Respir Viruses 2021;15:415-8. https://doi.org/10.1111/irv.12844*
21. *Lee H, Lee H, Song KH, Kim ES, Park JS, Jung J, et al. Impact of public health interventions on seasonal influenza activity during the COVID-19 outbreak in Korea. Clin Infect Dis 2021;73:e132-40. https://doi.org/10.1093/cid/ciaa672*
22. *Chan CP, Wong NS, Leung CC, Lee SS. Positive impact of measures against COVID-19 on reducing influenza in the Northern Hemisphere. J Travel Med 2020;27:taaa087. https://doi.org/10.1093/jtm/taaa087*
23. *Yayla BCC, Aykac K, Boluk O, Fidanci I, Tasar MA, Pamuk U, et al. The comparison of COVID-19 vs seasonal influenza in children. Pediatr Int 2023;65:e15684. https://doi.org/10.1111/ped.15684*
24. *Luo J, Zhang Z, Zhao S, Gao R. A comparison of etiology, pathogenesis, vaccinal and antiviral drug development between Influenza and COVID-19. Int J Mol Sci 2023;24:6369. https://doi.org/10.3390/ijms24076369*
25. *Dulkadir R, Oztelcan Gunduz B. Differentiating COVID-19 and influenza in children: Hemogram parameters as diagnostic tools. Front Public Health 2024;12:1377785. https://doi.org/10.3389/fpubh.2024.1377785*

26. *Prozan L, Shusterman E, Ablin J, Mitelpunkt A, Weiss-Meilik A, Adler A, et al. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 compared with influenza and respiratory syncytial virus infection. Sci Rep 2021;11:21519. https://doi.org/10.1038/s41598-021-00927-x*

27. *Wang C, Yang YN, Xi L, Yang LL, Du J, Zhang ZS, et al. Dynamics of influenza-like illness under urbanization procedure and COVID-19 pandemic in the subcenter of Beijing during 2013-2021. J Med Virol 2022;94:3801-10. https://doi.org/10.1002/jmv.27803*

28. *Tao J, Gao H, Zhu S, Yang L, He D. Influenza versus COVID-19 cases among influenza-like illness patients in travelers from Wuhan to Hong Kong in January 2020. Int J Infect Dis 2020;101:323-5. https://doi.org/10.1016/j.ijid.2020.09.1474*

29. *Shuai W, Chen X, Shan Y, Li W, Ma W, Lu Q, et al. Clinical characteristics and CT findings in 148 non-COVID-19 influenza-like illness cases: A retrospective control study. Front Public Health 2021;9:616963. https://doi.org/10.3389/fpubh.2021.616963*

30. *Grosso F, Castrofino A, Del Castillo G, Galli C, Binda S, Pellegrinelli L, et al. A comparative study between the incidence and epidemiological features of Influenza-Like Illness and laboratory-confirmed COVID-19 cases in the Italian epicenter (Lombardy). J Infect Public Health 2021;14:674-80. https://doi.org/10.1016/j.jiph.2021.02.003*

**Address for Correspondence/Yazışma Adresi**

Dr. Tuba KURUOĞLU

Department of Infectious Diseases and Clinical Microbiology, Ondokuz Mayıs University Faculty of Medicine
Samsun, Türkiye

E-posta: tuba.kuruoglu@omu.edu.tr