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Comparison of Clinical, Demographic Features and Costs in Respiratory Syncytial Virus, Rhinovirus and Viral Co-infections in Hospitalized Children with Lower Respiratory Tract Infections

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SUMMARY

Viruses are the most common cause of lower respiratory tract infections (LRTIs) in children. Our study aims to shed light on co-infections by comparing with the most common single agents, Respiratory syncytial virus (RSV) and Rhinovirus (RV), in terms of epidemiological, clinical, laboratory and cost. This retrospective study included infants under the age of five, hospitalized with a diagnosis of LRTI with RSV, RV or co-infection were analyzed. The study group consisted of 199 children, RSV was detected in 116 patients (58.3%), RV in 46 (23.1%) and co-infections in 37 (18.6%). The average age of RV was higher (P = 0.006) and the length of hospital stay of RSV-infected patients was longer (P = 0.03) than other agents. There was no significant difference between the groups in terms of oxygen need, intensive care unit admission, intubation, and development of complications. The cost was found to be significantly higher in the RSV group (P=0.02). Viral co-infections, RSV and RV constitute an important part of the etiology in patients under five years of age and co-infections do not cause more severe clinical findings compared to single viral agents. Moreover cost was found to be significantly higher in patients with RSV.
INTRODUCTION

Acute bronchiolitis, pneumonia, or a combination of the two is called lower respiratory tract infections (LRTIs). LRTIs are important causes of mortality and morbidity in children under five years of age, especially in developing countries. In the 2005 report of the World Health Organization, it was stated that pneumonia was responsible for 19% of 10.5 million child deaths that occur every year under the age of five (1).

Viruses constitute more than 50% of the LRTI in children under five years old. Respiratory syncytial virus (RSV) and Rhinovirus (RV), influenza virus (IV), parainfluenza virus (PIV), human metapneumovirus (HMPV), human bocavirus (HBoV), coronavirus, enterovirus, and adenovirus are viral agents responsible for LRTI in children. The most common viral agents are RSV and RV (1, 2). The coexistence of two or more of these agents is called co-infection. With advancing molecular techniques and the increasing frequency of their use, it has been understood that co-infections have been seen more frequently than expected in the last decade. Whether co-infections exhibit a more severe clinical picture than patients infected with single viral agents continues to be debated by researchers. Due to the wide variety of LRTI viruses and their difficulty to detect, viral examinations were often performed for epidemiological purposes. However, the awareness that viral infections cause hospital infections and early diagnosis of viral agents will decrease use of antibiotics has shown that diagnosis of respiratory tract infection viruses is very important (3).

In this current study, we aimed to compare patients who were hospitalized with a diagnosis of viral LRTI and found to have viral co-infections and the most common single agents, RSV and RV, in terms of clinical, demographic features and costs.
MATERIALS AND METHODS

Our study was conducted in the tertiary pediatric clinic in Ankara, Turkey. Patients under five years of age (excluding neonatal period) who were hospitalized with a diagnosis of LRTI between January 2015 and June 2018 were retrospectively analyzed. Hypoxemia (oxygen saturation [SpO2] <93%), inability to feed and hydration orally, respiratory distress, (tachypnea, retractions, apnea, grunting) toxic appearance, complications (eg, effusion, hearth failure ) and failure of outpatient therapy was defined as the indications for hospitalisation. Those with concomitant diseases were not included in the study. Approval was obtained from the local ethics committee for the study. (2018 date, 183. issue).

All of the respiratory swab samples were evaluated by the multiplex-PCR method in References Public Health Center Laboratories in our city. In these samples, nine different viral agents were analyzed: RSV, RV, IV, PIV, HMpV, HBoV, HCoV, enterovirus, and adenovirus. Patients with more than one respiratory tract virus were defined as co-infections.

In the study group, age (month), gender, month and season of admission, type of viral agent, co-infection subgroup, number of LRTI attacks (in order), presence of fever (≥38°C) and duration, oxygen need (SpO2 <93%), duration of oxygen replacement therapy, length of hospital stay (days), noninvasive mechanical ventilation need (NIMV), intensive care and mechanical ventilation (MV) need, and complications developed during the course of the disease, and cost were evaluated. Among the laboratory findings, values of white blood cell count (/ mm3) (WBC), eosinophil percentages, liver function tests (AST, ALT), kidney function tests (urea/creatinine) were recorded. Among the imaging methods, only lung X-ray findings (infiltration, consolidation, atelectasis) were evaluated. We collected data of cost per episode, including all medical (diagnosis, treatment) and nonmedical (food, care-bed) costs related to that hospitalization of the patient were evaluated. While evaluating the cost, collectively charged amount was included in the study.
Statistical analysis

All of data were analyzed by SPSS-2020 statistical package, Categorical variables between groups were analyzed using the χ² test. For descriptive statics, categorical variables are shown as number (n), percentage (%) and continuous variables are shown as mean (±) standard deviation. The compliance of the data to the normal distribution was executed using the Kolmogorov-Smirnov test. T-test was used for independent group comparisons in numerical parametric data, and Pearson Correlation Test was used in ANOVA correlation analysis. P˂0.05 was considered statistically significant.

RESULTS

During the study period 199 patients between the ages of one month and five years who were followed up with a diagnosis of LRTI and detected RSV, RV or co-infection in swab were examined. The mean age of all patients was found to be 9.09±9.78 months. The mean age was 7.4±8.3 months for RSV, 13.3±12.6 months for RV, and 8.9±8.6 months for co-infections. The mean age of the patients with RV was higher than the patients with RSV and co-infection (P = 0.006). In the study group 91 (45.7%) of the patients were female and 108 (54.3%) were male. Among these patients, RSV was detected in 116 (58.3%), RV in 46 (23.1%) and co-infections in 37 (18.6%) children. Co-infections included RSV, RV, IV, PIV, HMpV, HBoV, coronavirus, enterovirus, and adenovirus agents as well as 31 (83.7%) of the co-infections had at least one of the RSV and/or RV (Fig. 1). Although RV infections can be seen every year, in all months, RSV infections were predominantly observed in January and March (p <0.005) (Fig. 2).

Recurrent LRTI attacks were significantly higher in the RV group (P = 0.001). No significant difference was observed between the groups in terms of O₂ need and duration of O₂ uptake, and fever rate and duration of fever. The mean length of hospital stay in study group was 8.1±3.9 days and it was longer in RSV infected patients than other agents (P = 0.03). 40.2% of the patients had received
NIMV support and the average duration of NIMV was 3.9±2.2 days. There was no statistically significant difference between the groups in terms of the rate of receiving NIMV support. The duration of receiving NIMV support was 4.5±2.3 days in the RSV group, 2.6±1.4 days in the RV group, and 3.4±2.0 days in the co-infection group. Patients infected with RSV had a significantly longer duration of receiving NIMV than other agents (P = 0.005). There was no significant difference between the groups in terms of intensive care unit admission, intubation, and development of complications. During the study period no mortality was observed in any study group.

The most common chest radiography finding was bilateral diffuse interstitial infiltrates. No significant relationship was observed between the agents and chest radiography findings (P = 0.72). WBC elevation by age was detected in 52 (26.1%) patients. The rate of WBC elevation in the RV group was significantly higher than the other groups (P <0.005). AST and/or ALT were found to be elevated in 18 (9.1%) patients. Eight of these cases were in the co-infection group (P = 0.01). Eosinophil levels were found ≥500 /mm³ in 11 patients. Eight of these patients were in the RV group and three of them were in the RSV group, the mean eosinophil percentage in the RV group was found to be significantly higher than the other groups (P <0.005).

Since patients with an underlying chronic disease and a disease that would affect the LRTI clinic were not included in our study, it was thought that the resulting medical bill was only for the cost of viral infection. The average cost of all cases was determined as $753.6±684.6. The cost was calculated as $839.3±807.6 in RSV infected patients, $580±322 in RV-infected patients, and $702±547 in patients infected with co-infections. The highest cost was found in patients infected with RSV (P = 0.02). In the analysis of the co-infection group, length of hospital stay and cost in co-infections caused by RSV were found to be significantly higher than co-infections caused by agents other than RSV (P<0.005). Demographic data, clinical course, and cost analysis of the study groups were given in Table-1.
DISCUSSION

In this current study, co-infections compared with the two most common LRTIs agents and it was found that co-infections did not cause more severe clinical findings compared to single viral agents, also they showed a similar and intertwined clinical course and prognosis in practice. In addition length of hospital stay, duration of NIMV and cost, were found to be significantly higher in infants hospitalized with RSV and the number of LRTIs attacks and age of the patients were higher in RV group.

Considering the age distribution of the agents, respiratory viral agents are often one of the most important causes of LRTI in children under five years old. While RSV is more common in infants under one year of age, RV affects in children of all ages. Calvo et al. conducted that, the average age of the patients differed between the groups, the mean age was found to be 9.5 months for RSV infections, 26 months for RV infections, and 12.6 months in the co-infection group (4). In our study the mean age of RV was higher than RSV and co-infections. Also, recurrent attacks were observed more frequently in the RV group.

Oxygen need and duration of oxygen replacement therapy may change depending on the severity of the disease, underlying disease, age, and host immune status and less often thought to be due to viral agents. According to the meta-analysis performed by Asner et al. included 2294 patients from each age group to compare single viral infections and co-infections, no significant difference was found between the groups in terms of oxygen need (5). According to a study conducted by Garcia et al on HMpV infections and co-infections were compared, no significant difference was found in terms of oxygen need and duration of oxygen replacement therapy (6). In our study, 72.9% of the patients needed oxygen and the average duration of oxygen replacement therapy was 5.8 days and there was no significant difference between the groups in terms of oxygen need and duration of oxygen replacement therapy.
Richard et al. reported, the hospitalization period of patients with co-infection group in the intensive care unit was found to be longer than patients with a single infection, but it was not found to be statistically significant (7). In a meta-analysis conducted by Scotta et al. to determine the prognostic role of co-infections, no significant difference was found between co-infections and single viral infections in terms of hospitalization period (8). Similarly Asner et al., conducted a study in all age of patients with LRTIs and no significant difference was found between patients with single viral infection and patients with co-infection in terms of hospitalization period (5). The mean hospitalization period in our study was 8.1±3.9 days. It was found that, the hospitalization period of patients infected with RSV was found to be significantly longer in our study. This can be explained by the fact that 57.7% of patients infected with RSV consist of children younger than 6 months.

Lower respiratory tract infections are one of the leading causes of morbidity and mortality in all children worldwide. To decrease morbidity and mortality rates in severe LRTIs, hypoxia that may occur in children should be eliminated as soon as possible (9). Assisted breathing techniques (invasive and NIMV) are used for this purpose in patients with respiratory failure symptoms. According to the study conducted by Asner et al., no significant difference was found between single infections and co-infections in terms of the need for mechanical ventilation (5). Also Richard et al. reported, among patients admitted to the intensive care unit, no statistically significant difference was found between single infections and co-infections in terms of the rate and duration of receiving assisted ventilation support (7). In our study, co-infections group were the with the highest rate of receiving NIMV support. However, it was not found statistically significant. Among the cases, patients infected with RSV had longer NIMV receiving time compared to other agents. This situation may be caused by the fact that 57.7% of the patients infected with RSV are younger than six months.

In our study, no cost increase was demonstrated in the co-infection group compared to the RSV and RV groups. RSV cost analyzes have been evaluated in many studies in the literature. Prophylaxis with pavilizumab is the basis of RSV cost analysis studies, especially in risky infants.
(prematurity, congenital heart disease). In many studies, it has been emphasized that the high cost is due to the increased length of hospital stay due to RSV. It has been shown that the cost of inpatient treatment due to RSV is higher than the total health expenditures per capita in developed countries. (10, 11) In our study, it was shown that RSV significantly increases the cost both alone and in co-infections. In addition, RSV is the most important viral agent that increases the cost not only in risky infants but also in children under five years of age.

Considering the laboratory values of the cases, in a study conducted by Calvo et al to compare RSV, RV, and co-infections, the WBC level detected in the RV group was found to be higher than the other groups (4). In our study, the leukocytosis rate in the RV group was significantly higher than in the other groups. Midulla et al reported to compare RSV, RV, HBoV, and co-infections, blood eosinophil levels in the RV group were found to be significantly higher than the other groups (12). In our study, high eosinophils and the frequency of recurrent attacks in the RV group support the studies conducted to understand the relationship between the development of asthma and RV.

Our study has some limitations, first of all, it was designed as a retrospective study. In addition, it was carried out in a single center, on a relatively small number of patients. Another limitation is that the total invoice was evaluated in the cost data, and the invoice items were not detailed. Finally, as expected, only a small portion of the co-infection group contains viruses other than RSV and RV. There are relatively few cases in this co-infections group to compare.

In conclusion, viral co-infections constitute an important part of the etiology in patients younger than five years of age hospitalized for LRTI. Considering the burden of viral LRTI, the effect of viral co-infections on disease severity needs to be better understood. Co-infections do not cause more severe clinical findings than single viral agents. Although differences are seen with RSV and RV, they generally show a similar and intertwined clinical course and prognosis in practice. Well randomized studies with larger populations are needed to clarify the relationship between viral co-infections and the clinic of LRTIs.
Conflict of interest: All authors declare no conflict of interest.
References


**Figures legends**

1. **FIGURE 1**: Distribution of co-infections by agents.
2. **FIGURE 2**: Distribution of viral agents by months.
<table>
<thead>
<tr>
<th></th>
<th>RSV (n=116)</th>
<th>RV (n=46)</th>
<th>Co-infections (n=37)</th>
<th>Total (n=199)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender n (%)</td>
<td>55 (47.4)</td>
<td>20 (43.5)</td>
<td>16 (43.2)</td>
<td>91 (45.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Age (month±SD)</td>
<td>7.4±8.3</td>
<td>13.3±12.6</td>
<td>8.9±8.6</td>
<td>9.09±9.78</td>
<td>0.006*</td>
</tr>
<tr>
<td>Number of LRTIs attacks</td>
<td>1.54</td>
<td>2.17</td>
<td>1.27</td>
<td>1.66</td>
<td>0.001*</td>
</tr>
<tr>
<td>O2 need n (%)</td>
<td>86 (74.1)</td>
<td>29 (63)</td>
<td>30 (81.1)</td>
<td>145 (72.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>O2 uptake duration n (%)</td>
<td>6.13±4.2</td>
<td>5.04±2.6</td>
<td>5.7±2.3</td>
<td>5.84±3.6</td>
<td>0.44</td>
</tr>
<tr>
<td>Presence of fever n (%)</td>
<td>44 (37.9)</td>
<td>13 (28.3)</td>
<td>16 (43.2)</td>
<td>73 (36.7)</td>
<td>0.33</td>
</tr>
<tr>
<td>Duration of fever (days±SD)</td>
<td>2.47±1.05</td>
<td>1.73±0.64</td>
<td>2.08±0.76</td>
<td>2.26±0.97</td>
<td>0.06</td>
</tr>
<tr>
<td>Lung X-ray abnormality n (%)</td>
<td>110 (94.8)</td>
<td>41 (89.1)</td>
<td>34 (91.9)</td>
<td>185 (93)</td>
<td>0.72</td>
</tr>
<tr>
<td>Lenght of hospital stay</td>
<td>8.7±4.4</td>
<td>6.9±3.2</td>
<td>7.8±2.6</td>
<td>8.1±3.9</td>
<td>0.03*</td>
</tr>
<tr>
<td>Rate of NIMV n (%)</td>
<td>47 (40.5)</td>
<td>17 (37)</td>
<td>16 (43.2)</td>
<td>80 (40.2)</td>
<td>0.84</td>
</tr>
<tr>
<td>Duration of NIMV (days±SD)</td>
<td>4.5±2.3</td>
<td>2.6±1.4</td>
<td>3.4±2.0</td>
<td>3.9±2.2</td>
<td>0.005*</td>
</tr>
<tr>
<td>ICU admission rate n (%)</td>
<td>36 (31)</td>
<td>15 (32.6)</td>
<td>11 (29.7)</td>
<td>62 (31.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>Intubation rate n (%)</td>
<td>4 (3.4)</td>
<td>2 (4.3)</td>
<td>1 (2.7)</td>
<td>7 (3.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>Complication n (%)</td>
<td>5 (4.3)</td>
<td>2 (4.4)</td>
<td>1 (2.7)</td>
<td>8 (4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cost ($)</td>
<td>839.3±807, 6</td>
<td>580±322</td>
<td>702±547</td>
<td>753.6±684, 6</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

**TABLE 1**: Demographic data, clinical course, and cost analysis in infected patients by groups.
LRTI, Lower respiratory tract infections, O2, oxygen, NIMV, non-invasive mechanical ventilation, ICU, intensive care unit, RSV, Respiratory syncytial virus, RV, Rhinovirus
**FIGURE 1:** Distribution of co-infections by agents. RSV, Respiratory syncytial virus, RV, Rhinovirus, IV, influenza virus, PIV, parainfluenza virus, HMPV, human metapneumovirus, HBoV, human bocavirus.
FIGURE 2: Distribution of viral agents by months. RSV, Respiratory syncytial virus, RV, Rhinovirus