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Research Article

Syndromic Panel for Investigation of Agents in Patients with Acute Respiratory Tract Infections

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Abstract

Aim: The aim of this study was to evaluate the distribution, seasonal variations, co-infection patterns and age group differences of viral and bacterial agents detected by syndromic panel method in patients with acute respiratory tract infection (ARTI).

Material and Methods: In this retrospective cross-sectional study conducted in a single center between February 2023 and January 2024, nasopharyngeal swab samples of 453 patients with suspected ARTI were analyzed using QIAstat-Dx Respiratory Panel (Qiagen®). The panel detects 22 viral and atypical bacterial agents. Statistical analyses were performed with SPSS 26.0.

Results: At least one agent was detected in 45.2% of patients and positivity was significantly higher in the pediatric group (62.7%) compared to adults (33.2%) (p<0.001). The most common agents were rhinovirus/enterovirus (29.1%), SARS-CoV-2 (11.9%), influenza B (11.1%) and influenza A (11.1%). The positivity rate increased in winter and spring and decreased significantly in summer (p<0.001). Co-infection was observed in 22.9% of cases; the most common co-infection was adenovirus+rhinovirus. Bacterial agents were very rare (<1%).

Conclusion: Syndromic panel testing demonstrated that the spectrum of agents in ARTIs is broad and predominantly viral. The positivity rate is high in children and during cold seasons. The rapid and accurate results of the test, provide valuable information for epidemiological surveillance and support appropriate treatment selection; thus, it has the potential to reduce antibiotic use.

Keywords: Acute respiratory tract infections, Syndromic panel, Multiplex PCR, Viral pathogens, Co-infection

INTRODUCTION

Acute respiratory tract infections (ARTIs) are a major cause of morbidity and mortality worldwide, especially in children and adults at risk. The global annual number of deaths due to upper respiratory tract infections is estimated to have reached 3.5 million in 2008. Respiratory tract infections are one of the most common causes of hospital admission, especially in the pediatric population, and lower respiratory tract infections are among the leading causes of child mortality. In these infections, unnecessary empirical antibiotic use can frequently be observed because viral and bacterial agents cause similar clinical pictures (1). Although cough is the main complaint in more than half of the patients admitted due to upper respiratory tract infection, it has been reported that inappropriate antibiotics are prescribed to 85% of them (2). This shows that rapid and accurate viral-bacterial differentiation is critical in terms of reducing antimicrobial resistance by preventing unnecessary antibiotic use. The methods used in the diagnosis of upper respiratory tract infections show significant differences in terms of diagnostic time, sensitivity rate and clinical applicability. Although rapid antigen tests, which are among these methods, offer the advantage of rapid results, they may not accurately detect the

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presence of infection due to their low sensitivity levels. This may lead to false negative results, causing delays in disease management and erroneous clinical decisions (3,4). Although classical diagnostic methods such as virus culture offer reliability in diagnosis with their high sensitivity, the fact that it may take days to obtain the results may lead to delayed treatment decisions and delayed clinical intervention (5).

In recent years, especially in hospital settings, multi-targeted polymerase chain reaction (Multiplex PCR) tests have become an important diagnostic tool for rapid, sensitive and simultaneous diagnosis of respiratory pathogens. Among these tests, Qiastat-Dx Respiratory Panel-Qiagen is one of the tests with a wide range of targets and FDA approval. Capable of detecting more than 20 viral and bacterial agents in as little as two hours, this system has the potential to accelerate diagnosis and clinical decision-making processes by detecting viral and atypical bacterial agents with high sensitivity and specificity. With the use of respiratory panels, it is possible to switch from empirical antibiotics to targeted antiviral treatments and unnecessary antibiotic use can be prevented. However, despite its high diagnostic accuracy, the application of this method depends on limiting factors such as specialized laboratory infrastructure, high cost and the need for experienced personnel. non-pharmacological measures (masks, social distancing, etc.) implemented during the COVID-19 pandemic have significantly reduced the circulation of other respiratory viruses. With the lifting of pandemic restrictions, respiratory viruses increased again in the world in 2022-2023. It was reported that the incidence of respiratory tract infections increased significantly in 2023, especially in children, and even atypical pathogens such as Mycoplasma pneumoniae became unexpectedly dominant in some regions (6) In our country, respiratory viruses started to return to their classical seasonal cycles in the post-pandemic period. The increase in viruses such as influenza and RSV in autumn and winter, and rhinovirus circulation in spring and fall is a well-known pattern in the literature, and following these trends with up-to-date data at the local level is important for public health and clinical management (2).

In this study, the distribution of the causative agents investigated by syndromic panel (Qiastat-Dx Respiratory Panel-Qiagen) in nasopharyngeal swab samples obtained from patients with acute respiratory tract infection was examined and it was aimed to reveal the frequency, seasonal variations, co-infection patterns and distribution according to age groups of viral and bacterial agents detected according to respiratory panel results in the one-year period between February 2023 and January 2024 and to evaluate the findings obtained in the light of current literature.

MATERIAL AND METHODS

Study Design and Patient Population: This study was planned as a single-center retrospective cross-sectional analysis. Between February 2023 and January 2024, patients with suspected acute upper or lower respiratory tract infections in various departments of our hospital who were sent samples for respiratory syndromic panel by clinicians were included in the study. Each patient presentation (each specimen) was considered as a separate episode of infection. Readmissions or specimens collected for control purposes were excluded.

Laboratory Analysis (Syndromic Panel): QIAstat-Dx Analyzer 1.0 (Qiagen®, Hilden, Germany) and the QIAstat-Dx® Respiratory SARS-CoV-2 Panel were used to investigate respiratory pathogens at the molecular level. This fully automated syndromic panel system is capable of simultaneously detecting 22 viral and atypical bacterial agents in approximately 70 minutes, from sample to result in a single cartridge. This multiplex PCR-based panel includes influenza A (subtype level: H1, H1N1/2009, H3), influenza B, RSV (A/B), rhinovirus/enterovirus, four types of seasonal coronaviruses (HCoV-229E, -NL63, -HKU1, -OC43), human metapneumovirus (A/B), Parainfluenza viruses (1-4), Human bocavirus, SARS-CoV-2, Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila. PCR analyses were performed fully automatically according to the manufacturer's recommendations. Pathogen positivity was defined as positive detection of at least one target in the panel. Samples in which more than one agent was detected were defined as "co-infection".

Statistical Analysis

All data included in the study were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) software after preprocessing with Microsoft Excel® 365 (Microsoft Corp., Redmond, WA, USA). Descriptive statistics included median (interquartile range - IQR) for continuous variables and absolute number and percentage (%) values for categorical variables. Pearson's Chi-square test was used to evaluate the association of agent positivity rates with categorical variables such as age groups, gender, clinical unit, season and months: Pearson Chi-square test was used. Fisher's exact chi-square test was preferred in analyzes where more than 20% of the expected values in the cells were less than 5. When the total statistical difference was significant in the chi-square test, standardized residuals (Z-scores) were examined to understand which cells played an important role in this difference. $|Z| > 1.96$ was considered as a significant deviation. Standardized residuals (Z-scores) were also calculated to assess deviations

in the distribution of respiratory tract agents on a monthly and seasonal basis, and cut-off values of ±1.96 were accepted as indicators of statistical significance. In order to examine the relationship between co-infection status and age and ward information: Firstly, comparisons were made with the Kruskal-Wallis test, and post-hoc Dunn-Bonferroni corrected pairwise comparisons were performed for variables with significant differences. While evaluating the fluctuations in ward-based weekly positivity rates, Z-score analyses were performed for early warning purposes and Z > +1.96 was interpreted as a potential outbreak signal. In all analyses, a two-way $p < 0.05$ was accepted as the limit of statistical significance.

RESULTS

General Results

Data from a total of 453 patients who underwent syndromic panel testing during the study period were analyzed. Of these patients, 54.3% were male (n=246) and 45.7% were female (n=207). The age distribution ranged from 1 month to 96 years with a median age of 34 years (IQR: 8-69). 40.8% of patients were in the pediatric age group (0-17 years, n=185), 39.5% were in the 18-64 age range (n=179) and 19.7% were over 65 years of age (n=89). Most of the patients who underwent panel testing were hospitalized ward or intensive care unit patients, and about 30% were outpatients.

Of the 453 samples, 205 (45.2%) were positive for at least one pathogen in the panel test, while 248 (54.8%) were positive for no pathogen. Of the 205 positive cases, 109 were male and 96 were female; there was no statistical difference in positivity rates by gender (male 44.3%, female 46.4%; p=0.67). The mean age of the positive cases was 28.6 years, whereas the mean age of the negative cases was 45.3 years; it was noteworthy that the positivity rate increased with decreasing age. While the positivity rate was 62.7% (116/185) in the 0-17 age group, this rate was 33.2% (89/268) in the over 18 age group and the difference was statistically significant (p<0.001).

Distribution of Detected Agents: A total of 261 positive test results were obtained. Viral agents accounted for 99.1% of these positives, while the rate of bacterial agents remained at 0.9%. The most frequently detected pathogen was rhinovirus/enterovirus, which ranked first with 76 (29.1%) positives. This was followed by SARS-CoV-2 (11.9%; n=31), influenza B (11.1%; n=29), influenza A and its subtypes (11.1%; n=29), adenovirus (9.2%; n=24), human metapneumovirus (hMPV) (6.9%; n=18), RSV A/B (5.0%; n=13) and parainfluenza viruses (types 3 and 4 combined, n=17; 6.5%). Seasonal coronaviruses were positive in a total of 17 (6.5%) cases (most frequently HKU1). SARS-CoV-2 was detected in only 3 different months and the positivity rate was 6.8% for the whole year (Table 1).

Table 1. Frequency of Pathogens Detected by Respiratory Panel (February 2023–January 2024)

Agent	Number of Detec-ted Cases (n)	*Percentage within positive test results (%)	** Percentage within Positive Cases (%) (%)	***Percentage within All Tested Cases (%)
Rhinovirus/Enterovirus	76	29.1	%37.1	16.8
Influenza B	29	11.1	%14.1	6.4
SARS-CoV-2 (Covid-19)	31	11.9	%15.1	6.8
Adenovirus	24	9.2	%11.7	5.3
Human Metapneumovirus (hMPV)	18	6.9	%8.8	4.0
Influenza A (general) *	23	8.8	%11.2	5.1
– Influenza A (H1N1)pdm09 subtype	17	6.5	%8.3	3.8
– Influenza A H3 subtype	5	1.9	%2.4	1.1
– Influenza A H1 (old) subtype	1	0.4	%0.5	0.2
RSV (Respiratory Syncytial Virus)	13	5.0	%6.3	2.9
Parainfluenza virus 3	9	3.4	%4.4	2.0
Parainfluenza virus 4	8	3.1	%3.9	1.8
Seasonal Coronavirus HKU1	7	2.7	%3.4	1.5
Seasonal Coronavirus NL63	4	1.5	%2.0	0.9
Seasonal Coronavirus OC43	4	1.5	%2.0	0.9
Seasonal Coronavirus 229E	2	0.8	%1.0	0.4
Human Bocavirus (HBoV)	5	1.9	%2.4	1.1
Mycoplasma pneumoniae (atypi-cal)	1	0.4	%5.0	0.2
Bordetella pertussis	1	0.4	%5.0	0.2
(Chlamydophila pneumoniae)	0	0.0	%0.0	0.0
(Legionella pneumophila)	0	0.0	%0.0	0.0

** A total of 261 tests, ** A total of 205 cases, *** A total of 453 cases

Distribution of Factors by Age Groups: When our findings were analyzed according to age groups, it was found that some agents showed different distributions in pediatric and adult groups. In particular, agents such as adenovirus, influenza B, human metapneumovirus and rhinovirus were found mostly in pediatric patients. For example, 79% of adenovirus positive cases were from the pediatric age group and this difference was significant ($p<0.001$). Similarly, 26 of 29 influenza B positive cases were under 18 years of age ($p<0.001$). Most of the 18 patients with human metapneumovirus were children (17 children, 1 adult) and this difference was statistically significant ($p<0.001$). In the rhinovirus/enterovirus group, 67% of the 76 positive cases were pediatric patients and the rate of rhinovirus detection in children was significantly higher than in adults ($p<0.001$). In contrast, influenza A infections were predominantly seen in adults and older age groups; only two of the 24 influenza A positive patients were children and the rest were aged ≥18 years ($p<0.001$). SARS-CoV-2 infections were found in similar proportions in children (10 cases) and adults (21 cases) ($p>0.05$). Interestingly, RSV cases were distributed in only 4 children, 5 adults and 4 elderly patients in our study; since the numbers were low, the statistical difference was not significant ($p>0.05$), (Figure 1). Overall, positivity rates were significantly different between age groups (χ^2 test, $p < 0.001$). According to the standardized residual (Z-score) analysis performed to detail this difference; the positivity rate was found to be statistically significantly higher than expected, especially in the 0-5 age group (Positive Z = +3.01). Similarly, the positivity rate was significantly higher in the 6-12 age group (Positive Z = +2.31). This indicates that both the incidence of respiratory tract infections and the rate of detection with diagnostic tests are higher in the pediatric age group.

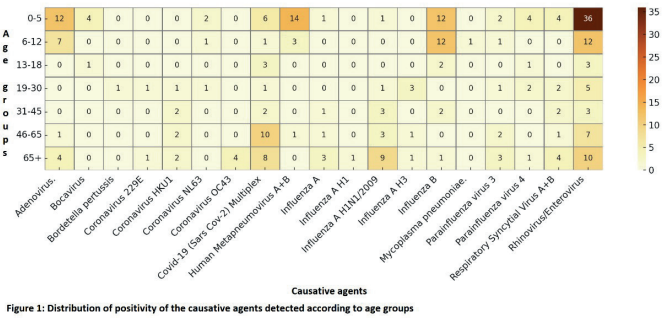

Figure 1: Distribution of positivity of the causative agents detected according to age groups

Seasonal Distribution: During the one-year period covered by our study, significant differences were found in the distribution of agents according to seasons and months (Figure 2). In general, there was an increase in positivity rates in the fall and winter months and a significant decrease in the summer months. In seasonal comparison, viral positivity rates were highest in winter (58.9%) and spring (60.7%), and lowest in summer with 13.8% ($p<0.001$) (Figure 3). Notably, 61 (70.1%) of the 87 patients tested in March 2023 were positive for at least one agent, the highest annual positivity rate. This was followed by high positivity rates of 54.1% in April 2023 and 59.7% in January 2024. During the summer months of June-August 2023, both the number of test requests decreased (around 15, especially in June and July) and the positivity decreased to the 10-20% range. In the fall 2023 period (September-November), positivity rates hovered between 25-40%. When analyzed on a monthly basis, it is understood that more than one agent such as rhinovirus, adenovirus, influenza B and hMPV were circulating at the same time in the March-April 2023 period (Table 2).

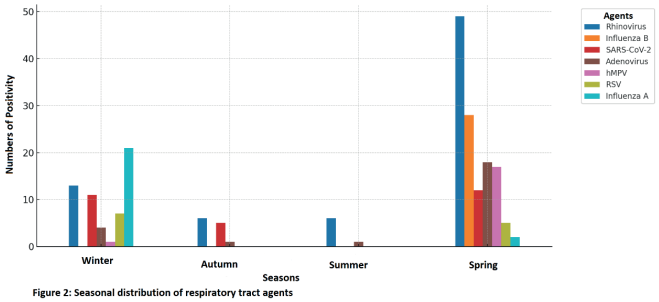

Figure 2: Seasonal distribution of respiratory tract agents

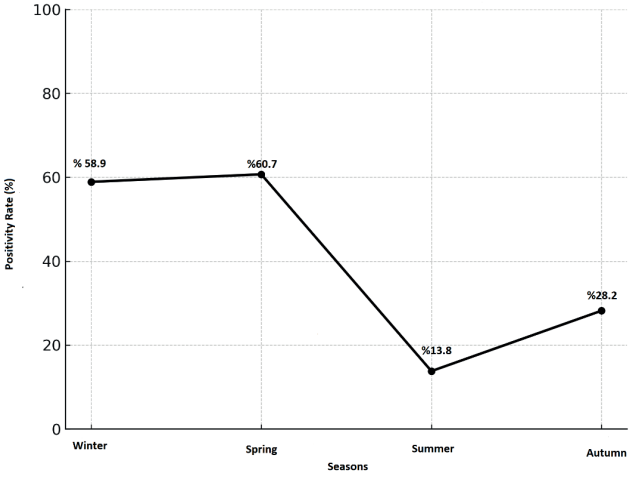

Figure 3: Seasonal positivity rates based on individual patient data

Table 2: Monthly Distribution of Positive Tests According to Pathogen

Pathogen Name	Feb. 2023	Mar. 2023	Apr. 2023	May. 2023	Jun. 2023	Jul. 2023	Aug. 2023	Sep. 2023	Oct. 2023	Nov. 2023	Dec. 2023	Jan. 2024	Total
Adenovirus.	0	12	6	0	1	0	0	0	1	0	0	4	24
Bocavirus	0	2	1	0	0	1	1	0	0	0	0	0	5
Bordetella pertussis	0	0	0	0	0	0	0	0	0	0	0	1	1
Coronavirus 229E	0	0	0	0	0	0	1	0	0	0	0	1	2
Coronavirus HKU1	0	0	0	1	0	0	0	0	1	2	0	3	7
Coronavirus NL63	0	0	3	0	0	0	0	0	0	0	0	1	4
Coronavirus OC43	0	0	0	0	0	0	1	0	1	0	0	2	4
Covid-19 (Sars Cov-2)	3	9	3	0	0	0	0	2	3	3	1	7	31
Human Me-tapneumovirus A+B	0	8	9	0	0	0	0	0	0	0	0	1	18
Influenza A	1	1	0	0	0	0	0	0	0	0	0	4	6
Influenza A H1	0	0	0	0	0	0	0	0	0	0	0	1	1
Influenza A H1N1/2009	1	1	0	0	0	0	0	0	0	0	0	15	17
Influenza A H3	0	0	0	0	0	0	0	0	0	0	0	5	5
Influenza B	1	10	18	0	0	0	0	0	0	0	0	0	29
Mycoplasma pneumoniae.	0	0	0	0	0	0	0	1	0	0	0	0	1
Parainfluenza virus 3	0	0	1	0	2	0	0	2	1	0	1	2	9
Parainfluenza virus 4	0	1	3	0	1	1	0	1	0	1	0	0	8
Respiratory Syncytial Virus A+B	1	5	0	0	0	0	0	0	0	0	1	6	13
Rhinovirus/ Enterovirus	2	30	18	1	2	1	3	4	2	2	3	8	76

Jan. : January, Feb. : February, Mar. : March, Apr. : April, Jun. : June, Jul. : July, Aug. : August, Sep. : September, Oct. : October, Nov. : November, Dec. : December

Co-Infections: The presence of more than one agent in the same sample (co-infection) was also investigated with the panel test. The co-infection rate in the entire study population (n=453) was calculated as 10.4%. Two different agents were detected together in 40 (19.5%) of the positive cases (double infection), three different agents were detected together in 5 (2.4%) cases and four agents were positive together in 2 (1.0%) cases. In other words, 47 patients (22.9%) were infected with more than one agent. The most common viral co-infection duos were adenovirus + rhinovirus (9 cases) and hMPV + rhinovirus (4 cases). In addition, SARS-CoV-2 + rhinovirus, adenovirus + RSV and hMPV + influenza B co-infection were detected in 3 cases each. When the demographic distribution of the cases with co-infection was analyzed, it was found that 26 were children and 21 were adults; there was no significant difference in the rates of co-infection between children and adults (22.4% of child positives and 23.6% of adult positives carried multiple agents; p>0.05). In the co-infection analysis, an inter-agent relationship network was created based on patients with more than one viral agent at the same time. In this network analysis, rhinovirus/enterovirus group was found to be the most co-infected agent with all other agents; it stood out as the agent at the center of the network and had the highest number of connections (centrality score: 0.647). The analysis also showed that Adenovirus, SARS-CoV-2, Respiratory Syncytial Virus (RSV A/B) and Influenza A also had a high number of connections in the network and were co-infected with many different viruses (Figure 4).

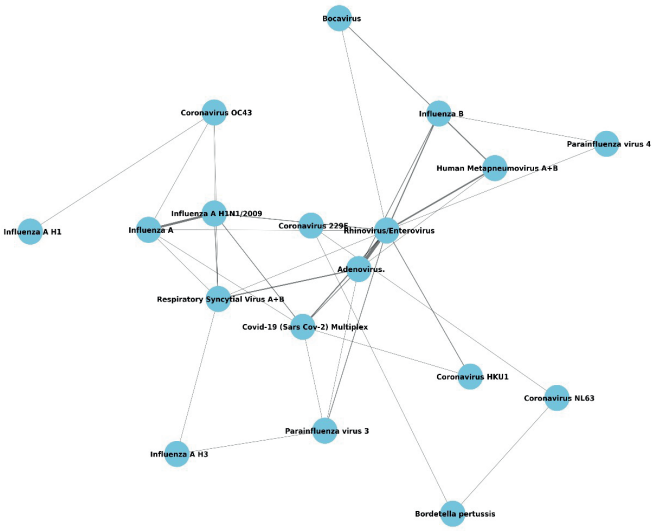

Figure 4: Co-Infection Network (Relationship between Agents)

In this study, we also grouped the positive test results according to the number of causative agents detected per patient and compared these groups with variables such as age, ward and test time. A statistically significant correlation was found between the number of positive tests and age (Kruskal-Wallis test, p = 0.040). In the post-hoc analysis performed to detail this difference, it was determined that the mean age of patients who were positive for ≥4 agents was significantly different from patients who were positive for 1 or 2 agents (p = 0.0263 for 1 vs 4+, p = 0.0473 for 2 vs 4+).

In this study, positivity rates between wards were found to differ significantly (p<0.001). According to the standardized residual (Z-score) analysis performed to evaluate the contribution of the wards to this difference, only two wards showed statistically significant deviation: Pediatrics and Intensive Care. The positivity rate in patients tested in the Pediatrics service was significantly higher than expected (Z=+ 3.75), whereas the positivity rate in the Intensive Care unit was statistically significantly lower than expected (Z= - 3.13).

In our study, possible sudden outbreak signals were statistically analyzed by evaluating weekly positivity rates by wards. For this purpose, standardized residuals (Z-scores) were calculated over weekly positivity rates in each ward and a Z > 1.96 was considered as an early outbreak indicator. As a result of the analysis, Z-score did not exceed this limit in any ward + week combination. The highest positivity rates were observed in Pediatrics, Pediatric Emergency, and outpatient clinic wards, reaching up to 100% in some weeks. However, these high rates occurred mostly in weeks when the number of tests was low, and therefore did not reach a level that would constitute a statistically significant outbreak signal.

DISCUSSION

In this study, nasopharyngeal swabs obtained from 453 patients with suspected acute respiratory tract infection were investigated for the causative agent using the syndromic panel method. The positivity rate found (45.2%) is compatible with the values reported in the literature and studies involving all age groups generally report positivity rates between 30-50% (7-9). When the seasonal distribution was analyzed, it was found that the positivity rates showed significant seasonal fluctuations. While the positivity rate was particularly high in winter (58.9%) and spring (60.7%), this rate decreased significantly in summer (13.8%) (P<0.001). This reflects the classical seasonal cycle of respiratory viral agents. It is well known that respiratory tract infections in the northern hemisphere increase in the fall and winter months and decrease in the summer (2). It has been shown that environmental temperature and humidity affect the transmission of viruses and especially low humidity and cold weather facilitate the spread of droplet-borne respiratory viruses (10,11). The findings of this study confirm that viral infections become more frequent in the winter season, when close contact increases due to low humidity and closed environments, and decrease in the summer.

In this study, he observed a very high positivity rate in March 2023, a month that is thought to have seen an increase in cases as the ongoing winter wave of influenza B and hMPV coincided with the early spring surge of rhinovirus and adenovirus. Similarly, a strong influenza A wave was detected in January 2024. These findings suggest that there may be variability in the circulation of viruses each year and that the timing of influenza and similar epidemic waves may change. Reports of shifts in the seasonal cycles of influenza viruses after the COVID-19 pandemic also support this finding (12-15).

When the distribution of the agents we detected was analyzed, it was noteworthy that the rhinovirus/enterovirus group was most frequently positive. Rhinovirus is the most common cause of the common cold, especially in children, and it is a virus that can remain in circulation throughout the year but can peak in spring and fall (16). In our data, an increase in rhinovirus positivity was observed especially in March-April and rhinovirus was detected in 37% (76 cases) of all positive cases. This rate is compatible with the 30-40% band reported in the literature and even higher in some pediatric cohorts (7,17). Although rhinovirus often causes upper respiratory tract infections with a mild course, it has been reported that it may also cause severe lower respiratory tract infections, especially in young infants and those with underlying chronic disease (16).

The second most common agents were influenza viruses. In total, 58 influenza cases (29 A and 29 B) were detected. The majority of influenza A cases belonged to the seasonal outbreak in winter 2023-24 (H1N1 and H3 subtypes in January 2024). Influenza B cases were clustered in March-April 2023. This suggests that influenza B can sometimes peak late in the season, after influenza A. In the winter of 2022-2023, a prolonged second wave of influenza B was reported in Turkey (18-20). Our data also support this. The total positivity rate for influenza A and B is 12.8% (58/453) when compared to all patients tested. These data indicate a moderate influenza activity in the post-pandemic period. In a study conducted in adult patients in Edirne, influenza A positivity was reported as 3.7% and influenza B positivity as 4.2% in the 2023-2024 season (21). Since our study included all ages and included pediatric cases during the period of intensive testing for influenza, influenza rates were slightly higher. When we looked at the age distribution of influenza cases, we found that influenza B was mostly seen in children and influenza A in adults. This difference has been reported before; influenza B generally causes infection at a higher rate in children and young people, while influenza A can cause serious epidemics especially in older adults (22, 23).

COVID-19 (SARS-CoV-2) cases also played an important role in this study. A total of 31 patients (15.1%) were positive for SARS-CoV-2 PCR. A slight increase in COVID-19 cases was also observed in autumn 2023 (a total of 6 cases in Octo-

ber-November). In January 2024, SARS-CoV-2 was detected in 7 cases. In this period, it can be said that although the pandemic effect of COVID-19 has decreased in our country, it has not completely disappeared and has started to follow a seasonal course. In a study conducted in adults alone in Edirne, COVID-19 positivity was found to be 18.6% in the 2023-24 season (21). In our study, COVID-19 was analyzed together with other viruses since all age groups and a wider agent panel were included. Although there was a slight dominance of the older age group among positive COVID-19 cases (14 adults, 8 older adults, 9 children), SARS-CoV-2 was detected in all age groups and the age/sex difference was not statistically significant ($p>0.05$).

Looking at the clinical presentation areas for SARS-CoV-2, the highest number of positive cases came from intensive care units (n=13) and infectious diseases units (n=8). In addition, positive cases, especially from pediatric health and diseases, pediatric emergency, and pediatric hematology-oncology services, indicate that COVID-19 still poses a significant morbidity risk in pediatric and immunosuppressed patient groups. It has also been shown in the literature that COVID-19 has a longer viral shedding and severe clinical course in immunocompromised individuals (24). The findings show that COVID-19 continues to be a pathogen that needs to be carefully monitored even during the transition to its endemic form. Although the pandemic intensity has decreased, case increases are observed especially in winter and spring months and vulnerable populations, especially immunocompromised individuals, are affected. Therefore, it may be recommended to develop seasonal surveillance systems for COVID-19, plan vaccine reminder doses in vulnerable groups and expand diagnostic tests seasonally.

Another frequently detected agent was adenovirus. Adenoviruses are viruses that cause frequent infections in childhood and usually lead to upper respiratory tract infections with a mild course. Some serotypes cause pharyngitis and conjunctivitis and rarely lead to severe pneumonia. In our study, adenovirus PCR positivity was detected in 24 patients and 79% of them were pediatric patients. In a significant proportion of adenovirus positive cases (9 cases), rhinovirus or another virus was also detected at the same time (co-infection). This finding suggests that adenovirus is a virus that can coexist with other viruses and can be a carrier. In a study conducted in Turkey, the rate of adenovirus detection in pediatric patients was reported to be 5% and it was determined that the infection progressed as co-infection with other pathogens in a large proportion of the cases in which adenovirus was detected (68%; 17/25) (2). In our pediatric group, it was found to be around 10%. This difference may be due to the season and population in which the tests were performed. Our study showed that adenovirus infections in Afyonkarahisar region became more prominent especially in the spring months (12 cases in March and 6 cases in April).

Human metapneumovirus (hMPV), similar to RSV, is a virus that can cause lower respiratory tract infections especially in young children. In our study, hMPV was detected in 18 cases and almost all of them were pediatric patients (mean age ~4 years). Most of the cases were in the March-April period (early spring). This finding confirms the knowledge that hMPV usually causes outbreaks in late winter and early spring. As a matter of fact, an increase in hMPV infections in our country in March 2023 was also reported by other centers (8). In our study, rhinovirus or influenza B was also detected in some of the hMPV cases; although it is known that hMPV may cause co-infection, the clinical course of this condition may generally be similar to single infection (25-27).

Among the seasonal coronaviruses in the panel, HKU1, NL63, OC43 and 229E subtypes were positive in a total of 17 cases. Most of these cases were adults and elderly patients. Considering that seasonal coronaviruses are widely circulated in the community and usually cause cold-like symptoms, the low number of detections is an expected finding. Probably because many mild cases were not admitted to hospital, the detection rate of these viruses in the tested population remained low.

Among the parainfluenza virus (PIV) subtypes in the panel, only type 3 (9 cases) and type 4 (8 cases) were found to be positive, while types 1 and 2 were not detected in any sample. In the literature, PIV-3 infections show a seasonal distribution with an increase every year, especially between April and June. Moreover, in years when PIV-1 infection is not endemic, PIV-3 may progress with a second peak with a lower intensity during a longer spring season or in November-December (28). In our study, in a year when PIV-1 was not detected, PIV-3 positivity was found compatible with the seasonal distribution reported in the literature with 3 cases in April-June and 4 cases in September-December. Although parainfluenza type 4 is generally a rare subtype, it was found to be positive in 7 cases in our study. The fact that PIV-1 and PIV-2 were not detected may be related to the fact that the sampling period may have been outside these cycles, especially since PIV-1 characteristically outbreaks every two years (biennially) and in the fall-winter months. In addition, it is thought that regional climatic differences may also have an effect on the circulation of these subtypes (28, 29).

Human bocavirus (HBoV) is a DNA virus that can cause respiratory tract infections, especially in young children. Although tested in our panel, HBoV positivity was found in only 5 pediatric patients in our study and all of them were associated with other viruses such as rhinovirus or adenovirus. In the literature, HBoV is frequently reported as co-infection and it is still controversial whether it causes disease alone (30). Our findings suggest that HBoV is rarely detected as the sole agent and its clinical significance may be limited.

Among the atypical bacterial agents investigated in the panel, Mycoplasma pneumoniae was positive in 1 patient (5-year-old child, March), while Bordetella pertussis was positive in 1 patient (75-year-old adult with COPD, February). Except for these two patients, all other samples were negative for bacterial agents. Chlamydophila pneumoniae and Legionella pneumophila were not detected in any patient. These results indicate that the majority of respiratory tract infections in our study population were viral in origin. Similarly, other studies have also found low rates of bacterial agent detection in the respiratory tract panel. For example, in one study, bacterial agents alone were detected in only 7 of 915 patients and virus-bacteria co-infection was detected in 12; viral agents alone were found responsible in the remaining 96% (2). In our study, 99.1% of the positive cases had at least one viral agent; bacterial agents played a role in only 0.9%. This finding suggests that antibiotics may be largely unnecessary in acute respiratory tract infections. It has been emphasized in many publications that unnecessary use of antibiotics can be prevented by rapid diagnosis of viral agents and this will contribute to the control of antibiotic resistance (7).

In this study, the positivity rate was significantly higher than expected in patients tested in the Pediatrics service (Z=+3.75). In parallel with this finding, it was found that respiratory syndromic panel test results differed significantly depending on age. In the 0-5 age group, the positivity rate was statistically significantly higher (Z = +3.01). Similarly, the positivity rate was found to be significantly higher in the 6-12 age group (Z = +2.31). This high positivity rate is associated with several reasons. Firstly, since the immune system in children is still in the process of development, they are more susceptible to viral agents. In addition, since there is more contact and droplet transmission in crowded environments such as nurseries, kindergartens and primary schools, the spread of respiratory tract infections can be expected to be easier. In addition, since test ordering in pediatric patients is generally more selective and symptom-oriented, the clinical accuracy of test positivity is also increased. The high positivity rate obtained is consistent with panel positivity data reported up to 60-80% in pediatric patients in the literature (31,32). In a multicenter study conducted by Kim et al. (2018), 78.9% positivity was reported in children aged 0-5 years, whereas this rate decreased to 27.2% in people over the age of 50 (33). In our study, positivity rates were lower in groups aged 13 years and older, and no significant deviation was observed in these age ranges. This finding may be explained by the fact that test requests in this age group are based on more heterogeneous clinical pictures or that the immune system in this age group is more prepared against the agents due to past contacts.

Among the wards, the positivity rate was found to be statistically significantly lower than expected in the Intensive Care Unit in contrast to the Pediatrics Unit (Z= -3. 13). This may be attributed to the fact that the threshold for requesting a test is lower in intensive care patients, i.e. they may be asymptomatic or sent tests with alternative diagnoses. In addition, factors such as early initiation of antibiotic or antiviral treatments or underlying comorbidities causing symptoms in these patients may reduce the rate of diagnosed active viral infection. In addition, positivity rates in clinics such as Infectious Diseases, Emergency Department and Internal Medicine were within expected limits and did not show significant deviation.

These results suggest that attention should be paid to the patient profile and sampling strategy in the ordering and interpretation of laboratory tests. Especially in patient groups with multifactorial symptoms such as intensive care unit and syndromic panel tests, ordering only with clinical correlation and appropriate indications will increase their diagnostic value; evaluation of test order indications and pretest possibilities by ward may make these tests more cost-effective.

In our study, the inter-agent relationship network was analyzed; in this network analysis, it was observed that the rhinovirus/enterovirus group was the most frequently co-infected agent with all other agents (Figure 4). In the literature, it has been determined in many studies that rhinovirus frequently co-infects with other respiratory tract viruses (33-35). The fact that rhinovirus shows such a widespread co-infection profile may be associated with the high circulation frequency of this virus and its capacity to produce widespread symptoms.

The analysis also revealed that Adenovirus, SARS-CoV-2, Respiratory Syncytial Virus (RSV A/B) and Influenza A had a high number of connections in the network and were detected together with many other viruses. This may be due to the common transmission routes of these agents and their peaks

during the same seasonal periods. It has been reported in the literature that the co-infection rates of these viruses can be up to 10% (35,36). These network analysis results support clinicians to consider the possibility of multiple viral agents, especially in patients with atypical symptoms or those who do not respond to treatment, considering the possibility of multiple infections. It also suggests that co-infections should be taken into account when planning in-hospital outbreak control and isolation measures.

In addition, there was a statistically significant correlation between the number of positive causative agents of co-infection and age (Kruskal-Wallis test, p = 0.040). In the post-hoc analysis performed to elaborate this difference, it was determined that the mean age of patients who were positive with ≥4 agents was significantly different compared to patients who were positive with 1 or 2 agents (p = 0.0263 for 1 vs 4+, p = 0.0473 for 2 vs 4+).

These findings suggest that cases with multiple viral agent positivity are concentrated in childhood. It can be said that the childhood age group is more prone to viral co-infections due to both environmental transmission risks (such as kindergarten, school) and immaturity of the immune system. In addition, immunological immaturity and receptor expression differences in the respiratory tract mucosa are among the factors that facilitate multi-agent colonization in this group (37). Therefore, it should be kept in mind that multiple agents detected in syndromic panel tests in the pediatric age group should be evaluated carefully; the specificity of symptoms may decrease and treatment management may be complicated.

In our study, possible sudden outbreak signals were statistically analyzed by evaluating weekly positivity rates according to wards. As a result of the analysis, Z- did not reach a level that would constitute a statistically significant outbreak signal in any ward + week combination. This analysis constitutes an important example for passive surveillance and early warning systems at hospital level and shows that syndromic panel results can also be used for epidemiologic surveillance. However, since non-routine requests for panel tests (e.g. immunosuppressed patients, intensive care cases) may lead to results independent of outbreak dynamics, test ordering behavior should also be taken into account in such analyses.

Study Limitation

Our study has several limitations. First, its retrospective and single-center design may cause the findings to be specific only to the patient population of the center where the study was conducted. This may limit the generalizability of the results to different geographical regions or healthcare institutions. In addition, due to the limited sample size, it needs to be supported by multicenter and prospective studies with larger samples. In particular, the imbalance in the number of patients tested according to months (such as fewer tests in summer months) may not reflect the true incidence of some agents. In addition, our study did not analyze the clinical correlates of the agents (severity of illness, length of stay, etc.) in depth. Clinical outcomes of co-infections were not analyzed. In the future, it would be useful to support these findings with prospective designed, multicenter studies including clinical data from different regions.

CONCLUSION

This syndromic panel study shows that the spectrum of causative agents in patients with acute respiratory tract infections is wide and viral agents play a dominant role. Rhinovirus, influenza, RSV, adenovirus, human metapneumovirus and SARS-CoV-2 were the most frequently detected agents during this period. Positivity rates increased significantly in the fall and winter months and decreased in the summer. The detection rate of viral agents in pediatric patients was significantly higher than in adults (p<0.001). Co-infections were seen in approximately one quarter of the cases and the most common association was adenovirus and rhinovirus. Bacterial agents investigated in the panel were found very rarely. Our data are consistent with other studies in the literature and confirm that molecular tests have high detection rates in the diagnosis of respiratory tract infections.

The use of rapid and sensitive diagnostic tools such as a respiratory panel provides clinicians with early information about the causative agent, allowing them to prevent unnecessary antibiotic use, start antiviral treatment on time and isolate the patient when necessary. This is critical for both patient health and public health. In our study, it was understood that empirical antibiotic treatment would not be necessary in a significant portion of this patient group, in which viral agent was detected in approximately half of them by syndromic panel. In conclusion, the rational use of syndromic panel tests in acute respiratory tract infections accelerates the correct diagnosis, directs appropriate treatment and reduces the burden on the healthcare system. The epidemiologic data obtained reveal the seasonal trends of respiratory tract pathogens circulating in our region and provide valuable information for future epidemic predictions.

Ethics committee approval

This study was conducted with the approval of Afyonkarahisar Health Sciences University Non-Interventional Clinical Research Ethics Committee (Date: 02.08.2024 - Number: 2024/275).

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