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Assessment of Respiratory Viral Co-infections Among SARS-CoV-2-Infected Patients

SARS-CoV-2 ile İnfekte Hastalarda Solunum Yolu Viral Koinfeksiyonların Değerlendirilmesi

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ABSTRACT

Introduction: *Emerging evidence suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients are at an increased risk for co-infections. The aim of this study was to assess the prevalence of respiratory viral co-infections among SARS-CoV-2 patients via molecular testing.*

Materials and Methods: *Nasopharyngeal swabs of 68 SARS-CoV-2 positive cases detected between December 1, 2020 and December 20, 2021 were subjected to nucleic acid isolation and screening using molecular techniques. Real-time-qPCR analysis was performed using the FTD Respiratory Pathogens 21 Panel Kit. Positive results were further confirmed by QIAstat-Dx™ Respiratory Panel.*

Results: *Co-infections were detected in 7.4% (n= 5/68) of SARS-CoV-2-infected patients. Commonly observed co-infecting pathogens were rhinovirus, parainfluenza virus 4, influenza A H3N2, bocavirus, respiratory syncytial virus, and adenovirus. Overall, co-infections were observed in the ≤35 age group. Patients with co-infections did not require hospitalization.*

Conclusion: *Simultaneous identification of respiratory co-infections in SARS-CoV-2 positive patients offers the possibility of implementing optimized treatment regimens preventing morbidity and mortality.*

Key Words: *COVID-19; SARS-CoV-2; Co-infection*

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ÖZ

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Giriş: *SARS-CoV-2 ile infekte hastaların koinfeksiyon riskinin arttığı birçok çalışma ile gösterilmiştir. Bu çalışmanın amacı, SARS-CoV-2 pozitif hastalarda solunum yolu viral koinfeksiyon prevalansının moleküler yöntemlerle değerlendirilmesidir.*

Materyal ve Metod: *Çalışmada, 1 Aralık 2020 ve 20 Aralık 2021 tarihleri arasında saptanan 68 SARS-CoV-2 pozitif olgunun nazofarengeal sürüntüleri nükleik asit izolasyonu ve moleküler teknikler kullanılarak solunum yolu viral patojenleri açısından tarandı. Gerçek zamanlı ters transkripsiyon-kantitatif polimeraz zincir reaksiyonu (RT-qPCR) analizi, FTD Solunum Patojenleri 21 Panel Kiti kullanılarak yapıldı. Pozitif sonuçlar, QIAstat-Dx™ Respiratory Panel ile konfirme edildi.*

Bulgular: *SARS-CoV-2 ile infekte hastaların %7.4'ünde (n= 5/68) koinfeksiyon tespit edildi. Koinfeksiyon oluşturan patojenler arasında rhinovirüs, parainfluenzavirüs 4, Influenza A virüs H3N2, bocavirüs, respiratuvar sinsityal virüs ve adenovirüs saptandı. Koinfeksiyonlar ≤35 yaş grubunda gözlendi. Koinfeksiyonu olan hastalarda hastaneye yatış gerekmediği belirlendi.*

Sonuç: *SARS-CoV-2 pozitif hastalarda eş zamanlı solunum yolu infeksiyonlarının tanımlanması, optimize edilmiş tedavi protokollerinin uygulanmasını sağlayarak morbidite ve mortaliteyi önleme olasılığını sunmaktadır.*

Anahtar Kelimeler: *COVID-19; SARS-CoV-2; Koinfeksiyon*

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA virus that causes severe fatal pneumonia[1,2]. The infection was first reported in Wuhan, China in late December 2019, and was later named coronavirus disease-19 (COVID-19). SARS-CoV-2 rapidly spread across continents and was later declared a pandemic by the World Health Organization (WHO) in March 2020[1]. In June 2022, there have been more than 546 million cases and more than six million deaths, which were attributed to SARS-CoV-2 infection[3].

Today, despite the initiation of a global vaccination program, the potential emergence of new variants poses a threat to the effectiveness of the vaccination strategies developed[4]. Moreover, effective treatment regimens for COVID-19 have not been established yet, despite the promising results obtained from various approaches that were investigated early in the pandemic[5]. Therefore, it is of paramount importance to identify factors associated with severe COVID-19 disease and initiate additional medical attention to those in need as early as possible in the treatment[6].

Co-infection of SARS-CoV-2 with other microbial pathogens such as viruses, bacteria, and fungi has been observed since the beginning of the pandemic. Co-infection has been suggested to be an important factor in COVID-19 as it can lead to difficulties in the diagnosis, treatment, and prognosis of the disease[1,7]. Of those microbial agents, respiratory viruses including human metapneumovirus (hMPV), respiratory syncytial virus (RSV), rhino/enterovirus (RV), influenza viruses (Inf A and Inf B), human parainfluenza virus (HPIV) and other human coronaviruses (hCoV) have been proposed to cause co-infection in at least 6.6% of the COVID-19 cases[8].

To date, there are no epidemiological data concerning the co-infection of SARS-CoV-2 with other respiratory viruses from Northern Cyprus. Our study aims to fill this gap in the literature by retrospectively screening nasopharyngeal swab samples collected from SARS-CoV-2-positive

patients admitted to a university hospital in Northern Cyprus between December 2020 to February 2021.

MATERIALS and METHODS

This study was retrospectively performed. A total of 68 laboratory-confirmed COVID-19 patients, diagnosed between December 1, 2020 and December 20, 2021 were evaluated for the presence of other viral respiratory pathogens. The time period was chosen to represent the peak season for respiratory viruses in Cyprus. Laboratory confirmation of COVID-19 was performed by real-time reverse transcription-PCR (RT-PCR) on combined oropharyngeal/nasal swab specimens. Patient demographic and clinical information including age, gender, laboratory results, and disease outcomes were collected.

Patients' oropharyngeal/nasopharyngeal specimens were collected using sterile swabs and placed in a three mL lysis buffer solution provided by the manufacturer (RTA Laboratories Inc., Türkiye). Patient samples were transported to the laboratory at 4°C. The samples were vortexed for 20 seconds in a lysis buffer and SARS-CoV-2 RT-PCR was performed directly from the lysate samples using Diagnovital® HS SARS-CoV-2 Real-Time PCR Kit (RTA Laboratories Inc., Türkiye) which detects SARS-CoV-2 N1 and N2 regions of the nucleocapsid gene as well as human extraction control RNaseP gene. For RT-PCR, 15 µL of master mix containing primer/probe sets and enzyme mix was used with 5 µL of swab extract. The thermal profile used was: 45°C for 10 min, 95°C for 2 min, 40 cycles of 95°C for 3s, and 60°C for 10s. Real-time-PCR was performed using Insta Q96TM Plus Real-time PCR Detection System (HiMedia Laboratories Pvt. Ltd.). Cycle threshold (Ct) value of <38 was considered to be positive for SARS-CoV-2.

Samples that were positive for SARS-CoV-2 RNA were further screened for the presence of other respiratory viruses. Total nucleic acid extraction was performed using GeneAll Ribospin vRD RNA Extraction Kit (GeneAll Biotechnology, South Korea). The FTD respiratory pathogens 21 (FTD-21) assay (Fast Track Diagnostics, Luxembourg) was performed, which is a one-step RT-PCR comprising primer-probe mixtures for the simultaneous amplification of 21 respiratory pathogens including Inf A virus, Inf A (H1N1) virus (swine lineage), Inf B virus, rhinovirus (RV), coronavirus NL63, 229E, OC43, HKU1, HPIV-1, 2, 3, 4, hMPV A/B, bocavirus (BoV), RSV A/B, adenovirus, enterovirus, parechovirus and *Mycoplasma pneumoniae*, and equine arteritis virus which serves as an internal control. The FTD-21 assay was performed according to the manufacturer's instructions. For RT-PCR, 10 µL of extracted nucleic acid samples were mixed with 15 µL of master mix containing 12.5 µL of 2x RT-PCR buffer, 1.5 µL of the primer/probe mix, and 1 µL of the enzyme. RT-PCR was performed using Insta Q96TM Plus Real-Time PCR Detection System (HiMedia Laboratories Pvt. Ltd.) and RotorGene Q Real-Time PCR System (Qiagen, Hilden, Germany). The thermal profile for the multiplex RT-PCR was: 50°C for 15 min, 94°C for 1 min, 40 cycles of 94°C for 8s, and 60°C for 1 min. A patient sample was considered to be positive for a specific pathogen if an amplification with a sigmoidal curve within a Ct value of <40. Internal control was used to assess the quality of nucleic acid extraction and PCR inhibition. Samples that were found to be co-infected with another viral pathogen were confirmed using the QIAstat-Dx System (Qiagen, Hilden, Germany) with Respiratory SARS-CoV-2 Panel. For confirmation, 330 µL of the nasopharyngeal swab was used to load the panel cartridge according to the manufacturer's recommendations. All commercial kits used in this study are CE-IVD certified. Additionally, Diagnovital® HS SARS-CoV-2 Real-Time PCR Kit and QIAstat- Respiratory SARS-CoV-2 Panel Kit were both Food and Drug Administration (FDA) (Emergency Use Authorization, EUA) approved during the time of use.

RESULTS

A total of 68 patients who were SARS-CoV-2 positive were screened for the presence of other viral respiratory infections. Out of 68 patients, 40 (58.8%) were male and 28 (41.2%) were female, with a mean (± standard deviation) age of 43.3 ± 15.7 years (range of age 19-80

years). Overall, five (7.4%) patients were positive for other viral respiratory viruses. Among the co-infected COVID-19 patients, two were positive for RV, one patient was identified to have a triple co-infection with HPIV-4 and BoV, one patient was co-infected with Influenza A H3N2 while another patient had a triple co-infection with RSV and adenovirus.

One of the RV co-infected individuals (patient 9) was a 27-year-old female who was not vaccinated at the time of infection. The patient presented with fever, loss of taste and smell, joint pain, myalgia, shortness of breath, and fatigue, which lasted for a week. The patient was hospitalized for one night and was later followed up at home until recovery. The second RV co-infected patient (patient 12) was a 35-year-old male who was not vaccinated at the time of infection. The patient experienced severe headaches, fatigue, and loss of taste and smell. Notably, the loss of taste and smell persisted for an extended duration of up to three months.

The COVID-19 patient (patient 18) with HPIV-4 and BoV triple co-infection was a 34-year-old female, who was unvaccinated at the time of infection. The patient presented with fever, throat pain, runny nose, cough, myalgia, and fatigue, which lasted for ten days, and was followed up as an out-patient in a government-allocated pandemic residence. The COVID-19 patient (patient 67) who had a co-infection with Influenza A H3N2 was a 22-year-old female. The patient had a high fever, severe cough, and loss of taste and smell which lasted for a week. The patient was examined upon admission to the hospital and posteroanterior chest radiography was normal. The patient presented with post-COVID symptoms such as malaise for up to a week. The patient did not have any comorbidities and was reported to be vaccinated with two doses of the CoronaVac vaccine and two doses of the Pfizer BioNTech vaccine, of which the second dose was administered three weeks prior to the COVID-19 infection. The patient also tested positive for Influenza A + B antigen rapid test.

Similarly, a 34-year-old male patient (patient 68) was found to have a triple co-infection with RSV and adenovirus. The patient presented with cough and nasal congestion symptoms prior to testing positive for SARS-CoV-2 RT-PCR. The patient did not take any preventive medicine. Following the COVID-19 infection, the patient had severe headaches for up to 4 days. The patient was reported to be vaccinated with three doses of the CoronaVac vaccine and a single dose of the Pfizer BioNTech vaccine at the time of SARS-CoV-2 infection. The amplification curves of respiratory viral pathogens detected in co-infected COVID-19 patients are given in Figure 1.

Overall, the predominant infection observed in the infected patients was SARS-CoV-2, as indicated by a lower Ct value. However, in the case of patient nine, the viral load of respiratory virus (RV) was found to be higher than that of SARS-CoV-2. Details of the molecular characterization of co-infected patients can be found in Table 1.

DISCUSSION

The recent outbreak of COVID-19 continues to threaten global public health. Nevertheless, despite their potential influence on COVID-19 severity, the current literature on respiratory microbial co-infections with SARS-CoV-2 is still scarce[9]. The aim of the current study was to provide preliminary data on the respiratory viral co-infection rates among SARS-CoV-2 positive patients in Northern Cyprus, which will encourage additional association studies to determine their possible effect on disease severity in the region.

The molecular analysis in our study demonstrated the presence of respiratory viral co-infection in 7.4% of the COVID-19 patients screened. A recent meta-analysis of studies which was performed between December 2019 and March 2021 estimated a higher rate (6.6%) of respiratory viral co-infection[8]. This difference in viral detection can be attributed, at least in part, to the limitations of the RT-PCR kit used, as it may not be capable of detecting certain viruses such as Epstein-Barr virus (EBV) and Human Herpesvirus-6 (HHV-6). These two respiratory viral pathogens have been reported to have a high rate of co-infection with SARS-CoV-2[8].

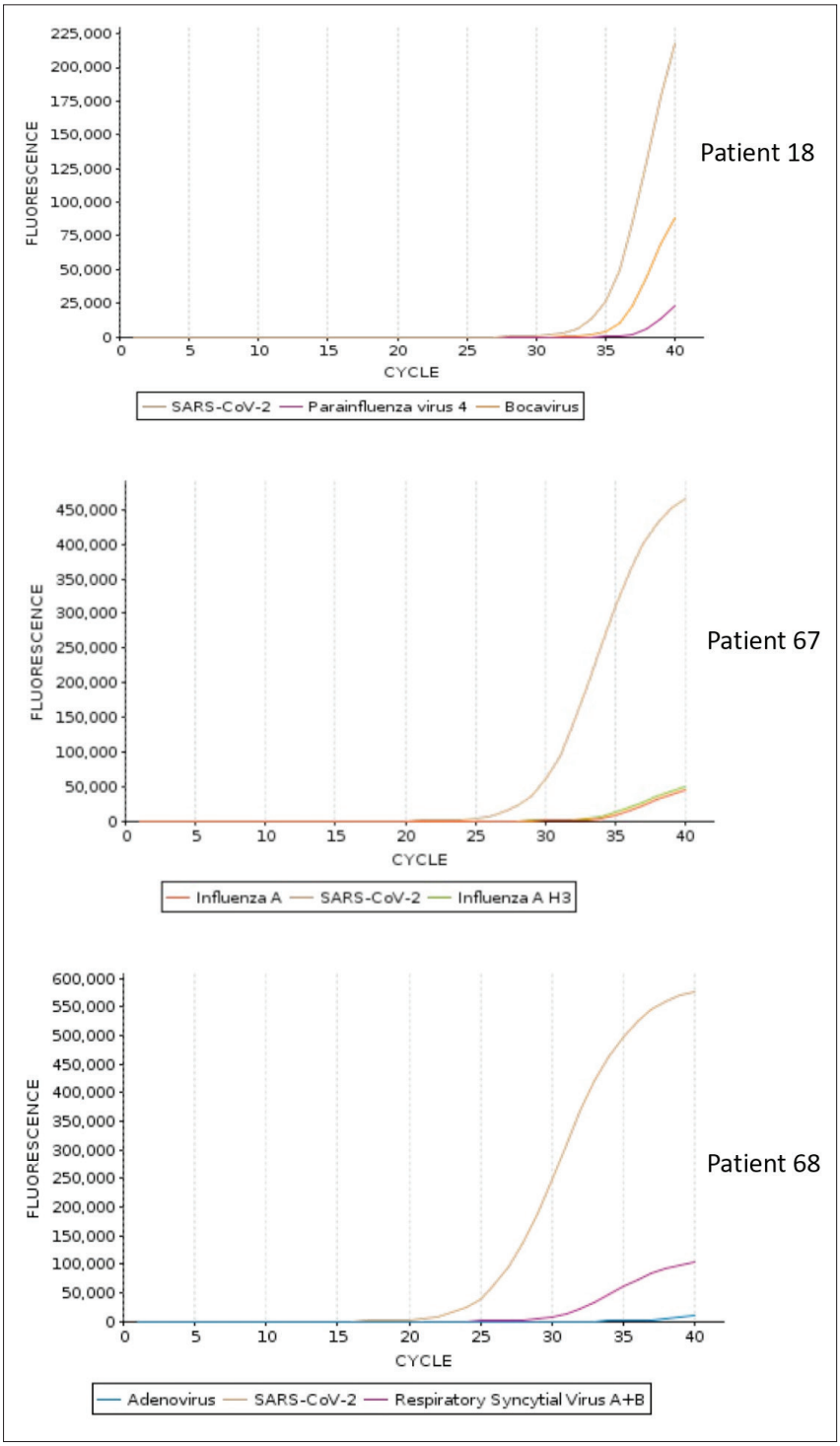

Figure 1. Amplification curves of respiratory viral pathogens co-detected in COVID-19 patient on the QIAstat-Dx Sytem.

Table 1. Molecular characterization of COVID-19 patients with a co-infection

Patient no	SARS-CoV-2 (Ct)	Other viral pathogen(s) (Ct)
Patient 9	27.84	RV 22.10
Patient 12	22.40	RV 30.06
Patient 18	32.21	HPIV-4 37.0, BoV 35.3
Patient 67	28.0	Inf A H3N2 32.5
Patient 68	23.9	RSV 29.2, Adenovirus 34.9

Overall, the low co-infection rate in the current study can be due to reduced transmission of respiratory viruses as a result of gradually increased levels of restrictions (e.g., strict lockdowns, compulsory face mask regulations) endorsed by policymakers since the beginning of the COVID-19 pandemic[10].

The results obtained from COVID-19 patients suggest the circulation of RV, HPIV-4, and BoV, but not others including Inf and RSV during the winter months in Northern Cyprus. This contradicts the seasonal trend of the viruses, since RV and BoV are among the "all-year viruses", while Inf and RSV are regarded as the "winter viruses"[11]. The conflicting data could be due to the small sample size, which was a major weakness of our study, as well as the lower prevalence of the "winter viruses" due to anti-SARS-CoV-2 control measures[12].

Among the viral infectious agents detected in our study, RV was previously shown to be affected by the COVID-19 control measures more than the other 16 respiratory viruses including Inf, RSV, HPIV, and BoV[13]. They also displayed faster spread after the relaxation of strict non-pharmaceutical interventions following the lockdown[14]. Accordingly, RV prevalence was suggested as an indicator of the efficiency of non-pharmaceutical interventions exerted against the SARS-CoV-2 transmission[13]. This raises concerns about the association between RV co-infection and COVID-19 disease severity which is still to be addressed[8]. Due to their higher replication rate, RV was initially thought to exert suppressive activities on SARS-CoV-2 growth rate if the infection starts simultaneously[15]. Accordingly, RV was demonstrated to block SARS-CoV-2 replication within primary human bronchial epithelial cells, mainly via induction of the interferon response[16]. In contrast to these beneficial effects on the host, human RV A16 was shown to upregulate angiotensin-converting enzyme-2 (ACE-2) and transmembrane protease serine-2 (TMPRSS2) expression in epithelial cells[17].

In accordance with the interference data, the RV Ct value was lower than that of SARS-CoV-2 in one of two COVID-19 subjects with RV co-infection in our study. One of the RV co-infected patients was hospitalized due to severe symptoms, which is in correlation with a previous report showing a lack of association between disease severity and viral load detected at admission[18]. On the other hand, the other patient with RV co-infection was not hospitalized but had suffered from loss of taste and smell for up to three months after recovery. To our knowledge, there has not been any data on the association between post-COVID-19 symptoms and co-infection with other microbial agents. Therefore, future studies with a higher number of patients with RV co-infection are needed not only to enlighten its effect on disease severity but also on post-COVID-19 syndrome.

In addition to the two COVID-19 patients co-infected with RV, one patient's nasopharyngeal sample demonstrated the presence of HPIV-4 and BoV. Unlike RV transmission, HPIV and BoV spread has not yet received enough attention in literature; while there is a lack of data regarding all modes of transmission for human BoV, HPIV infection prevention and control practices recommended by the WHO include contact and droplet but not airborne precautions

which are similar to that advised for RV infections[19,20]. Nevertheless, despite the detection of HPIV and RV on hands, surfaces, droplets, and aerosols; transmission via these routes was demonstrated only for the latter, but not for the former by volunteer and observational studies[20].

Human HPIVs are common respiratory viral pathogens responsible for upper and lower respiratory tract infections, particularly in children. The family members show type-specific patterns of seasonal circulation with little information on HPIV-4 due to its low prevalence, but it was suggested to circulate mostly during late autumn and winter in temperate countries[21]. On the other hand, while HPIV-4 is not regarded as an important pathogen as it is mostly associated with mild illnesses, it was also reported to cause more severe symptoms such as bronchiolitis in children[21]. Moreover, BoV which was recently discovered in children with acute respiratory infection[22], and shown to cause severe lower respiratory tract infections[23], was reported to be one of the most frequent co-infecting viruses in HPIV-4 patients[21]. Therefore, despite the lack of severe symptoms in the adult patient with HPIV-4 and BoV co-infection, our data encourages future studies on the association between HPIV co-infection and COVID-19 disease severity.

One of the main limitations of our study is the small sample size. The association between co-infection and disease severity could not be extrapolated due to the small patient number. Future studies should include the detection of other viral agents, such as EBV, using a molecular approach, as well as the analysis of respiratory infection rates among SARS-CoV-2-negative subjects, for comparison purposes.

ETHICS COMMITTEE APPROVAL

This study was approved by the Yakın Doğu University Scientific Research Ethics Committee (Decision no: YDU/2021/95-1403, Date: 30.09.2021).

CONFLICT of INTEREST

We declare that we have no financial, commercial, or other relationships that could potentially cause a conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: BB, UG

Analysis/Interpretation: All of authors

Data Collection or Processing: AB, EÜE, BB

Writing: AB, BB, UG

Review and Correction: All of authors

Final Approval: All of authors

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