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Blood test results from simultaneous infection of other respiratory viruses in COVID-19 patients

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Abstract

Since 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly, infecting millions of people worldwide. On March 11, 2020, the World Health Organization declared coronavirus disease (COVID-19) a pandemic owing to the worldwide spread of SARS-CoV-2, which created an unprecedented burden on the global healthcare system. In this context, there are increasing concerns regarding co-infections with other respiratory viruses, such as the influenza virus. In this study, clinical data of patients infected with SARS-CoV-2 and other respiratory viruses were compared with patients infected with SARS-CoV-2 alone. The hematology and blood biochemistry results of 178 patients infected with SARS-CoV-2 , who were tested on admission, were retrospectively reviewed. In patients with SARS-CoV-2 and adenovirus co-infection, C-reactive protein levels were elevated on admission, whereas lactate dehydrogenase (LDH), prothrombin time, international normalized ratio, activated partial thromboplastin clotting time, and bilirubin values were all within the normal range. Moreover, patients with SARS-CoV-2 and human bocavirus co-infection had low LDH and high bilirubin levels on admission. These findings reveal the clinical features of respiratory virus and SARS-CoV-2 co-infections and support the development of appropriate approaches for treating patients with SARS-CoV-2 and other respiratory virus co-infections.

Keywords: *SARS-CoV-2, Co-infection, Respiratory virus, COVID-19*

1. INTRODUCTION

On March 11, 2020, the World Health Organization declared the coronavirus disease (COVID-19) as a pandemic owing to the worldwide spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], which created an unprecedented burden on the global healthcare system. In this context, there are increasing concerns regarding co-infections with other respiratory viruses, such as the influenza virus [2]. This study aimed to explore the underlying clinical and biochemical features of co-infection of SARS-CoV-2 and other respiratory viruses, to support the establishment of improved medical approaches for such patients.

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Therefore, we retrospectively reviewed the clinical records of patients diagnosed with COVID-19 and compared the data between those with SARS-CoV-2 monoinfection and those with respiratory virus co-infections.

2. EXPERIMENTS

2.1 Ethical approval

This study was approved by the institutional review committee of Dankook University (approval number: 2022-02-020) and was conducted in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration). Because this study was based on retrospective data analysis without disclosing patient personal information, the requirement for patient consent was waived by the institutional review committee.

2.2 Study Subjects

A total of 178 patients with COVID-19 who were admitted to Dankook University Hospital in Cheonan, Republic of Korea, were enrolled in the study. Only patients who had co-infection with other respiratory viruses between the end of November 2020 and December 2021 were included in the study. Hematological and biochemical data were collected from all patients on admission.

2.3 Polymerase chain reaction (PCR)

Patients were tested for SARS-CoV-2 and influenza viruses using pharyngeal and nasal secretions collected using a single cotton swab. All samples were refrigerated at 2–8°C. For COVID-19 diagnosis, samples were tested for SARS-CoV-2 using a PowerChek 2019-nCoV Real-time PCR Kit (Kogen Biotech, Seoul, Republic of Korea). In addition, the presence of other respiratory viruses was detected using SLAN real-time PCR analysis system and RV Plus real-time RT-PCR kits (LG Chem Life Sciences, Cambridge, MA, USA). After testing, the samples were refrigerated at 2–8°C until further testing. Briefly, isolated RNA from the samples was reverse transcribed and used as a template for PCR detection of genes related to 13 respiratory viruses using TaqMan-specific probes. The fluorescence intensity of the probe was measured using a real-time PCR inspection device (LG Chem Life Sciences).

3. RESULTS

Of all patients with COVID-19 who were admitted to Dankook University Hospital (n=178), three had co-infections with respiratory virus (1.68%) and no patients had co-infection with three or more viruses. Among these three co-infected patients, one was infected with SARS-CoV-2 and adenovirus (0.56%), and two (1.11%) were infected with SARS-CoV-2 and human bocavirus (HBoV).

The patient with adenovirus co-infection first experienced mild fever on November 22, which improved after taking cold medicine; however, on November 23, their senses of taste and smell decreased. The patient was confirmed to have COVID-19 on PCR testing, was hospitalized on November 26 in an isolation room, and was discharged on December 9. The patient had unremarkable medical and family histories and had only visited one friend in Seoul on November 16, who was later confirmed to also be infected with SARS-CoV-2. The two patients HBoV co-infection had a history of liver disease, asthma, and chronic obstructive pulmonary disease, were confirmed to be SARS-CoV-2 positive on November 23, hospitalized on November 24, and discharged on December 18.

Table 1. Demographic and clinical characteristics of the patients with SARS-CoV-2 and other respiratory virus co-infections

	Normal range	Co-infection type	
		SARS-CoV-2 + adenovirus (*n*=1)	SARS-CoV-2 + human bocavirus (*n*=2)
Sex, age (years)		Female, 86	Male, 37
CRP (mg/dL)		3.34	0.92
LDH (U/L)		270	167
PT/INR		1.01	1.11
aPTT (sec)		25.9	30.9
Total bilirubin (mg/dL)		0.42	1.69

CRP: C-reactive protein; LDH: lactate dehydrogenase; PT/INR: prothrombin time and international normalized ratio; aPTT: activated partial thromboplastin time.

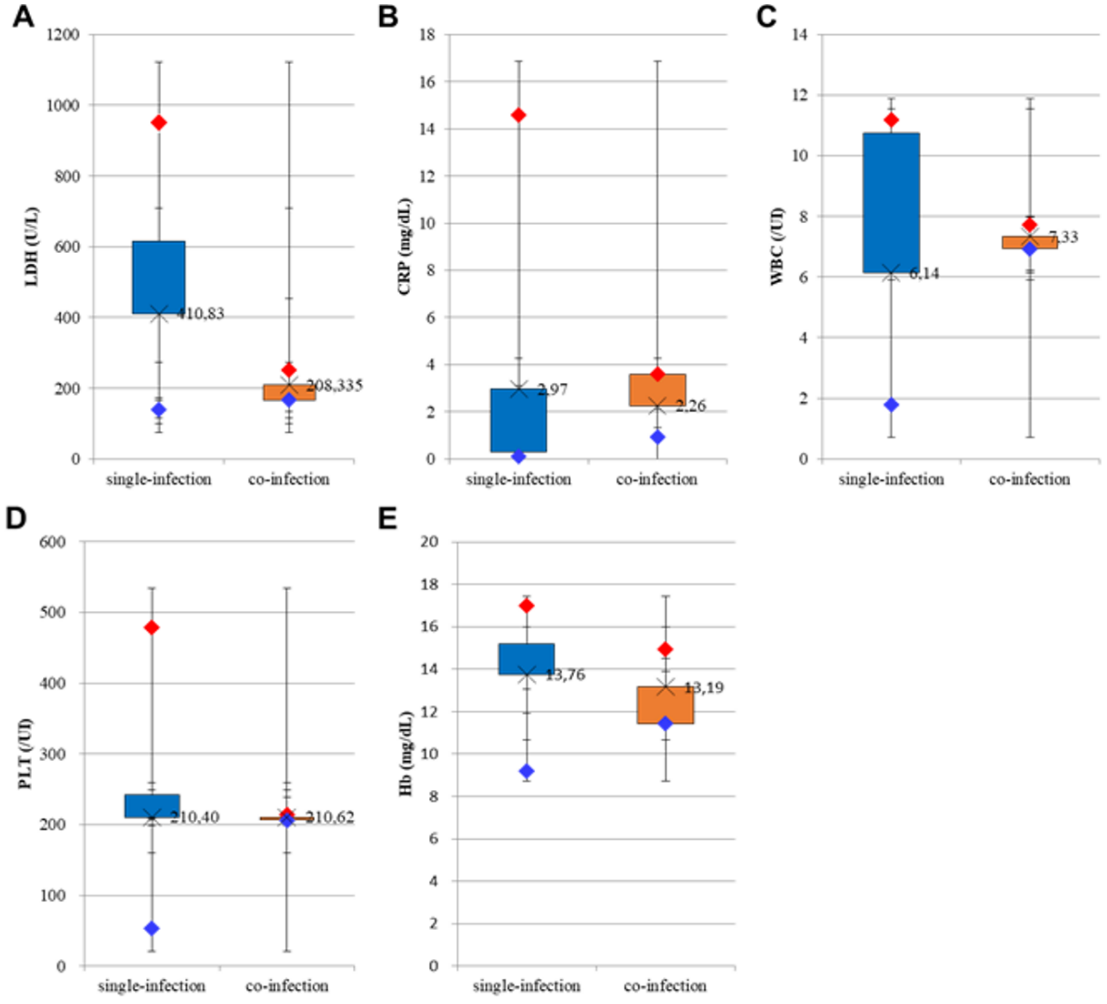

Figure 1. Comparison of patients with SARS-CoV-2 monoinfection and SARS-CoV-2 and other respiratory virus co-infection. (A) lactate dehydrogenase (LDH) levels, (B) C-reactive protein (CRP) levels, (C) white blood cell (WBC) counts, (D) platelet (PLT) counts, and (E) hemoglobin (Hb) levels.

The hematology and blood biochemistry results on admission of the three patients with respiratory co-infections are shown in Table 1. C-reactive protein (CRP) and total bilirubin levels in patients with HBoV co-infection were higher than normal levels on admission. CRP was within normal limits on the 5th day of hospitalization, and total bilirubin remained high at 1.65 mg/dL until discharge. In the patient with adenovirus co-infection, the CRP level peaked at 13.37 mg/dL on the 5th day of hospitalization and then decreased, returning to normal on the 21st day of hospitalization. Lactate dehydrogenase (LDH) was slightly elevated (259 U/L) on admission, then recovered to normal, rose to 345 U/L on the 10th day of hospitalization, and recovered to normal (222 U/L) on the 14th day of hospitalization. As shown in Figure 1, the white blood cell (WBC) counts were elevated in the three patients with infections, but other factors showed no significant difference.

4. DISCUSSION

With the advances in molecular biological techniques, several studies have reported co-infection of respiratory viruses and SARS-CoV-2 [3-5]. One previous study reported that a high proportion of critically ill patients have co-infections with SARS-CoV-2 and other respiratory viruses [2]. However, few co-infections have been reported in Korea. This study provides new clinical insights into co-infections of SARS-CoV-2 and other respiratory viruses.

A previous study, which evaluated a total of 634 pediatric patients, reported that approximately 57.4% of the patients were positive for respiratory syncytial virus (RSV, n=290) or influenza (n=74), among whom 181 and 36 patients had single RSV and influenza infections, respectively, and 147 had co-infections with other viruses [6]. Patients with co-infections showed significantly more clinical manifestations than those RSV or influenza virus monoinfection [6]. However, another study found that the prevalence of co-infection in children with COVID-19 was very low [7]. In this study, only a few patients (1.67% of the study population) were found to be co-infected with SARS-CoV-2 and other respiratory viruses, including HBoV and adenovirus. HBoV was first described in Sweden in September 2005 in a child who used a nasopharyngeal aspiration inhaler for respiratory infections [8]. Since then, several studies have found HBoV in respiratory and gastrointestinal samples [9,10]. HBoV causes respiratory and gastrointestinal viral infections [10]. Similarly, the human adenovirus infects the respiratory and gastrointestinal systems, but can also infect the corneal epithelium synergistically with other viruses[11]. Our findings suggest that co-infection with SARS-CoV-2 and HBoV leads to elevated CRP and bilirubin levels, and increased WBC counts, whereas co-infection with SARS-CoV-2 and adenovirus leads to an initial rise in CRP and LDH levels, followed by a decline. The LDH level has been suggested as a measure of disease severity in patients with COVID-19 and shown to be a useful biomarker for monitoring response to treatment [12]. Therefore, patients with severe COVID-18 should undergo continuous coagulation treatment to track the severity of the disease. Moreover, partial thromboplastin time (PTT) and activated PTT (aPTT) test levels were reported to not change significantly in patients with COVID-19 [13]. In our patients, the levels of aPTT were all within the normal ranges, which supports their good clinical outcome.

Co-infection is common in patients with COVID-19, with one or more pathogenic viruses being able to co-exist with SARS-CoV-2, which is an important factor in targeted treatment [14,15]. For example, co-infection with adenovirus and SARS-CoV-2 can lead to dyspnea syndrome; therefore, these patients should be admitted to the intensive care unit [16]. However, studies have shown that co-infection is not related to mortality and that the co-infection period is relatively short [17,18].

This study had some limitations. First, the study population was small, which made it difficult to accurately compare patients with SARS-CoV-2 monoinfection to those with co-infections. Moreover, the pathogens

assessed in the co-infections were limited to respiratory viruses. Hence, further studies should be conducted with larger cohorts, and should explore the effects of co-infection with SARS-CoV-2 and fungi or bacteria on patient outcomes. Despite these limitations, this is one of only a few reports describing co-infection with SARS-CoV-2 and adenovirus and co-infection with SARS-CoV-2 and HBoV. If influenza virus or other respiratory viruses are expected to co-infect during the COVID-19 pandemic, then there may be complications with the administration of vaccines, which may confuse patients and medical staff. Further large-scale investigations on SARS-CoV-2 co-infections are warranted for a better understanding of its pathological processes and clinical features, and to establish adequate healthcare management and vaccine application strategies.

5. CONCLUSION

In patients infected with respiratory viruses, including SARS-CoV-2, the HboV simultaneous infection group had significantly higher CRP, bilirubin, and WBC levels than patients with SARS-CoV-2 monoinfection and the patient with SARS-CoV-2 and adenovirus co-infection. In HboV co-infected patients, CRP and LDH levels decreased after an initial rise. Although CRP levels initially rose in a single infection, the overall distribution was lower than that of concurrent infection patients, and the WBC level was higher in a single infection patient distribution, but the average level was lower. Both the average value and distribution of LDH items were high. There was no significant difference in other factors tested. As co-infection is expected to become more common as the COVID-19 pandemic continues, future studies should investigate ways to diagnose and treat patients with co-infection.

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