Comparison of Blood Test Results and Symptoms of Patients with COVID-19 Monoinfection and with COVID-19 and Influenza Virus Co-Infection

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INTRODUCTION

In December 2019, an outbreak of a novel severe acute respiratory syndrome coronavirus 2 (COVID-19) occurred in Wuhan, Hubei Province, China [1]. The virus was named COVID-19. Several clinical studies have observed coinfection with COVID-19 and other respiratory infections [2-4]. Patients infected with annual respiratory viruses such as influenza A and B viruses, that can occur as coinfections with COVID-19, show similar symptoms [5]. Each year, influenza causes significant morbidity and mortality, including more than

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ABSTRACT

In December 2019, the coronavirus disease 2019 (COVID-19) caused by the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China and spread rapidly around the world, infecting millions of people. Cases of COVID-19 infection were observed to lead to viral pneumonia. Thirty-five patients admitted to the Gyeonggi Medical Center, South Korea, between November 2020 to January 2021, were found to have been infected with the influenza virus A and B, which cause symptoms similar to COVID-19. The records of these patients and those of COVID-19 patients who visited the hospital for medical examination were compared. The study patients included thirty patients with COVID-19 and/or influenza, five of those with influenza alone. A group of 121 patients without infection was used as control. Patients with COVID-19 and influenza had significantly higher lactate dehydrogenase levels than the patients with COVID-19 alone. The erythrocyte sedimentation rate (ESR) was higher in patients with COVID-19 alone than in other groups. Significant clinical outliers were observed in the COVID-19 and influenza infection group compared with the COVID-19 alone group. These results are expected to play an important role in the analysis of the hematological data of infected patients and the comparison of simultaneous and single infection data to determine clinical symptoms and other signs. These results may also assist in the development of vaccines and treatments for COVID-19.

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200,000 hospitalizations and 3,000~49,000 deaths in the United States alone [6]. This disease can affect the upper and lower respiratory tracts and is often accompanied by fever, headache, cough, and neck pain. Worldwide, influenza is estimated to cause 3~5 million severe infections and 2.9~6.5 million respiratory condition-related deaths each year [7]. According to a previous study, respiratory coinfection of influenza virus and COVID-19 has not been investigated because of its relatively short duration [8]. However, these viruses exhibit similar transmission characteristics and clinical manifestations [9].

The characteristics, clinical symptoms, factors affecting severity, and diagnostic methods of COVID-19 have been reported in numerous studies; consistent characteristics have been reported that can be used for reference in diagnosing and treating patients with COVID-19 [10]. We aimed to identify consistent hematologic and biochemical characteristics of influenza virus and COVID-19 coinfection based on blood test statistics at hospitals in Gyeonggi-do and Cheonan, Chungcheongnam-do.

**MATERIALS AND METHODS**

1. **Patients**

Between November 2020 and January 2021, thirty-five patients were hospitalized with COVID-19 infection at Anseong Hospital of Gyeonggi Medical Center. Among them, 30 patients had COVID-19 monoinfection, and five patients had influenza virus and COVID-19 coinfection (Table 1). Using laboratory records, the results of hematologic and biochemical tests conducted on the day of hospitalization were analyzed.

2. **Ethical considerations**

The study was approved by the institutional review board of Dankook University (date of approval: March 13, 2021; approval No.: 2021-03-013). This study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The requirement for patient consent was waived by the institutional review board as the study was based on a retrospective data analysis without revealing patients’ personal information.

3. **Methods**

Patients were sampled at 09:00 on the day of hospitalization. Patients were tested for COVID-19 and influenza viruses via pharyngeal and nasal secretions. Upper respiratory tract samples were collected from inpatients with influenza using a single swab. Nasopharyngeal and oral swabs were collected, respectively. All samples were refrigerated at 2~8°C after collection. These samples were tested using a rapid antigen detection method with the influenza virus-Ag/-A/B Kit (Wonmed, Bucheon, Korea) to detect the presence or absence of influenza virus f-200 (SD Biosensor, Suwon, Korea). Prior to result analysis, clinical symptoms and characteristics of each patient, according to the type of infection, were recorded. Data were prepared by dividing them into biochemical and hematological test items.

4. **COVID-19 PCR**

COVID-19 was detected in patient samples using the Real-2019-nCov Detection Kit (Biosam, Seoul, Korea)

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**Table 1.** Characteristics of patients with COVID-19 monoinfection and COVID-19 and influenza virus coinfection

| Characteristic | Patients with COVID-19 monoinfection (N=30) | Patients with COVID-19 and influenza virus coinfection (N=5) | Patients without infection (N=121) |
|---------------|-------------------------------------------|--------------------------------------------------|---------------------------------|
| Sex           | Male                                      | 15                                               | 2                               | 70                              |
|               | Female                                    | 15                                               | 3                               | 51                              |
| Age (years)   | 0~29                                      | 10                                               | 1                               | 6                               |
|               | 30~59                                     | 10                                               | 2                               | 80                              |
|               | ≥ 60                                      | 10                                               | 2                               | 35                              |
in a CFX96 DX ORM System (Bio-Rad, Seoul, Korea). All samples were refrigerated at 8°C after collection. As the genetic material of COVID-19 consists of unstable RNA, reverse transcription-polymerase chain reaction (RT-PCR) was performed to convert the RNA into stable cDNA. When specific DNA is amplified, viral infection can be detected by the expression of fluorescent proteins.

5. Data collection

Patients’ medical records were reviewed to collect data on their sex, age, clinical symptoms, test results, clinical diagnosis, and influenza virus type (A or B) to compare the hematology and blood biochemistry of patients with COVID-19 monoinfection and patients with COVID-19 and influenza virus coinfection.

6. Statistical analysis

Patient characteristics on admission were retrospectively analyzed, including age and sex. Medcalc ver. 20.105 (Medcalc software Ltd, Ostend, West-Vlaanderen, Belgium) was used to perform all statistical analyses, including descriptive statistical analysis and frequency analysis. Statistical significance was set at P<0.05.

RESULTS

1. Patient characteristics

Five patients (three men and two women) were simultaneously infected with COVID-19 and influenza virus, their average age was 70.2 years.

Two patients had COVID-19 and influenza A virus coinfections. One was a 77-year-old man who had a cerebral infarction five years ago, and had been diagnosed with hypertension and hyperlipidemia approximately 20 years ago. He was admitted to hospital with dyspnea, chest discomfort, muscle pain, chills, and fever. His symptoms worsened, hence, he was transferred to the intensive care unit. He was hospitalized for 28 days. The other patient was a 74-year-old man who was admitted with a headache, fever, rhinitis, diarrhea, and abdominal pain. He was discharged after 12 days following an improvement in his symptoms.

Two patients (average age of 44 years) had COVID-19 and influenza B virus infections. One patient was a 53-year-old woman, who was asymptomatic at the time of hospitalization; she was discharged after 3 days without developing any symptoms. The other patient was a 25-year-old woman who was admitted with fever, muscle pain, and chills. She was discharged after 9 days following an improvement in her symptoms. Another patient, a 96-year-old man who had been diagnosed with angina and dementia five and ten years ago, respectively, was coinfected with COVID-19 and influenza A and B viruses. He was admitted to hospital with a sore throat and headache; his symptoms subsequently improved, and he was discharged after 16 days.

2. Biochemical tests

1) Lactate dehydrogenase

Average lactate dehydrogenase (LDH) levels in patients with simultaneous COVID-19 and influenza A virus infection (554 mg/dL) were significantly higher than in patients with COVID-19 single infection (Figure 1, Table 2).

2) C-reactive protein

The C-reactive protein levels were elevated to 16.6 mg/dL in patients with COVID-19 and influenza virus coinfection and 0.1 mg/dL in patients without infection.
and patients with coinfection tended to have elevated C-reactive protein levels (Figure 2).

3. Hematology

1) White blood cells

White blood cell (WBC) levels were higher in patients with simultaneous COVID-19 and influenza B virus infection than in patients with COVID-19 single infection. However, WBC was lower in patients with simultaneous COVID-19 and influenza A virus infection than in patients with COVID-19 single infection (Figure 3, Table 3).

2) Neutrophil-to-lymphocyte ratio

The neutrophil-to-lymphocyte ratio was slightly higher in patients with COVID-19 and influenza virus coinfection than in patients without infection. The lymphocyte levels tended to be lower in patients with COVID-19 and influenza coinfection or COVID-19 monoinfection than in patients without infection.

3) Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) was highest (51 mm/hr) in patients with COVID-19 and influenza A virus coinfection than in those without infection.

4) Hemoglobin

Hemoglobin (Hb) levels were lower in patients with COVID-19 and influenza B virus coinfection than in the other groups.

Table 2. Lactate dehydrogenase and C-reactive protein levels according to COVID-19 and influenza virus infection status

| Infection type                        | Age group (years) | LDH (mg/dL) | P value | CRP (mg/dL) | P value |
|---------------------------------------|-------------------|-------------|---------|-------------|---------|
| COVID-19 and influenza virus coinfection (N=5) | Influenza A       | 544         | 0.181   | 5.8         | 0.396   |
|                                       | Influenza B       | 379         | 0.106   | 5.5         | 0.552   |
|                                       | Influenza A, B    | 438         |          | 16.6        |         |
| COVID-19 mono infection (N=30)        | 0~29              | 368         | 0.015   | 0.5         | 0.055   |
|                                       | 30~59             | 388         | 0.002   | 2.2         | 0.462   |
|                                       | >60               | 475         | 0.011   | 6.2         | 0.012   |
| Patients without infection (N=121)    | 0~29              | 185         | 0.1     |             |         |
|                                       | 30~59             | 199         | 0.1     |             |         |
|                                       | >60               | 199         | 0.1     |             |         |

Abbreviations: LDH, lactate dehydrogenase; CRP, C-reactive protein.

Figure 2. Comparison of C-reactive protein levels in patients with COVID-19 mono infection and patients with COVID-19 and influenza virus coinfection.

Figure 3. Comparison of white blood cell counts in patients with COVID-19 mono infection and patients with COVID-19 and influenza virus coinfection.
### Table 3. White blood cell counts according to COVID-19 and influenza virus infection status

| Infection type (N=156) | Age group (years) | WBC (10^3/µL) | P value |
|------------------------|------------------|--------------|---------|
| COVID-19 and influenza virus coinfection (N=5) | Influenza A | 5.8 | 0.199 |
| | Influenza B | 6.8 | 0.433 |
| | Influenza A, B | 6.0 | |
| COVID-19 mono infection (N=30) | 0~29 | 5.9 | <0.001 |
| | 30~59 | 6.3 | <0.001 |
| | >60 | 6.3 | <0.001 |
| Patients without infection (N=121) | 0~29 | 6.3 | |
| | 30~59 | 6.3 | |
| | >60 | 6.3 | |

Abbreviation: WBC, white blood cells.

5) Platelets

The platelet counts were substantially lower in patients with COVID-19 and influenza virus coinfection than in patients without infection.

### DISCUSSION

Hematologic and biochemical characteristics of patients infected with COVID-19 and influenza A or influenza B were investigated. Coinfection of COVID-19 and influenza virus was confirmed in 14% of all patients. Significant values were found in three categories: LDH, CRP, and WBC. Patients with COVID-19 and influenza virus coinfection had significantly higher LDH and CRP levels, and significantly higher WBC counts but showed no significant difference in other factors (Hb, platelet count, neutrophil-to-lymphocyte ratio, and ESR). Previous studies have shown that patients with severe COVID-19 tend to have lower Hb levels than those with mild disease [11]. In contrast, other studies have found no significant difference in the platelet count among patients of various ages hospitalized with COVID-19 [12].

COVID-19 can cause serious illness or death, particularly in older adults with age-related vulnerabilities [13]. In patients with COVID-19, high levels of LDH are associated with severe disease and mortality [14]. The LDH levels were high in patients with COVID-19 and influenza virus coinfection, particularly among patients with influenza A virus coinfection. Therefore, LDH levels could be used to screen for COVID-19 severity and for coinfection with influenza A virus prior to COVID-19 PCR testing. Moreover, CRP is produced in the liver and is often measured to identify and predict various inflammatory and necrotic reactions as a non-specific but sensitive marker, as its level increases rapidly during acute inflammatory responses [15]. CRP production is induced by interleukin-6, a marker of systemic inflammation [16]. A sudden increase in the CRP level in the absence of other factors suggests the presence of infection [17]. CRP levels averaged higher in concurrent infections of COVID-19 and influenza viruses than in monoinfections, indicating the possibility of screening for COVID-19 infections using CRP.

The WBC counts did not significantly differ between patients without infection and patients with COVID-19 mono infection, although the WBC counts were slightly increased in patients with COVID-19 and influenza B virus coinfection. In addition, patients without infection had relatively high Hb levels. The WBC count is increased in several infectious diseases and a high WBC count is associated with increased mortality [18]. In this study, the patients with COVID-19 had varying changes in their WBC count and differential WBC count according to disease severity. The Hb levels were lower in patients with COVID-19 monoinfection and in patients with COVID-19 and influenza A virus coinfection than in patients without infection and patients with COVID-19 and influenza B virus coinfection. These results suggest that COVID-19 and influenza virus coinfection may decrease the Hb levels.
Further studies are needed to determine whether the decrease in the Hb level is related to decreased immunity caused by hemolysis related to viral infection. Finally, it is clinically meaningful that platelet counts were low in the group with COVID-19 and influenza virus coinfection; however, the cause of this change requires further investigation.

There are some limitations to this study. The biggest limitation is that it was difficult to draw definitive conclusions from the results because of the limited number of cases of COVID-19 and influenza virus coinfection. This made it difficult to distinguish whether differences between groups were due to differences in age and underlying disease or due to COVID-19 and influenza virus coinfection; consequently, further research is required with a larger number of coinfected patients. In addition, it was difficult to conduct more influenza tests in patients with COVID-19 owing to budget limitations: hence, it was not possible to identify a sufficient number of patients with COVID-19 and influenza virus coinfection. Moreover, rapid antigen testing was used as the influenza testing method. In other studies, the sensitivity of the rapid antigen test was 55%, which means that only 55 out of 100 patients with influenza virus infection tested positive using RT-PCR [19]. Finally, this was a retrospective study, and therefore only previously obtained results could be analyzed.

To summarize, in patients infected with COVID-19, those with influenza virus coinfection had significantly higher levels of LDH, CRP, and WBC compared to the single COVID-19 infection group. Other tested factors showed no significant differences (Hb, neutrophil-to-lymphocyte ratio, and ESR). The ESR values and lymphocyte counts in patients with COVID-19 monoinfection were higher than in the other groups, and Hb values were high even in patients without infection. If there are influenza virus epidemics during the COVID-19 pandemic, this could cause problems with administering the vaccine, causing confusion in patients and medical staff. Continuous large-scale research should be conducted on COVID-19 and influenza virus coinfection, as it could be used to manage infected patients and to provide vaccines and treatment according to coinfection.

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