

# Epstein–Barr Virus and Cytomegalovirus Reactivation in Patients with COVID-19

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## Research article

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# Abstract

## Background

Since first report of COVID-19 in December 2019, it has spread to a pandemic, making many deaths. Dysfunction of immune function is considered as one of the reasons for high mortality. Epstein–Barr virus (EBV) and Cytomegalovirus (CMV) reactivation in severe patients is thought to be related to immune dysfunction but is not yet known in COVID-19.

## Methods

We conducted EBV and CMV real-time PCR confirmed patients with COVID-19 who were admitted to our hospitals.

## Results

Of the 61 COVID-19 patients, nine EBV and two CMV viremia were found. The group with EBV viremia had a higher probability of progressing to severe COVID-19 infection than the group without, but it was not statistically significant. One out of two people with CMV viremia died and one survived after Extracorporeal Membrane Oxygenation use.

## Conclusions

Our study suggests immune dysfunction in COVID-19, and further research is needed on the role of EBV/CMV in COVID-19.

## 1. Background

In December 2019, a novel pneumonia was first reported in Wuhan, China[1], and the pathogen of pneumonia was named SARS-CoV-2 [2]. COVID-19 spreads worldwide from China and occurs in almost all countries in March 2020 [3]. COVID-19 not only causes rapid transmission, but is also fatal to patients with advanced and underlying diseases, causing a very serious disease burden[4].

In severe patients, reactivation of viruses such as Herpes simplex, CMV, and EBV occurs, and functional exhaustion of cytotoxic lymphocytes is suggested as the cause[5, 6]. COVID-19 can cause cellular immune dysfunction[7], so it can induce reactivation of the latent viruses, but there is no research on this. We planned a study to investigate Epstein–Barr virus (EBV) and Cytomegalovirus (CMV) viremia in COVID-19 patients.

## 2. Methods

We conducted EBV and CMV real-time polymerase chain reaction (PCR) confirmed adult patients with COVID-19 who were admitted to Inha University Hospital from February 1 to June 30, 2020. Children

(under 15 years old) and foreigners were excluded from the study. And, patients with HIV, CIVD, hematologic malignancy and taking immunosuppressants were excluded from the study. For diagnosis of COVID-19, the Allplex™ 2019-nCoV Assay kit (Seegene™, Republic of Korea) was used for PCR of secretion of the upper or lower respiratory tract. Real-Q EBV Quantification Kit (Biosewoom/ Republic of Korea) was used for the detection of EBV virus, and Real-Q CMV Quantification Kit kit (Biosewoom/ Republic of Korea)) for CMV viremia. The cut-off of EBV viremia was defined as 72copies/ml and 49copies/ml, by reference value of manufacture's insert. EBV and CMV viremia were examined within 7 days since administration. The patients with COVID-19 were subdivided into groups with EBV and without viremia, the fisher's exact test was used for comparison. P-value was considered significant when it was 0.05 or less.

### 3. Results

During this period, 83 adult patients diagnosed with COVID-19 were hospitalized, but 15 were foreigners and 3 were simply missing the prescription. A total of 50 patients underwent EBV and CMV real-time PCR. The average age was 57 and men accounted for 55%. The median date from hospitalization to examination was 2 days. EBV showed viremia in 35%. The median EBV viremia in patients with viremia was 570 copies/μl. Of the total patients, 9 patients had severe COVID-19 (treatment with high-flow nasal canula or higher), and 3 of them had EBV viremia. At the time of admission, one person had CMV viremia, and one developed CMV viremia during treatment. Results for patients with severe COVID-19 are described in Table 2.

In the subgroup analysis of EBV viremia in COVID-19 patients, the Simplified Acute Physiology Score II score was 19.3 in the EBV viremia group, which was higher than in the without EBV group, but there was no statistical difference. Patients with EBV viremia progressed more severely to severe COVID-19 but were not statistically significant. Two patients with CMV viremia showed all severe COVID-19 (Extracorporeal Membrane Oxygenation and death).

### 4. Discussions

Reactivation of EBV is significantly related to the dysfunction of cellular immunity[8]. EBV is latent in near 90% of people, which is the highest rate of herpes virus[9]. Therefore, EBV viremia can also be considered as one of the measures of functional exhaustion of cellular immunity. SARS-CoV-2 virus infection can cause functional exhaustion of antiviral lymphocytes as well as the cytopathic effect[10], This study showed that EBV reactivation in many COVID-19 patients. Various treatments have been proposed for COVID-19, but there is no established treatment yet. In this regard, immune dysfunction is likely to have a profound effect on the patient's prognosis, and patients with EBV viremia need more careful observation and treatment.

The possibility that EBV is not simply an indicator of reduced immunity, but also a cause of worsening of immune function cannot be ruled out. During the reactivation of EBV, EBV can interfere with the activity of

NK cells and helper T cells. EBV occurs B cell's transformation[11], and produces proteins that primarily impair the production of interferons during the lysis phase[12]. With this mechanism, infection or reactivation of EBV can reduce defense to infection with other pathogens. However, the role of EBV has not been studied in COVID-19.

The real pathogenicity of the reactivated EBV is still being discussed. A study has reported that EBV DNA is detected in the low respiratory tract of patients with severe respiratory tract with no other pathogen detected[13]. However, it is difficult to conclude that EBV has a cytopathic effect in all cases where other pathogens have not been identified, because it is not easy to identify the pathogen of pneumonia in many cases. Still, some say reactivated EBV may be pathogenic as a result of immunocompromise, others claim it is just an indicator of severe illness[8].

CMV showed a lower incidence than EBV. This tended to be similar in previous studies of EBV and CMV viremia in severe patients[5]. CMV may be overlooked due to low incidence, but it needs to be noted because it can cause serious complications such as pneumonia, enteritis, and CNS infection[14]. In our study, 2 patients developed CMV viremia. One of them developed CMV pneumonia and esophagitis, and the patient eventually died. Considering the frequent use of steroids in severe patients with COVID-19, it is necessary to pay attention to the immunocompromised status. Invasive aspergillosis has attracted attention with relatively many reports[15]. In addition to aspergillosis, other opportunistic infections such as CMV need to be noted, but not yet. physicians need to be cautious about monitoring for opportunistic infections such as CMV.

This study has several limitations. First, it was a very small number of patients. Second, the incidence of EBV viremia may vary depending on the severity of the infection. Third, because it is a simple observational study, it was not possible to observe the prognosis of EBV viremia and the cellular immunity associated with EBV viremia. Further studies are needed for more patients and the mechanism of EBV viremia.

In conclusion, it was found in patients with EBV and CMV viremia COVID-19, suggesting an immunocompromised condition. Further studies are needed to determine the role of EBV and CMV viremia in COVID-19.

## **Abbreviations**

Cytomegalovirus: CMV, Epstein–Barr virus: EBV, polymerase chain reaction: PCR

## **Declarations**

### *Funding*

This study had no funding.

### *Ethical approval*

This study was approved by the Inha University Hospital Institutional Review Board (Incheon, Republic of Korea), which waived the need for informed consent.

### *Consent for publication*

Not Applicable

### *Competing Interests*

All authors declare no conflict of interest related to this study.

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### *Author contributions*

JHI: conceptualization, drafting and editing the manuscript; JSL, MHC, HYK, and MJL: writing review and editing; JHB: conceptualization and supervision. All authors read and approved the final manuscript.

### *Availability of data and materials*

The datasets used during the current study are available from the corresponding author upon reasonable request.

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## Tables

Due to technical limitations, table 1 & 2 is only available as a download in the Supplemental Files section.

## Supplementary Files

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- [EBVCMVtable08011.xlsx](#)