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Original Article

CMV reactivation in immunocompetent critically ill intensive care unit patients: a retrospective study

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Abstract

Introduction: Cytomegalovirus (CMV) reactivation is observed in immunosuppressive patients and causes adverse clinical outcomes. CMV reactivation in immunocompetent patients is less known. We aimed to retrospectively investigate CMV reactivation in immunocompetent critically ill patients with bacterial growth in lower respiratory tract; and investigate the relationship between reactivation and outcomes such as length of stay (LOS), mechanical ventilation duration, and mortality.

Methodology: Intensive care unit (ICU) patients that were CMV IgG-positive, CMV IgM-negative immunocompetent, mechanically ventilated for over 48 hours, and were diagnosed with respiratory tract colonization with *Acinetobacter baumannii* or ventilator-associated pneumonia (VAP) were included. Reverse transcriptase polymerase chain reaction (RT-PCR) was performed on serum and endotracheal aspirate samples. The patients were divided into groups of those with and without VAP and sepsis. Reactivation rates and CMV DNA levels were compared between the groups.

Results: CMV reactivation was seen in 27 of 34 patients (79.4%). CMV DNA level was 5.8 times higher in patients with VAP and sepsis than patients without, but the difference was not statistically significant ($p = 0.717$). LOS and mechanical ventilation duration were higher in patients with reactivation ($p = 0.047$ and 0.036). No relationship was found between reactivation and mortality ($p = 0.774$).

Conclusions: The rate of CMV reactivation was 79.4%. This was the second-highest reactivation rate reported in the literature. The reactivation was associated with prolonged hospitalization and mechanical ventilation.

Key words: critical illness; cytomegalovirus; immunocompetent; intensive care unit; reactivation.

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Introduction

Cytomegalovirus (CMV), also known as human herpes virus 5, is a deoxyribonucleic acid (DNA) virus in the Herpesviridae family and Betaherpesvirinae subfamily. This virus causes a lifelong latent infection after primary infection of its host [1]. CMV causes widespread infection worldwide, does not show seasonal distribution pattern, and affects all ages. Seropositivity rates in the adult population are 50–60% in developed countries and 90–100% in developing countries [2]. CMV can be found in saliva, breast milk, tears, blood, urine, cervicovaginal secretions, semen, and feces samples. Various ways of transmission have been reported such as sexual contact, blood transfusion, transplantation, breastfeeding, and, most importantly, close contact with an infected person. Infection during pregnancy may cause vertical transmission. Incubation period of the infection is approximately 4 to 12 weeks [3].

CMV reactivation is frequently seen in immunocompromised patients and it results in poor clinical outcomes. Knowledge about CMV reactivation in immunocompetent patients is limited. Literature shows that CMV reactivation can be found in immunocompetent critically ill patients, especially those with sepsis and mechanical ventilation support. It is shown that this condition negatively affects the duration of hospitalization, mechanical ventilation, severity of illness and mortality rates [4–6].

Invasive mechanical ventilation is a life saving intervention for patients with respiratory failure. Inpatient invasive mechanical ventilation rate has been reported to be 2.8%. This rate increases to up to 29.1–89.9% in patients with COVID-19 [7,8]. Sepsis is an

important problem of hospitalized patients and its reported incidence is 15.4/1000 among ward patients and 44.8/1000 among intensive care unit (ICU) patients [9]. Considering these findings and the CMV seropositivity rates, it is expected that numerous patients are at risk for CMV reactivation.

We aimed to retrospectively investigate the presence of CMV reactivation and its relation to prognostic parameters such as length of stay (LOS), duration of mechanical ventilation and mortality in immunocompetent critically ill patients.

Methodology

This observational study was conducted in a tertiary care center. Patients who received care in mixed ICUs between 1 May 2019 and 31 March 2020 were included in the study population. Patients who had been mechanically ventilated for at least 48 hours and had a pre-diagnosis of respiratory tract colonization or ventilator associated pneumonia (VAP) with *A. baumannii* were included.

The following inclusion criteria were used: >18 years; invasive mechanical ventilation for at least 48 hours; anti-CMV IgG (+) and anti-CMV IgM (-); were immunocompetent [patients who were not infected with the human immunodeficiency virus (HIV), had not had a known or suspected diagnosis such as hematological malignity, congenital immunosupression, transplantation history, had not had chemotherapy in the past year, or steroids in the past 30 days]; and had not used any antiviral therapy that could be effective against CMV (cidofovir, foscarnet, gancyclovir, valgancyclovir etc.) 7 days prior to collection of samples.

All the patients included in the study tested negative for anti-CMV IgM. Consequently, nosocomial infection-reinfection related to CMV was not considered in the patients.

As soon as bacterial growth was detected in endotracheal aspirate (ETA) cultures, additional ETA and serum samples were collected from the patients for CMV testing. Patients' serum and ETA samples were kept at -80 ºC after being centrifuged at 3500 rpm for 10 minutes. All sample analyses were conducted after defrosting the samples properly.

Demographic data, comorbidities, LOS, duration of mechanical ventilation, severity of illness and mortality, acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores, and laboratory data of included patients were obtained from the hospital's automated information system. For each patient, detection of bacterial growth in the ETA culture was considered as the study origin. The following 28 days after the origin were retrospectively examined, and the presence of mortality was assessed. The APACHE II, SOFA scores, and laboratory values of the patients on the origin day were recorded. LOS in the ICU from the initial admission day until the mentioned origin, and the duration of mechanical ventilation for patients, were retrospectively assessed and included in the statistical analysis.

The automated complete blood count system DxH (Beckman Coulter, Miami, FL) was used for spectrophotometric measurement of hemoglobin levels, impedance technique, and light scattering analysis for leucocyte and thrombocyte counts. Cobas 6000 (Roche Diagnostics, Manheim, Germany) autoanalyzer was used for measuring alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The Image 800 (Beckman Coulter, Miami, FL) nephelometer was used for measuring C reactive protein (CRP) levels.

The patients were divided into two groups. The first group consisted of the patients who had sepsis with VAP (group 1). The second group consisted of patients without sepsis and who had bacterial colonization in their ETA samples (group 2). CMV reactivation rates and CMV DNA copy counts were compared between groups by the real-time polymerase chain reaction (RT-PCR) method.

CMV RT-PCR tests were done on 4 August 2022 at the Duzen Laboratory Group (Ankara, Turkiye). The test results were assessed according to the guidelines provided by the kit's manufacturer. DNA for the Artus CMV protocol, was isolated to a final volume of 95 mL by EZ1 advanced instrument device Qiagen Virus EZ1 mini kit (Qiagen, Valencia, CA, USA). Artus CMV PCR (Qiagen, Valencia, CA, USA) is a hydrolysis probe-based RT-PCR that targets CMV's major immediate-early gene. The reactions were performed on the Rotor-Gene Q (RGQ) instrument (Qiagen, Valencia, CA, USA).

IBM SPSS Statistics for Windows, version 19.0. (IBM Corp. Armonk, NY: USA. Released 2010) program was used for data analysis. Mean ± standard deviation, median (min–max), and percentages were used as descriptive measures. Statistical assesment were evaluated using parametric or non-parametric significance tests in accordance with the normal distribution compliance requirements. p value of 0.05 or lower was considered statistically significant.

The principles of the Helsinki Declaration were followed during this investigation. Permission was obtained from the Canakkale Onsekiz Mart University

Table 1. Baseline characteristics of patients.

Characteristic	Patients (n = 34)
Male, n (%)	22 (64.7)
Age (years), mean ± sd, median (min–max)	72.2 ± 10.4, 72.0 (48.0–91.0)
Comorbidity, n (%)	
None	2 (5.9)
Hypertension	10 (29.4)
Diabetes mellitus	6 (17.6)
Chronic obstructive pulmonary disease	7 (20.5)
Congestive heart failure	8 (23.5)
Chronic kidney disease	5 (14,7)
Acute kidney injury	2 (5.9)
Cerebrovascular disease	13 (38.2)
Coronary artery disease	6 (17.6)
Malignancy	10 (29.4)
APACHE II score, mean ± sd, median (min–max)	20.5 ± 6.8, 20,0 (11.0–37.0)
SOFA score, mean ± sd, median (min–max)	4.3 ± 3.5, 4,0 (0.0–12.0)
LOS, mean ± sd, median (min–max)	23.7 ± 19.3, 16.5 (6.0–83.0)
Ventilator days, mean ± sd, median (min–max)	22.9 ± 19.2, 16.0 (4.0–83.0)
Mortality, n(%)	18 (52.9)
ETA CMV reactivation, n(%)	26 (76.5)
Serum CMV reactivation, n(%)	14 (41.2)
ETA CMV DNA load (copy/mL), mean ± sd, median (min–max)	52489.0 ± 172531.0, 1003.0 (0.0–952943.0)
Serum CMV DNA load (copy/mL), mean ± sd, median (min–max)	24325.0 ± 100377.0, 0.0 (0.0–510699.0)

APACHE-II: acute physiology and chronic health evaluation II; CMV: cytomegalovirus; ETA: endotracheal aspirate; LOS: length of stay; sd: standard deviation; %: column percentage; SOFA: sequential organ failure assessment.

Clinical Research Ethics Committee (Approval No: 2011-KAEK-27/2021-2100092235).

Results

The study included 34 patients who met the inclusion criteria. There were 22 males (64.7%) whose mean age was 72.2 ± 10.4 years. 27 of 34 patients (79.4%) had CMV reactivation. Both the reactivation rate and the copy count were higher in ETA samples than in serum samples. The general characteristics of the patients are summarized in Table 1.

No statistical significance was found between the two groups in terms of CMV reactivation ($p = 0.722$). The mean of CMV PCR copies in group 1 was 5.8 times higher than in group 2, but this difference was not statistically significant ($p = 0.717$). Table 2 provides a summary of the CMV reactivation data for each group.

To evaluate the relationship between CMV reactivation and scoring systems used for predicting severity of illness, mortality, organ dysfunction and sepsis, APACHE II and SOFA scores were compared between patients with and without CMV reactivation. The correlations between CMV PCR counts, and APACHE II and SOFA scores were also investigated. There was no statistically significant difference between the two groups with and without CMV reactivation in terms of both APACHE II and SOFA scores ($p = 0.571$ and $p = 0.747$). No statistically significant correlation was found between both APACHE II and SOFA scores and CMV PCR copy counts ($p = 0.699$ and $p = 0.909$).

Hemoglobin, leukocytes, neutrophils, lymphocytes, monocytes, platelets, CRP, ALT, and AST levels were examined across patients with and without CMV reactivation in order to determine whether there was a correlation between the variables. In addition, the correlation between these laboratory values and CMV PCR copy numbers was examined. There was no statistically significant difference between the two groups with and without CMV reactivation in terms of these laboratory parameters (hemoglobin $p = 0.676$, leukocyte $p = 0.954$, neutrophil $p = 0.141$, lymphocyte $p = 0.120$, monocyte $p = 0.347$, platelet $p = 0.565$, CRP $p = 0.676$, ALT $p = 0.705$, and AST $p = 0.623$). In addition, no statistically significant correlation was found between these laboratory parameters and CMV PCR copy counts (hemoglobin $p = 0.918$, leukocyte $p = 0.201$, neutrophil $p = 0.153$, lymphocyte $p = 0.163$,

Table 2. CMV reactivation status of patient groups.

Characteristic	Group 1	Group 2	*p*
CMV reactivation, n(%)			
Yes	18 (78.3)	8 (72.7)	0.722
No	5 (21.7)	3 (27.3)	
CMV DNA load (copy/mL), mean ± sd, median (min–max)	71668.0 ± 208201.0, 679.0 (0.0–952943.0)	12389.0 ± 15844.0, 1574.0 (0.0–46367.0)	0.717*

p: Chi-square test; *p**: Mann-Whitney u test; CMV: cytomegalovirus.

Table 3. Comparison of prognostic parameters and ETA CMV reactivation.

Characteristic	ETA CMV PCR (+)	ETA CMV PCR (-)	*p*
LOS, mean ± sd, median (min–max)	26.0 ± 21.5, 17.0 (6.0–83.0)	16.0 ± 4.7, 16.0 (9.0–22.0)	0.510*
Ventilator days, mean ± sd, median (min–max)	25.5 ± 21.3, 17.0 (4.0–83.0)	14.3 ± 3.6, 14.5 (9.0–20.0)	0.347*
Mortality, n (%)	14 (53.9)	4 (50.0)	0.849

p: Chi-square test; *p**: Mann-Whitney u test. ETA CMV: endotracheal aspirate cytomegalovirus; LOS: length of stay; PCR: polymerase chain reaction.

monocyte $p = 0.640$, platelet $p = 0.172$, CRP $p = 0.700$, ALT $p = 0.815$, and AST $p = 0.565$).

LOS, mechanical ventilation duration, and 28-day mortality data were compared between patients with and without CMV reactivation in the ETA, and correlation between the LOS and mechanical ventilation duration data and the ETA CMV PCR copy counts were also examined. There was no statistically significant difference in LOS between the ETA CMV PCR (+) and (-) groups ($p = 0.510$). There was no statistically significant difference between the ETA CMV PCR (+) and (-) groups in terms of average mechanical ventilation duration ($p = 0.347$). In addition, there was no statistically significant difference between the ETA CMV PCR (+) and (-) groups in terms of 28-day mortality ($p = 0,849$).

No statistically significant correlation was found between ETA CMV PCR copy counts and both LOS and mechanical ventilation duration ($p = 0.367$, and $p = 0.278$). Table 3 provides a summary of the comparison between ETA CMV reactivation and clinical data.

LOS, mechanical ventilation duration, and 28-day mortality data were compared between patients with and without serum CMV reactivation. In addition, correlations between LOS and mechanical ventilation duration data, and serum CMV PCR copy counts were examined. In terms of the average LOS, there was a statistically significant difference between the groups with serum CMV PCR (+) and serum CMV PCR (-) ($p = 0.047$). In addition, a statistically significant difference was found between the group with serum CMV PCR (+) and the group with serum CMV PCR (-) in terms of average mechanical ventilation duration ($p = 0.036$). There was no statistically significant difference in 28-day mortality between the group with serum CMV PCR (+) and the group with serum CMV PCR (-) ($p = 0.774$). There was no statistically significant correlation between both the LOS and the mechanical ventilation duration, and serum CMV PCR copy counts ($p = 0.248$, and $p = 0.206$). Table 4 provides a summary of the comparison between serum CMV reactivation and clinical data.

Discussion

Innate immune response elements are activated during pneumonia and sepsis that are caused by extracellular bacteria. The immune begins with the detection of pathogen-associated molecular pattern and damage-associated molecular pattern (DAMP) by patern recognizing receptors (PRR), and continues with nuclear factor kappa B (NF-κB) activation and cytokine release. However, in the immune response developed against intracellular microorganisms, a state of suppression, also called "immune paralysis", is observed. This may cause intracellular infection agents like CMV and herpes simplex virus (HSV) to reactivate [10]. Activation of NF-κB triggers innate immune response and immune paralysis. In addition, it can activate the expression of immediate-early genes of CMV, thus causing CMV reactivation [11]. Another mechanism that triggers the expression of CMV immediate-early genes in monocytes is the activation of β-2 adrenergic receptors which is caused by sympatic hyperactivity and catecholamine discharge from the organism under stress [12]. CMV reactivation can lead to secondary bacterial and fungal infections, which can cause increased morbidity and mortality in patients [13]. With this background, this study was planned to investigate the presence of CMV reactivation in our patients who were in immune paralysis despite not having classical etiology for immunosuppression; but received mechanical ventilation support, were in the critically ill group, had bacterial growth in the lower respiratory tract, and had sepsis and extracellular bacterial pneumonia.

The rate of CMV reactivation has been found to range between 0–80% in studies examining the condition in immunocompetent individuals admitted to ICUs [14–20]. In our study, the CMV reactivation rate was 79.4%, which was, to the best of our knowledge. the second highest reactivation rate in the literature. The

Table 4. Comparison of prognostic parameters and serum CMV reactivation.

Characteristic	Serum CMV PCR (+)	Serum CMV PCR (-)	*p*
LOS, mean ± sd, median (min–max)	32.6 ± 24.5, 23.0 (6.0–83.0)	17.5 ± 11.8, 15.0 (7.0–62.0)	0.047*
Ventilator days, mean±sd, median (min–max)	32.2 ± 23.8, 25.0 (6.0–83.0)	16.4 ± 12.1, 14.0 (4.0–62.0)	0.036*
Mortality, n(%)	7 (50.0)	11 (55.0)	0.774

p: Chi-square test; *p**: Mann-Whitney u test. CMV: cytomegalovirus; LOS: length of stay; PCR: polymerase chain reaction.

highest reactivation rates were recorded in sepsis patients [21]. All 25 patients who were a part of the study by Lambe *et al.* [16] had sepsis, which may account for the study's 80% CMV reactivation rate, the highest recorded in the literature. Our study also has the distinction of being the second study in this area in our country. The first study in this area in our country was conducted by Coşkun *et al.* [15], and the CMV reactivation rate was found to be 8.3%. The reasons of high CMV reactivation rates in our study may be the following: the patients included in our study were all mechanically ventilated, CMV IgG positive, had bacterial growth in lower respiratory tract, and 67.6% had sepsis and VAP. Existence of CMV was evaluated by PCR, which is a more sensitive method than pp65 antigenemia and culture. Both lower respiratory tract and serum samples were tested.

The lungs are the principal organ affected by latent CMV infection and reactivation [22]. Even if there are no risk factors of lung origin, bacterial sepsis can cause CMV reactivation in the lung [23]. In a study by Chilet *et al.*, CMV reactivation was evaluated in both plasma and ETA sample; the reactivation rate in ETA sample was found to be 39.7%, and the reactivation rate in plasma was 30.2% [24]. Similar to this literature data, in our study, both the CMV reactivation rate and the CMV PCR copy counts were found to be higher in the ETA sample compared to the serum.

Sepsis is one of the most important causes of CMV reactivation in immunocompetent patients treated in the ICU [4]. In addition to sepsis, VAP has also been associated with CMV reactivation [20]. In our study, the patients were split into two groups: group 1 included those who had VAP and sepsis, while group 2 included those who did not. The two groups were compared to assess CMV reactivation. Similar to the current literature data, both the CMV reactivation rate and the CMV PCR copy counts were found to be higher in group 1 patients compared to group 2. Although the CMV PCR copy counts of patients in group 1 was 5.8 times compared to group 2 patients, the differences between CMV PCR copy counts and reactivation rates were not statistically significant. The small sample size in our study and the inconsistency of the number of patients between the groups may have caused this situation. Interestingly, in our study, a high rate of CMV reactivation was observed in group 2 patients (72.7%), although they did not have sepsis or VAP. This observation leads to the conclusion that, even if bacterial colonization does not result in VAP, it may result in a high rate of CMV reactivation in patients who are mechanically ventilated.

SOFA scoring for the diagnosis of sepsis and organ failure, and APACHE II scoring for determining severity of illness and mortality are frequently used in management of ICU patients. It is well established that critical illness and sepsis increase CMV reactivation. Therefore, many studies have been conducted to evaluate the relationship between these scoring systems and CMV reactivation [17–19]. However, none of these studies found a relationship between SOFA and APACHE II scores and CMV reactivation. In our study, similar to these literature data, no statistically significant correlation was found between SOFA and APACHE II scores and CMV reactivation and CMV PCR copy counts. The characteristics utilized in the scoring may not be risk factors for CMV reactivation, which may explain why there was no correlation between the SOFA and APACHE II scoring systems and CMV reactivation, despite the fact that these scoring systems attempt to predict the severity of critical illness.

Previous studies evaluating CMV reactivation in immunocompetent patients followed in the ICU, along with risk factors for CMV reactivation, prognosis factors like length of stay, ventilation duration and mortality were also investigated for their relation to CMV reactivation. In nearly all systematic reviews and meta-analyses, CMV reactivation was linked to prolonged LOS, prolonged mechanical ventilation, and increased secondary bacterial and fungal infections [4,21,25]. Bacterial and fungal superinfections on the basis of CMV reactivation may both be the cause or the result of prolonged LOS and mechanical ventilation. In our study, similar to previous reports, CMV reactivation was found to be associated with both prolonged hospitalization and mechanical ventilation, and this relationship was statistically significant. It is interesting to note that in our study, CMV reactivation detected in serum was associated with prolonged hospitalization and mechanical ventilaton; however, CMV reactivation detected in ETA was not associated with prolonged hospitalization or mechanical ventilaton. Although the lung is the primary site of CMV reactivation, it can be said that CMV reactivation found in ETA samples were less successful in predicting prolonged hospitalization and mechanical ventilation compared to blood samples.

Systematic reviews and meta-analysis in the literature have shown contradictory findings regarding the connection between CMV reactivation and mortality. A review by Schildermans *et al.* reported that mortality was twice as high in the patient group with CMV reactivation [21]. In a review by Osawa *et al.*, it

was reported that there was no significant relationship between CMV reactivation and mortality [4]. According to Li *et al*.'s systematic review and meta-analysis, there was no correlation between reactivation and mortality when CMV reactivation was assessed just from blood samples, but there was a correlation when all sample types and methodologies were considered [26]. In our study, no statistically significant relationship was found between CMV reactivation and mortality.

The limitations of our study were the small sample size, use of old samples to assess CMV reactivation, and using ETA samples to assess CMV reactivation in the respiratory tract. By using a larger sample size, more patients can be statistically evaluated, and the comparison groups' patient populations can be equalized, and logistic regression analysis can be done to evaluate risk factors for CMV reactivation. In order to assess the impact of bacterial pneumonia on CMV reactivation, a third patient group without sepsis but with pneumonia can be added to the study. Another group of patients who are mechanically ventilated but do not have bacterial colonization in the lower respiratory tract can also be added to investigate the effect of bacterial colonization on CMV reactivation. To examine the connection between bacterial type and CMV reactivation, comparisons might also include bacteria other than *A. baumannii*. To investigate the effect of mechanical ventilation alone on CMV reactivation, another group of ICU patients who are not mechanically ventilated can be included. Using fresh clinical samples may increase sensitivity of CMV PCR. Bronchoalveolar lavage (BAL) instead of ETA samples can be used, because BAL is a more preferred method of diagnosis for CMV pneumonia [27]. Although we used old samples and ETA, the sensitivity did not significantly decline because we recorded a high rate of CMV reactivation in our study.

Conclusions

The CMV reactivation rate of immunocompetent ICU patients who have bacterial growth in lower respiratory tract was 79.4%. CMV PCR copy counts of the patients with VAP and sepsis were 5.8 times higher than those who did not have these conditions. CMV reactivation was found to be related with both prolonged hospitalization and prolonged mechanical ventilation. CMV reactivation was not found to be associated with mortality.

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