



Original Article

Associated Factors on Cytomegalovirus Reactivation in Patients with COVID-19 in the Intensive Care Unit

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Abstract. Background: Critically ill patients in intensive care units (ICUs) are susceptible to cytomegalovirus (CMV) reactivation. Previous studies have identified an association between CMV reactivation and increased mortality, length of ICU stay, and duration of mechanical ventilation (MV).

Methods: The study compared severe COVID-19 patients who received antiviral therapy (ganciclovir) for CMV reactivation (n=39) with a control group of patients without reactivation (n=39).

Results: The reactivation group exhibited higher mortality rates (n=28, 71.8%) than the control group (n=15, 38.5%). Duration of steroid treatment, prolonged MV, and lower hemoglobin levels were identified as factors associated with CMV reactivation. The optimal cut-off value of hemoglobin was found to be ≤ 9.8 g/dL ($p < 0.001$, AUC: 0.708, sensitivity: 56.41, specificity: 84.62). Furthermore, significantly higher ALT (alanine aminotransferase) levels were observed in the reactivation group ($p < 0.001$), and an association was found between elevated ALT and reactivation (AUC: 0.721). Within the reactivation group, the baseline CMV DNA levels were higher in non-survivors (n=28) than in survivors (n=11), although this difference was not statistically significant. A downward trend in CMV DNA levels was observed during follow-up in both survivors and non-survivors, eventually reaching undetectable levels.

Conclusions: In critically ill patients, CMV reactivation was associated with prolonged ICU stay, mechanical ventilation, and steroid therapy. Lower hemoglobin and elevated ALT levels may serve as useful clinical indicators for CMV reactivation.

Keywords: Cytomegalovirus; Critically ill; Intensive care unit; COVID-19; Antiviral therapy; Hemoglobin.

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Introduction. Cytomegalovirus (CMV), a member of the Herpesviridae family, typically presents asymptomatic primary infection during childhood. Following this, the virus establishes lifelong latency; however, reactivation can occur under specific conditions, particularly in immunocompromised individuals.¹ Furthermore, accumulating evidence suggests that the physiological stress of critical illness

itself induces immune dysregulation, which may facilitate viral reactivation even in previously immunocompetent patients.² Plasma CMV viral load is the preferred method for assessing reactivation and for guiding initiation of antiviral therapy and monitoring response to treatment.³

The clinical spectrum of CMV ranges from asymptomatic reactivation to life-threatening organ involvement. In immunocompromised transplant cohorts, CMV syndrome (fever, malaise, and cytopenia) and CMV disease (organ involvement) are clearly defined.^{4,5} Conversely, in critically ill patients, it is difficult to suspect and define CMV disease. At the same time, the necessity of monitoring CMV reactivation and the optimal strategies for treatment or prophylaxis remain unclear.⁶

In critically ill patients, CMV reactivation is associated with increased mortality, prolonged mechanical ventilation (MV), and extended hospital stay.⁷⁻¹⁰ Evidence shows that mortality rates among patients with CMV reactivation are nearly double those without reactivation.^{3,6} In critically ill patients, CMV reactivation can cause worse clinical outcomes with direct and indirect lung injury.¹¹ Recent data indicated that CMV pneumonitis may occur in approximately 50% of intensive care unit (ICU) patients with acute respiratory distress syndrome (ARDS). Furthermore, CMV reactivation may exacerbate the clinical course of ARDS. Given that the lungs are a primary site of latent CMV, understanding the relationship between CMV reactivation and the duration of mechanical ventilation is clinically important.^{9,12,13}

Up to the present, risk factors such as high disease severity, prolonged ICU stay, MV, sepsis, steroid use, raised C-reactive protein (CRP), and lower hemoglobin have been associated with CMV reactivation in immunocompetent critically ill patients.^{6,11,14}

Determining whether CMV reactivation is pathogenic or coincidental is crucial for guiding ICU management.⁹ While an animal model suggests that ganciclovir blocks CMV reactivation and can prevent pulmonary fibrosis,¹⁵ antiviral therapy in critically ill patients published to date has been limited.¹⁶⁻¹⁸

Although clinically significant, the definitive impact of CMV reactivation on outcomes in critically ill populations remains poorly defined, necessitating further investigation. This study aimed to identify risk factors for CMV reactivation by comparing patients who received antiviral therapy with those who did not. Additionally, we performed a subgroup analysis of patients with CMV reactivation to identify parameters associated with mortality.

Methods. Approval of the local ethics committee was obtained for this study (Confirmation date and number: 12.01.2022/ E1-22-2276). This study was conducted in

accordance with the principles of the Declaration of Helsinki.

Study Design and Participants. From February 1, 2021, to March 1, 2022, mechanically ventilated patients with COVID-19 were retrospectively screened. All patients included in this study (age ≥ 18 years) had no history of pre-existing immunosuppressive conditions such as hematological malignancy, solid organ transplantation, HIV infection, or long-term immunosuppressive therapy before ICU admission. Although COVID-19 itself and corticosteroids may exert immunomodulatory effects, patients were classified as immunocompetent based on the absence of established chronic immunosuppression before hospitalization. In the 24-bed ICU, patients (reactivation and control groups) who underwent CMV monitoring via quantitative polymerase chain reaction (PCR; Rotor-Gene Q, QIAGEN) weekly were included in the study. CMV reactivation was treatment-defined. Patients with a viral load threshold ≥ 1000 U/mL and assessed clinical conditions (fever, diarrhea, absence of bacterial diagnosis for pneumonia, cytopenia, and hepatitis) who received ganciclovir treatment (5 mg/kg twice daily for 14 days for induction, followed by 5 mg/kg once daily for maintenance) were included in the reactivation group. Nine patients with viral loads above 1000 copies/mL were not treated with ganciclovir because DNA levels decreased during follow-up, and no clinical indicators were present. Due to the very small number of patients, a control group could not be formed. The CMV reactivation group was matched to the control group according to the following criteria: age within ± 10 years, similar SAPS (Simplified Acute Physiology Score), and admission date. The control group included patients with CMV PCR consistently < 50 copies/mL monitored weekly.

Clinical data, outcomes, laboratory findings (hematological parameters, liver function tests, acute-phase reactants), and CMV PCR results were obtained from patients' files and electronic medical records. The laboratory parameters were recorded twice (on admission and on the 14th day of treatment).

Statistical analysis. All statistical calculations were made using the "SPSS for Windows version 26" software program (IBM Corporation, IL). Comparisons for categorical variables were executed using the Pearson chi-square test or Fisher's exact test. The Shapiro-Wilk test was performed to check the normality of the continuous variables. Differences between the two groups were compared using the Mann-Whitney U and Independent Samples T-tests. Multivariate logistic regression (Forward LR) was performed and found to be significant in the univariate analysis to assess the associated factors for CMV reactivation. The odds ratio (OR) was calculated for variables with significant

Table 1. Demographics and laboratory findings of patients on admission.

	No Reactivation (n=39)	CMV Reactivation (n=39)	Total (n=78)	X ² -Z	p-value
Age (years)	67 (24-97)	61 (24-85)	64.5 (24-97)	-1.175	0.240
Gender (male)	29 (74.4)	27 (69.2)	56 (71.8)	0.253	0.615
APACHE	13 (3-31)	13 (5-33)	13 (3-33)	-1.776	0.076
SAPS	27 (4-69)	24 (6-79)	26 (4-79)	-0.661	0.509
SOFA	5 (2-12)	3 (1-14)	4 (1-14)	-1.936	0.053
PaO ₂ /FiO ₂	80 (45-250)	70 (30-160)	75 (30-250)	-1.339	0.181
Steroid treatment (days)	12 (2-28)	24 (3-70)	17 (2-70)	-5.295	<0.0001
Duration of MV (days)	8 (3-125)	35 (5-135)	19 (3-135)	-4.867	<0.0001
Length of ICU stay (days)	13 (5-142)	40 (15-141)	30 (5-142)	-4.660	<0.001
Mortality	15 (38.5)	28 (71.8)	43	8.759	0.003
Liver enzyme abnormalities	4 (10.3)	19 (48.7)	23	13.874	<0.001
Cytopenia	0 (0)	24 (61.5)	24 (61.5)	34.667	<0.001
Leucocytes (μ/L)	10.380 (2.390-21.900)	11.150 (4.650-26.740)	10.390 (2.390-26.740)	-0.784	0.433
Neutrophils (μ/L)	9.190 (1.690-20.730)	9.550 (3.940-23.340)	9.540 (1.690-23.340)	-0.879	0.379
Lymphocytes (μ/L)	570 (200-2.100)	690 (140-2.130)	580 (140-2.130)	-0.630	0.529
Monocytes (μ/L)	384 (216-1041)	236 (74-503)	468 (216-1041)	-1.625	0.104
Platelets (μ/L)	292000 (105000-533000)	233000 (8000-574000)	262000 (8000-574000)	-1.594	0.111
Hemoglobin (g/dL)	12.6 (6.7-17)	9.4 (7.6-15.7)	11.1 (6.7-17)	-3.159	0.002
ALT (U/L)	29 (9-301)	56 (8-588)	38 (8-588)	-3.364	0.001
AST (U/L)	43 (16-247)	49 (13-1355)	44.5 (13-1355)	-1.110	0.267
CRP (g/L)	0.13 (0.01-5.77)	0.07 (0-0.35)	0.1 (0-5.77)	-1.695	0.090
Procalcitonin ((μg/L)	0.17 (0.03-46.73)	0.36 (0.06-117)	0.24 (0.03-117)	-1.130	0.259
Interleukin-6 (pg/mL)	50.1 (2.7-3734)	30.6 (2.7-1294)	33.25 (2.7-3734)	-0.070	0.944
Ferritin (μg/L)	500 (24-3838)	703 (131-3931)	582 (24-3931)	-1.669	0.095

Data are n (%) or median (min-max). APACHE; Acute Physiology and Chronic Health Evaluation, SAPS; Simplified Acute Physiology Score, SOFA; Sequential Organ Failure Assessment, MV; Mechanical ventilation, ICU; Intensive care unit, ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, CRP; C-reactive protein.

Table 2. Multivariate logistic regression analysis for cytomegalovirus reactivation.

Parameters	B	S.E.	p	Exp(B)	95% CI	Tolerance	VIF	Nagelkerke R ²
Length of ICU stay	-0.063	0.033	0.056	0.939	0.880 1.001	0.180	5.538	0.756
Duration of MV	0.137	0.045	0.002	1.147	1.051 1.251	0.189	5.288	
Steroid treatment	0.242	0.078	0.002	1.274	1.093 1.485	0.839	1.192	
Hemoglobin	-0.475	0.176	0.007	0.622	0.440 0.879	0.942	1.062	

ICU; Intensive care unit. MV; Mechanical ventilation.

associations. Receiver operating characteristic (ROC) curve analysis was performed to assess the efficacy of laboratory parameters. Statistical significance was defined as $p < 0.05$.

Results. In total, 39 patients with CMV reactivation and 39 controls participated in the study. In the reactivation group, the day of steroid treatment, length of MV, cytopenia, and elevated liver function tests were significantly higher than in the control group. The reactivation group had significantly higher alanine

aminotransferase (ALT) levels and lower hemoglobin levels (**Table 1**).

Univariate logistic regression analysis showed that ICU length of stay, the day of steroid treatment, MV duration, ALT, and hemoglobin levels were associated with reactivation. In the model created with the variables found to be significant in univariate logistic regression, it was found that the duration of MV, steroid treatment, and hemoglobin level had a statistically significant effect in the 4th step ($p < 0.05$) (Nagelkerke R² = 0.756), showing that the model has high explanatory power over

the data (**Table 2**). After the ROC analysis for laboratory parameters, the optimal cut-off value of ALT was found to be >58 IU/ml ($p<0.001$, AUC: 0.721, sensitivity: 56.41, specificity: 87.18), and hemoglobin was found to be ≤ 9.8 g/dL ($p<0.001$, AUC: 0.708, sensitivity: 56.41, specificity: 84.62) (**Figures 1 and 2**).

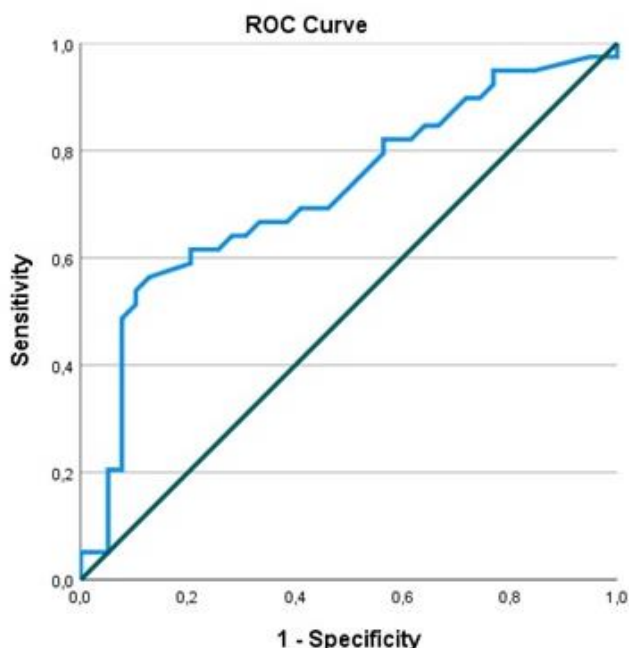


Figure 1. Supportive performans of alanine aminotransferase for CMV reactivation. (optimal cut-off value: > 58 , a sensitivity: 56.41 and a specificity: 87.18, AUC: 0.721, $p=0.0002$).

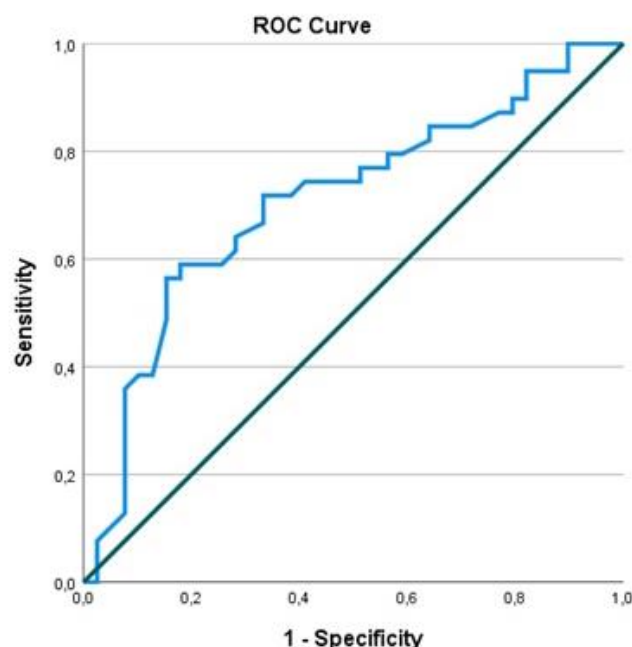


Figure 2. Supportive performans of hemoglobin for CMV reactivation. (optimal cut-off value: ≤ 9.8 g/dL, a sensitivity: 56.41, and a specificity: 84.62, AUC: 0.708, $p=0.0005$).

The reactivation group had higher mortality rates ($n=28$, 71.8%) than the control group ($n=15$, 28.5%). The patients with CMV reactivation were analyzed into non-

survivor ($n=28$) and survivor ($n=11$) groups. In the non-survivor group, no patients achieved successful weaning from mechanical ventilation (MV), a finding that was statistically significant compared with survivors ($p<0.001$). Higher CRP levels and lower monocytes and platelets were found in the non-survivor group on admission. On the 14th day of the treatment, higher aspartate aminotransferase (AST), CRP, procalcitonin, IL-6, ferritin, and lower lymphocytes and platelets were found in the non-survivor group (**Tables 3 and 4**).

Mean $\pm$ SD value of CMV DNA levels of patients with CMV reactivation is shown in **Table 5**. Baseline DNA (mean $\pm$ SD) levels were higher in the non-survivor group, but no statistically significant difference was detected. A downward trend was seen in both groups (**Figure 3**).

Discussion. CMV reactivation in this cohort was linked to extended ICU stay and prolonged MV. Lower Hb levels were associated with CMV reactivation. Based on these results, critically ill patients with prolonged hospitalization and mechanical ventilation should be monitored for CMV reactivation. Clinicians should maintain a higher index of suspicion for CMV reactivation in patients presenting with supportive laboratory indicators, such as decreased hemoglobin and elevated ALT levels. While these parameters lack primary diagnostic specificity, they may serve as useful signals to initiate closer virological monitoring.

In this study, the baseline CMV DNA level was higher in non-survivor patients than in survivors in the reactivation group. However, during follow-up, CMV levels declined similarly in both survivors and non-survivors, eventually reaching undetectable levels in both groups. This finding suggested that, while initial DNA levels are a marker of severity, viremia clearance occurs regardless of clinical outcome. However, it is essential to recognize that clinical outcomes in critically ill patients are multifactorial and are significantly influenced by a wide array of confounding variables beyond viral reactivation.

There are significant uncertainties regarding CMV infection in immunocompetent critically ill patients monitored in intensive care units. CMV reactivation episodes, during critical illness, are associated with worsened outcomes.⁸ CMV reactivation has been shown in many studies to increase mortality, duration of intensive care, and mechanical ventilation.^{5,19,20} In a meta-analysis, all-cause mortality of patients with CMV reactivation was 2.16-fold higher compared with those without infection.¹⁰ A systematic review including 13 studies ($n=1258$) revealed that the mortality rate is significantly increased by 2-fold with CMV.³ In this study, mortality was found to be higher in patients with reactivation than in those with no reactivation (71.8% vs. 38.5%, $p=0.003$). The duration of MV was found to be associated with reactivation. (OR:1.15). Heininger et al.

Table 3. Characteristics and laboratory parameters of patients for mortality with cytomegalovirus reactivation.

	Survivors (n=11)	Non-survivors (n=28)	Total (n=39)	Z	p-value
Age	57 (24-63)	69 (39-85)	61 (24-85)	-2.733	0.006
APACHE	13 (5-28)	13 (8-33)	13 (5-33)	-1.330	0.183
SAPS	23 (6-71)	27 (13-79)	24 (6-79)	-0.219	0.827
SOFA	2 (1-11)	3 (2-14)	3 (1-14)	-0.621	0.535
PaO2/Fio2	80 (44-160)	66 (30-125)	70 (30-160)	-1.142	0.254
Steroid treatments (days)	23 (11-70)	24 (3-48)	24 (3-70)	-0.344	0.731
Duration of MV (days)	50 (5-135)	34 (5-80)	35 (5-135)	-0.547	0.585
Length of ICU stay (days)	71 (23-141)	37 (15-92)	40 (15-141)	-1.608	0.108
Duration of MV after the beginning of CMV treatment	17 (0-110)	9 (1-57)	10 (0-110)	-0.703	0.482
MV-free days after CMV treatment	5 (0-26)	0 (0-0)	0 (0-26)	-4.954	<0.0001
Length of ICU stay after treatment	28 (0-90)	6 (0-57)	7 (0-90)	-2.065	0.039
Duration of antiviral treatment	28 (10-56)	9 (1-41)	12 (1-56)	-3.393	0.001
Time to start treatment in ICU	31 (4-60)	30 (7-63)	30 (4-63)	-0.031	0.975
Initiation of treatment after PCR positivity	7 (1-23)	5 (1-38)	0 (0-38)	-0.989	0.322

APACHE; Acute Physiology and Chronic Health Evaluation, SAPS; Simplified Acute Physiology Score, SOFA; Sequential Organ Failure Assessment, MV; Mechanical ventilation, CMV; Cytomegalovirus, ICU; Intensive care unit.

Table 4. Evaluation of the admission and 14th day of treatment laboratory parameters of patients for mortality with cytomegalovirus reactivation.

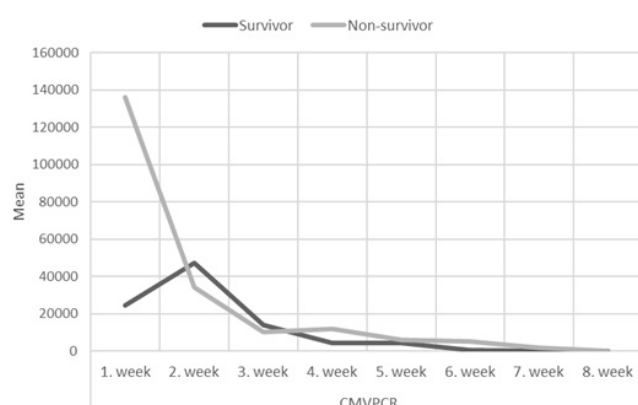
	Survivors (n=11)	Non-survivors (n=28)	Total (n=39)	Z	p-value
Leucocytes	10.250 (6.220-19.100)	11.650 (4.650-26.740)	11.150 (4.650-26.740)	-0.094	0.925
Leucocytes (14 th)	11.110 (4.970-16.650)	11.160 (760-27.780)	11.110 (760-27.780)	-0.094	0.925
Neutrophils	9.430 (5.200-17.250)	11.270 (3.940-23.340)	9.550 (3.940-23.340)	-0.437	0.662
Neutrophils (14 th)	7.460 (3.440-13.750)	9.160 (430-24.490)	9.030 (430-24.490)	-0.546	0.585
Lymphocytes	87 (180-1.7)	60 (140-2.130)	69 (140-2.130)	-0.718	0.473
Lymphocytes (14th)	150 (70-2.740)	83 (10-3.010)	96 (10-3.010)	-2.450	0.014
Monocytes	370 (198-625)	130 (74-503)	236 (74-503)	-2.718	0.007
Monocytes (14 th)	420 (205-540)	271 (63-450)	258 (63-540)	-1.578	0.115
Platelets	342000 (233000-574000)	168500 (8000-479000)	233000 (8000-574000)	-3.153	0.002
Platelets(14th)	436000 (212000-915000)	159500 (8000-583000)	233000 (8000-915000)	-3.027	0.002
Hemoglobin	9.8 (8.3-15.7)	9.3 (7.6-15.6)	9.4 (7.6-15.7)	-1.297	0.195
Hemoglobin (14 th)	9.2 (7.8-12.3)	8.6 (7.7-11.6)	8.7 (7.7-12.3)	-1.782	0.075
ALT	82 (19-138)	50.5 (8-588)	56 (8-588)	-0.078	0.938
ALT (14 th)	37 (17-122)	52 (2-2943)	48 (2-2943)	-0.734	0.463
AST	50 (16-130)	47.5 (13-1355)	49 (13-1355)	-0.343	0.731
AST (14th)	33 (18-123)	86 (19-10212)	68 (18-10212)	-2.872	0.004
CRP	0.04 (0-0.18)	0.09 (0.01-0.35)	0.07 (0-0.35)	-2.328	0.020
CRP (14th)	0.02 (0.01-0.06)	0.12 (0.03-0.6)	0.08 (0.01-0.6)	-4.497	<0.0001
Procalcitonin	0.14 (0.06-16.79)	0.4 (0.06-117)	0.36 (0.06-117)	-1.827	0.068
Procalcitonin (14th)	0.15 (0.03-0.46)	1.58 (0.1-42.3)	0.59 (0.03-42.3)	-4.370	<0.0001
Interleukin-6	24.4 (2.7-164.5)	38 (7.2-1294)	30.6 (2.7-1294)	-1.779	0.075
Interleukin-6 (14th)	9.85 (2.7-34.7)	382.5 (18.1-8542)	117.5 (2.7-8542)	-4.428	<0.0001
Ferritin	886 (195-2650)	664 (131-3931)	703 (131-3931)	-0.234	0.815
Ferritin (14th)	499 (113-1283)	1237 (196-77626)	970 (113-77626)	-2.528	0.011

ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, CRP; C-reactive protein.

Table 5. CMV DNA levels of patients with CMV reactivation.

	Survivor (n=11)	Non-survivors (n=28)	Total (n=39)	Z	p-value
Viral load (Baseline)	24629±53498	135868±588104	104493±499071	-0.234	0.815
Viral load (Second week)	47369±96430	33987±106856	37965±102717	-0.532	0.595
Viral load (Third week)	14006±20319	10306±16189	11760±17652	-0.518	0.605
Viral load (Fourth week)	4267±4741	11748±14434	133034±623676	-0.784	0.433
Viral load (Fifth week)	4411±10280	5799±8283	5947±9327	-1.167	0.243
Viral load (Sixth week)	427±526	5096±6661	2744±4904	-1.774	0.076
Viral load (Seventh week)	92±163	1878±3757	807±2360	0.000	1.000
Viral load (Eighth week)	0±0	0±0	0±0	0.000	1.000

CMV; Cytomegalovirus. Data are mean±SD.

**Figure 3.** Weekly CMVPCR levels (mean±SD) in survivor and non-survivor patients with CMV reactivation.

reported that prolonged MV (HR: 2.6) was associated with CMV reactivation.²¹ Steroid use was found to be another factor contributing to reactivation in this study, consistent with previous reports in the literature.^{5,19} In this study, all patients were treated with steroids, so the duration of steroid treatment was evaluated, and it was found that steroid treatment was associated with reactivation (OR: 1.27, $p<0.001$).

Immunocompetent ICU patients in whom CMV reactivation is frequently underrecognized and rarely considered in the differential diagnosis of worsening breathing and unexplained cytopenias. In this study, a lower hemoglobin level was defined as an associated factor for reactivation. Cytopenia is part of CMV syndrome, and lower hemoglobin levels have previously been identified as a predictor of reactivation.^{3,14,22} Zhang et al. reported that AST and hemoglobin levels were found to be higher in patients with CMV reactivation.²² They also found that hemoglobin was a predictor of reactivation. (with the cut-off: ≤ 8.7 g/dL, $p=0.02$, AUC: 0.70, sensitivity: 100, specificity: 48.3). In this study, the optimal cut-off value for hemoglobin level ≤ 9.8 g/dL was found to have a limited sensitivity of 56.41% and specificity of 84.62% ($p<0.001$, AUC: 0.708) for CMV reactivation.¹⁴ This study also showed that ALT levels increase during reactivation. However, ALT may be considered a non-specific marker because its elevation

may reflect certain conditions such as drug-induced liver injury, hypoxic hepatitis, and COVID-19-related inflammation. But in the intensive care, making a clear distinction between these conditions is often not possible.

The diagnosis of CMV infection is difficult in ICU patients because clinical signs are nonspecific.⁵ Plasma CMV viral load is used by clinicians to guide initiation of antiviral treatment and to monitor treatment response.³ In this study, although the initial viral load was higher in survivors, the course of viral load during follow-up was similar in survivors and non-survivors. This observation hypothesis-generating suggests whether weekly viral load monitoring is necessary or not in patients who have received treatment.

Antiviral therapy for CMV in critically ill patients published to date has been limited. Some experts recommend against antiviral therapy in critically ill immunocompetent patients.⁸ However, others suggested that regular viral load monitoring of patients in the ICU, and treatment initiated only in those patients with viral reactivation above a certain threshold.^{9,23} Hraiech et al. reported that no difference in clinical outcomes was found between treated ($n=34$) and untreated ($n=33$) patients with herpes virus reactivation, except for a trend towards longer duration of MV.¹² The question of whether treatment should be initiated in patients with CMV reactivation remains. Since there was no comparator group (untreated CMV-positive patients) in this study, it is not possible to comment on the treatment's effectiveness. However, given the high mortality rate observed, the treatment's clinical benefit is debatable. On the other hand, it should be noted that CMV reactivation may be an indicator of immune dysfunction and disease severity rather than a direct cause of poor outcomes. Randomized controlled trials are needed on these subject issues.

Several limitations of this study warrant consideration. First, its retrospective nature and a relatively small sample size ($n=78$) may limit the statistical power of the findings. Second, there is potential selection bias, as the reactivation group was defined by the initiation of antiviral therapy. This

treatment-dependent definition may have led to an overestimation of the association between CMV reactivation and clinical outcomes. Furthermore, the limited number of untreated patients with CMV reactivation (n=9) precluded the determination of a definitive viral load cut-off value or a comparative analysis. Finally, as the study population was focused on patients with severe COVID-19, the generalizability of the findings to other critically ill cohorts remains to be established.

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Conclusions. CMV reactivation is observed in critically ill patients; therefore, it should be considered and monitored in those with extended ICU stays and prolonged mechanical ventilation. Furthermore, lower hemoglobin and elevated ALT levels may serve as valuable laboratory indicators, aiding in the early clinical suspicion of reactivation.

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