Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2026;51(1):234-243
DOI: 10.17826/cumj.1842223

RESEARCH

Clinical and laboratory features of cytomegalovirus reactivation in immunosuppressed patients with rheumatic diseases

Romatolojik hastalık nedeniyle immünsüpresif tedavi alan hastalarda sitomegalovirüs reaktivasyonunun klinik ve laboratuvar özellikleri

Merve Sungur Özgünen[1], Emre Tekgöz[1], Seda Çolak[1], Özlem Kılıç[1], Mehmet Nur Kaya[1], Muhammet Çınar[1], Sedat Yılmaz[1]

[1]University of Health Sciences, Ankara, Türkiye

Abstract

Purpose: This study aimed to evaluate the clinical and laboratory features of cytomegalovirus (CMV) reactivation in immunosuppressed patients with rheumatic diseases and to compare the characteristics of patients with and without mortality.

Materials and Methods: This retrospective cohort study included 30 adult patients with rheumatic diseases who were receiving immunosuppressive therapy and underwent CMV polymerase chain reaction (PCR) testing due to clinical and/or laboratory suspicion between November 2016 and April 2024. Patients with CMV PCR positivity were included in the analysis. Demographic, clinical, and laboratory data were collected. Comparisons of clinical and laboratory parameters were conducted according to antiviral treatment use and survival status.

Results: Granulomatosis with polyangiitis (23%) and adult-onset Still's disease (20%) were the most frequent underlying diagnoses. CMV reactivation predominantly occurred during periods of intensive immunosuppressive therapy. Antiviral treatment with ganciclovir was administered in 70% of patients, who had higher CMV viral loads, lower lymphocyte and albumin levels, and higher C-reactive protein levels compared with untreated patients. The overall mortality rate was 23.3%. In multivariable analysis, CMV-associated pneumonia was the only variable independently associated with mortality.

Conclusion: CMV reactivation is a serious complication in immunosuppressed patients with rheumatic diseases and is associated with substantial mortality, particularly in the presence of pulmonary involvement.

Keywords:. Cytomegalovirus infections, rheumatic diseases, immunosuppressive agents, virus reactivation

Öz

Amaç: Bu çalışmanın amacı, romatolojik hastalık nedeniyle immünsüpresif tedavi alan hastalarda sitomegalovirüs (CMV) reaktivasyonuna bağlı mortalite gelişen ve gelişmeyen hastaların klinik ve laboratuvar özelliklerini karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif kohort çalışmasına, Kasım 2016 ile Nisan 2024 tarihleri arasında klinik ve/veya laboratuvar şüphe nedeniyle CMV polimeraz zincir reaksiyonu (PCR) testi yapılan, immünsüpresif tedavi alan 30 erişkin romatizmal hastalığı olan hastalar dâhil edilmiştir. CMV PCR pozitifliği saptanan hastalar analize alınmıştır. Demografik, klinik ve laboratuvar veriler kaydedilmiştir. Klinik ve laboratuvar parametreler, antiviral tedavi kullanımı ve sağkalım durumuna göre karşılaştırılmıştır.

Bulgular: Altta yatan tanılar sıklıkla granülomatöz polianjiit (%23) ve erişkin başlangıçlı Still hastalığı (%20) idi. CMV reaktivasyonu çoğunlukla yoğun immünsüpresif tedavi dönemlerinde ortaya çıkmıştır. Hastaların %70'ine gansiklovir ile antiviral tedavi uygulanmıştır. Antiviral tedavi alan hastalarda, tedavi almayanlara kıyasla CMV viral yükü daha yüksek, lenfosit ve albümin düzeyleri daha düşük, C-reaktif protein düzeyleri ise daha yüksek saptanmıştır. Genel mortalite oranı %23,3 olarak bulunmuştur. Çok değişkenli analizde, CMV ilişkili pnömoni, mortalite ile bağımsız olarak ilişkili tek değişken olarak belirlenmiştir.

Sonuç: CMV reaktivasyonu, immünsüpresif tedavi alan romatizmal hastalarda ciddi bir komplikasyon olup özellikle pulmoner tutulum varlığında yüksek mortalite ile ilişkilidir.

Anahtar kelimeler: Sitomegalovirüs enfeksiyonları; romatizmal hastalıklar; immünsüpresif ajanlar; viral reaktivasyon

Address for Correspondence: Merve Sungur Özgünen, University of Health Sciences, Gülhane Training and Research Hospital, Department of Rheumatology, Ankara, Türkiye E-mail: merve.sungur.dr@gmail.com
Received: 15.12.2025 Accepted: 07.02.2026

INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous beta-herpesvirus that establishes lifelong latency following primary infection. In immunocompetent individuals, CMV infection is typically asymptomatic or may present as an infectious mononucleosis–like syndrome characterized by prolonged fever, myalgia, and lymphadenopathy. Rarely, CMV may lead to complications such as arthritis, colitis, hepatitis, pneumonia, aseptic meningitis, or myocarditis[1,2].

In healthy individuals, viral latency is maintained through effective immune surveillance. However, CMV reactivation may occur in the setting of significant physiological stressors, including major surgery, sepsis, or catecholamine surges[3,4]. These mechanisms have been well characterized in populations such as solid organ and hematopoietic stem cell transplant recipients and individuals with HIV/AIDS, resulting in clearly defined approaches to CMV prophylaxis and antiviral management in these settings[2,5,6].

In recent years, CMV reactivation has been increasingly recognized in patients with autoimmune rheumatic diseases (ARDs), particularly among those receiving long-term immunosuppressive therapy[7-10]. Immunosuppressive agents, including systemic corticosteroids and biologic therapies, impair immune surveillance and increase susceptibility to opportunistic infections such as CMV[11, 12]. Moreover, the underlying immune dysregulation inherent to ARDs may further contribute to the risk of CMV reactivation. The clinical spectrum in this patient population resembles that observed in transplant recipients and includes asymptomatic viremia, gastrointestinal or pulmonary involvement, hepatitis, and cytopenias[7-10,13].

Among ARDs, patients with systemic lupus erythematosus (SLE) appear to be particularly vulnerable to CMV reactivation. In this context, CMV infection may closely mimic disease flares, posing significant diagnostic and therapeutic challenges[14,15]. Despite growing recognition, data regarding CMV reactivation and its clinical consequences in patients with rheumatic diseases remain limited. Many previous studies are constrained by small sample sizes, heterogeneous patient populations, or reliance on less sensitive diagnostic methods such as the pp65 antigenemia assay, rather than quantitative polymerase chain reaction (PCR)–based CMV DNA detection[16-18].

Despite increasing recognition, data on the clinical and laboratory characteristics of cytomegalovirus (CMV) reactivation in immunosuppressed patients with rheumatic diseases remain limited, particularly from real-world settings, and studies comparing patients with and without mortality are scarce. The originality of this study lies in its real-world evaluation of CMV reactivation in immunosuppressed patients with rheumatic diseases, with a systematic comparison of clinical and laboratory features between survivors and non-survivors. Accordingly, this study aimed to evaluate the clinical and laboratory characteristics of CMV reactivation and to compare patients with and without mortality. We hypothesized that specific clinical manifestations and laboratory abnormalities associated with CMV reactivation under immunosuppressive therapy are related to increased mortality.

MATERIALS AND METHODS

Study design and sample

This retrospective cohort study was conducted among patients with autoimmune rheumatic diseases receiving immunosuppressive therapy at the Rheumatology Department of University of Health Sciences, Gülhane Training and Research Hospital between November 2016 and April 2024. During this period, adult patients who developed unexplained cytopenias, fever, elevated liver enzymes, pneumonia, or diarrhea—after exclusion of disease activity or drug-related adverse effects—were screened using CMV DNA PCR. In total, 261 patients were assessed, and 30 patients with confirmed CMV DNAemia were identified and included in the final analysis (Figure 1).

The diagnoses of underlying rheumatic diseases were established by experienced rheumatologists in accordance with internationally accepted classification criteria.

Vasculitic conditions, including granulomatosis with polyangiitis, microscopic polyangiitis, IgA vasculitis, giant cell arteritis, and Behçet's disease, were categorized based on the revised nomenclature and definitions of the 2012 Chapel Hill Consensus Conference[30], which classifies vasculitides according to vessel size, histopathological features, and clinical

involvement. Adult-onset Still's disease was diagnosed using the Yamaguchi classification criteria[31], which are based on characteristic clinical features such as spiking fever, arthritis, and systemic inflammatory findings after exclusion of infectious and malignant causes. Systemic lupus erythematosus was classified according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria[32], incorporating clinical manifestations and immunological abnormalities to improve diagnostic sensitivity.

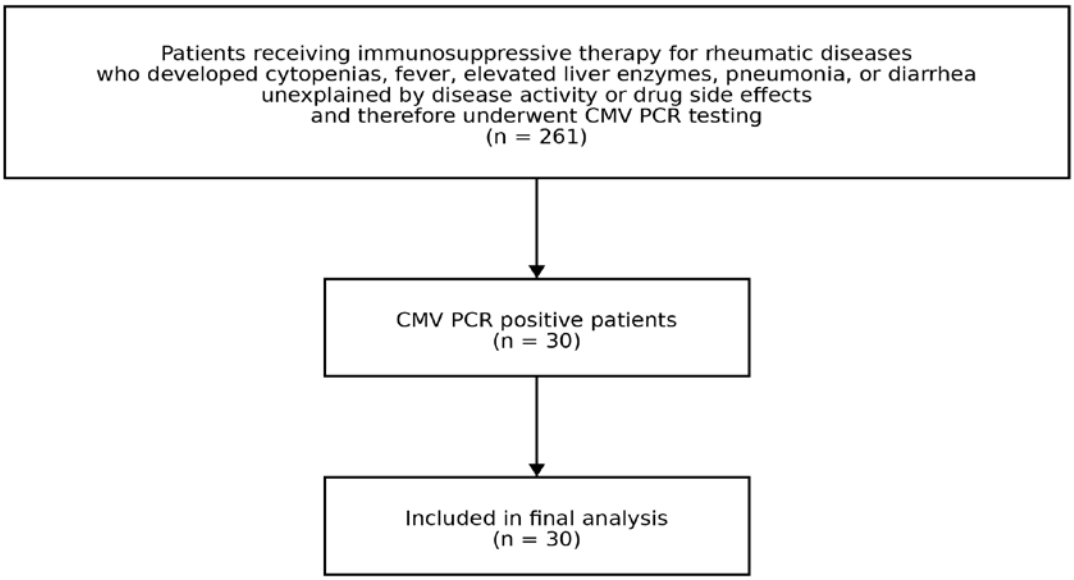


Figure 1. Flow diagram of the study population and CMV PCR results.

As the study population included patients diagnosed prior to 2016, inflammatory myopathies were classified using the Bohan and Peter criteria[33], which rely on proximal muscle weakness, elevated muscle enzymes, electromyographic findings, and muscle biopsy results, and represented the standard classification approach before the introduction of the 2017 EULAR/ACR criteria[34]. Sjögren syndrome was classified in accordance with the 2016 ACR/EULAR criteria[35], which emphasize objective evidence of glandular dysfunction and autoantibody positivity.

Polymyalgia rheumatica was classified using the 2012 EULAR/ACR classification criteria[36], based on clinical symptoms, inflammatory markers, and imaging findings when available. Rheumatoid arthritis was defined according to the 2010 ACR/EULAR classification criteria[37], which incorporate joint involvement, serological markers, and inflammatory activity, while gout was classified according to the 2015 ACR/EULAR criteria[38], based on clinical features, laboratory findings, and imaging or crystal identification when applicable.

Procedure

The study protocol was approved by the institutional ethics committee of University of Health Sciences, Gülhane Scientific Research, Protocol Number [2024-310], Date [28.05.2024]. Due to the retrospective nature of the study, the requirement for patient consent was waived by the ethics committee.

Patient data were retrieved from electronic medical records, including demographic characteristics, underlying rheumatic disease, comorbidities, and immunosuppressive treatment type, dose, and duration.

CMV detection and definitions

Patients receiving immunosuppressive therapy for rheumatic diseases who developed cytopenias, fever, elevated liver enzymes, pneumonia, or diarrhea that

could not be explained by disease activity or drug side effects and therefore underwent CMV PCR were retrospectively analyzed. CMV PCR positivity was not determined based on a single measurement. In patients with detectable CMV DNAemia, serial CMV PCR measurements were performed during follow-up. Patients with low-level CMV DNAemia who demonstrated an increasing viral load trend in association with compatible clinical findings were classified as having CMV infection and received antiviral therapy. In contrast, patients whose CMV PCR levels remained stable or showed a declining trend without clinical deterioration were classified as having CMV reactivation and were managed with close clinical and laboratory monitoring without antiviral treatment. The CMV PCR values presented in this study represent the initial CMV PCR measurements at the time of first positivity.

CMV DNA levels were measured using the Anatolia Genework Bophore CMV Quantification Kit, a high-sensitivity platform that provides direct viral load quantification. Other diagnostic modalities (e.g., ELISA, pp65 antigen, viral cultures) were not used due to their lower sensitivity and longer turnaround time. In cases of CMV pneumonia, diagnosis was made based on clinical symptoms, imaging findings, and PCR positivity; no biopsy was performed.

Treatment criteria

Treatment decisions were made in consultation with the Infectious Diseases Department, taking into account viral load, the trend in increasing viral load, the presence of clinical findings such as cytopenia, diarrhea, pneumonia, and elevated liver function tests associated with CMV, the activity of the patient's existing rheumatologic disease, and the prescribed/planned treatments.

Patients with high initial CMV PCR viral loads received immediate antiviral therapy without waiting for serial PCR measurements, and antiviral treatment was continued until CMV PCR negativity was achieved. In patients with low-level CMV DNAemia, repeated CMV PCR measurements were performed, and antiviral therapy with ganciclovir was initiated only if an increasing viral load trend was observed in the presence of clinical findings that could not be explained by another infectious etiology. All antiviral therapy and supportive measures were documented.

Statistical analysis

Continuous variables were first assessed for normality using the Shapiro–Wilk test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's *t*-test, while non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann–Whitney *U* test. Categorical variables were expressed as counts and percentages and compared using the chi-square test or Fisher's exact test, as appropriate, based on expected cell counts. Univariate logistic regression analyses were performed to evaluate the association between individual clinical and laboratory variables and mortality. Variables that were clinically relevant and showed a statistically significant association in univariate analyses ($p < 0.05$) were entered into the multivariable logistic regression model to identify factors independently associated with mortality. Given the limited sample size, the number of variables included in the multivariable model was restricted to avoid model overfitting, and results were interpreted as exploratory with acknowledgment of wide confidence intervals.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA), and a two-sided *p*-value < 0.05 was considered statistically significant. Due to the retrospective design of the study, no a priori sample size calculation was performed; instead, the sample size was determined by the number of eligible patients identified during the study period. A post-hoc power analysis based on the primary outcome (mortality) demonstrated that the available sample size provided sufficient statistical power to detect clinically meaningful differences between groups.

RESULTS

A total of 30 patients with autoimmune rheumatic diseases and CMV PCR positivity were included in the study. The mean age of the cohort was 59.0 ± 18.3 years, and 70% (n = 21) of the patients were male. In 20 of the 30 patients with CMV PCR positivity, CMV detection occurred early after the diagnosis of the underlying rheumatic disease (mean, 72.3 ± 42 days), during periods of intensive immunosuppressive therapy. All of these patients had received intravenous pulse methylprednisolone, and the median daily glucocorticoid dose at the time of CMV PCR positivity was 40 mg/day (range, 4–80). In contrast, the remaining 10 patients developed CMV PCR positivity later in the disease course (mean disease duration, 6.5 ± 3.8 years), frequently in

association with recent increases in immunosuppressive therapy due to disease activation or underlying immune dysregulation.

Table 1 summarizes the demographic and diagnostic characteristics of the cohort. Granulomatosis with polyangiitis (23%) and adult-onset Still's disease (20%) were the most frequently observed diagnoses. The remaining diagnoses, in order of frequency, were systemic lupus erythematosus (SLE; n = 4, 13.3%), microscopic polyangiitis (n = 2, 6.7%), dermatomyositis-associated interstitial lung disease (n = 2, 6.7%), IgA vasculitis (n = 2, 6.7%), Sjögren syndrome (n = 2, 6.7%), giant cell arteritis (n = 1, 3.3%), gout with a history of renal transplantation (n = 1, 3.3%), polymyalgia rheumatica (n = 1, 3.3%), Behçet's disease (n = 1, 3.3%), and rheumatoid arthritis (n = 1, 3.3%). At the time of CMV PCR positivity, 29 patients (96.7%) were receiving glucocorticoid therapy, and 20 patients had previously received pulse methylprednisolone, with a median cumulative dose of 5 g (range, 2–10 g). The median daily dose of ongoing glucocorticoid therapy was 32 mg/day (range, 4–80). A wide range of immunosuppressive therapies was observed, including mycophenolate mofetil (MMF; n = 7), rituximab (RTX; n = 6), cyclophosphamide (n = 6), and anakinra (n = 6).

Table 1. Demographic and clinical characteristics of CMV PCR–positive patients

Characteristic	Value
Sex (Male/Female)	21 / 9
Age (years), mean ± SD	59.0 ± 18.3
Pulse methylprednisolone use	20 patients (66.6%)
Daily steroid dose* (mg/day), median	32 (range: 4–80)
Most common diagnoses	GPA (23%), Still's (20%)
CMV treatment (ganciclovir)	21 patients (70%)
Duration of ganciclovir (days)	19.5 (range: 2–56)

*: Methylprednisolone; if another medicine was used, the equivalent dose of methylprednisolone.

Antiviral treatment with ganciclovir was initiated in 21 patients (70%) following consultation with the Infectious Diseases Department. Treatment decisions were made through a multidisciplinary approach, taking into account the CMV viral load, trends in viral load increase, the presence of CMV-related clinical findings, the activity of the underlying rheumatic disease, and current or planned immunosuppressive therapies. The median duration of ganciclovir therapy was 19.5 days (range, 2–56 days).

The median CMV PCR viral load among patients who received ganciclovir was 1,957 copies/mL (range, 26.6–1,832,000), which was significantly higher than the median viral load of 349.3 copies/mL (range, 70.5–3,195) observed in patients who did not receive antiviral therapy. The diagnosis of CMV reactivation was primarily based on quantitative PCR results and compatible clinical findings. Anti-CMV IgM and IgG serology results at the time of CMV PCR positivity were available for only 10 patients. Among these patients, anti-CMV IgM was negative in seven, previously negative anti-CMV IgM became positive in two, and one patient had a borderline (gray zone) anti-CMV IgM result. All 10 patients had positive anti-CMV IgG levels at the time of CMV PCR positivity. CMV antigen testing was not performed in any patient.

Clinical manifestations among patients with CMV PCR positivity included fatigue (73.3%), fever (50%), anemia (63.3%), pneumonia (46.7%), and gastrointestinal symptoms, such as diarrhea (26.7%). Coinfections were identified in nine patients (30%), including urinary tract infections, bacterial pneumonia, and *Pneumocystis jirovecii* pneumonia. Table 2 presents the frequency of clinical symptoms in patients with CMV PCR positivity who received ganciclovir treatment and in those who did not.

The most commonly reported symptoms in both groups were fatigue, anemia, and pneumonia. A significantly higher proportion of treated patients reported fatigue and exhaustion compared with untreated patients ($p = 0.032$). Other symptoms, including fever, pneumonia, and diarrhea, were more frequent in the treatment group; however, these differences did not reach statistical significance. Table 3 presents the laboratory parameters of patients with CMV PCR positivity who did and did not receive ganciclovir treatment.

Patients who received ganciclovir treatment had significantly lower lymphocyte and albumin levels

and significantly higher C-reactive protein (CRP) levels compared with those who did not receive antiviral therapy. These findings likely reflect a more pronounced inflammatory state and greater degree of immunosuppression in the treated group. Table 4 presents the comorbidities of patients with CMV PCR positivity according to survival status.

Table 2. Clinical symptoms in CMV PCR–positive patients receiving vs. not receiving ganciclovir treatment

Symptom	Treatment Group (n=21)	No Treatment Group (n=9)	p-value
Fatigue / Exhaustion	18 (85.7%)	4 (44.4%)	0.032
Fever	13 (61.9%)	2 (22.2%)	0.109
Diarrhea / Colitis	7 (33.3%)	1 (11.1%)	0.374
Pneumonia	11 (52.4%)	3 (33.3%)	0.440
Anemia	14 (66.7%)	5 (55.6%)	0.687
Thrombocytopenia	8 (38.1%)	1 (11.1%)	0.210
Leukopenia	7 (33.3%)	1 (11.1%)	0.374
Esophagitis	1 (4.8%)	0 (0%)	1.000
Elevated Liver Enzymes	7 (33.3%)	2 (22.2%)	0.681

Chi-square test is used

Table 3. Laboratory parameters in CMV PCR–positive patients receiving vs. not receiving ganciclovir treatment

Parameter	Treatment Group (n=21)	No Treatment Group (n=9)	p-value
Lymphocytes[1] (cells/mm³)	771.4 ± 484.6	1604.4 ± 924.7	0.003
Hemoglobin[1] (g/dL)	9.8 ± 2.3	10.9 ± 1.1	0.168
Hematocrit[1] (%)	28.8 ± 6.9	33.0 ± 3.8	0.097
Platelet[1] (×10³/mm³)	180.7 ± 132.6	255.9 ± 174.5	0.206
CRP[1] (mg/L)	89.0 ± 85.5	27.3 ± 18.4	0.043
ESR[1] (mm/h)	65.1 ± 37.3	48.4 ± 25.5	0.261
Albumin[1] (g/dL)	2.8 ± 0.5	3.5 ± 0.5	0.005
WBC[2] (cells/mm³)	6000 (200–17920)	8000 (3180–15500)	0.288
Neutrophils[2] (cells/mm³)	4800 (100–16220)	6300 (780–14600)	0.821
Creatinine[2] (mg/dL)	1.4 (0.5–5.8)	1.0 (0.7–4.6)	0.342
Ferritin[2] (ng/mL)	1126.5 (65–7842)	480.5 (12–1685)	0.190
AST[2] (U/L)	19 (9–157)	15 (11–22)	0.167
ALT[2] (U/L)	23 (9–333)	15 (11–99)	0.123

Data are presented as mean±SD or median [IQR], as appropriate. [1]: Independent t-test, [2]: Mann–Whitney U test CRP: C- reactive protein, ESR: Erythrocyte Sedimentation Rate, WBC:White blood cell, AST:Aspartate aminotransferase, ALT:Alanine aminotransferase

Table 4. Comorbidities in CMV PCR–positive patients by survival status

Comorbidity	Deceased (n=7)	Survived (n=23)
Hypertension	2 (28.6%)	6 (26.1%)
Diabetes mellitus	1 (14.3%)	6 (26.1%)
Polyneuropathy	1 (14.3%)	0 (0%)
Hyperthyroidism	1 (14.3%)	0 (0%)
Multiple myeloma	1 (14.3%)	0 (0%)
Thalassemia minor	1 (14.3%)	0 (0%)
Hypothyroidism	1 (14.3%)	1 (4.3%)
Chronic kidney disease	0 (0%)	2 (8.7%)
Congestive heart failure	0 (0%)	1 (4.3%)
Polycythemia vera	0 (0%)	1 (4.3%)
History of stroke (SVO)	0 (0%)	1 (4.3%)
None	3 (42.9%)	12 (52.2%)

Due to the small number of patients in each comorbidity subgroup, statistical comparisons were not performed and data are presented descriptively.

There was no statistically significant difference in the overall comorbidity burden between deceased and surviving patients. Table 5 summarizes the clinical and laboratory findings in patients who tested positive for CMV PCR and survived or died.

The overall mortality rate among patients with CMV PCR positivity was 23.3%. Factors associated with mortality identified through logistic regression analysis are presented in Table 6. Variables were selected for inclusion in the multivariable logistic regression model based on both their clinical relevance and statistical significance in univariate analyses ($p < 0.05$). Accordingly, CMV-associated pneumonia was included as a clinically meaningful variable reflecting severe organ involvement, while lymphocyte count and serum albumin level were incorporated as indicators of immune status and nutritional/inflammatory burden, respectively. Given the small number of mortality events ($n = 7$), the number of covariates was deliberately limited to reduce the risk of model overfitting. In univariate analyses, lower lymphocyte count (lymphopenia) and lower serum albumin levels were associated with increased mortality. However, these associations did not remain statistically significant after adjustment in the multivariable model. CMV-associated pneumonia was the only variable independently associated with mortality in multivariable analysis, with patients exhibiting pneumonia having approximately 26-fold higher odds of death. The wide confidence interval observed for serum albumin likely reflects uncertainty attributable to the limited sample size.

The regression model was statistically significant overall (Omnibus Test p = 0.003), demonstrated good calibration (Hosmer–Lemeshow p = 0.902), and explained 57.2% of the variance in mortality (Nagelkerke $R^2 = 0.572$). Model classification accuracy was 86.7%, with high specificity (95.5%) but moderate sensitivity (57.1%).

Table 5. Clinical and laboratory findings by survival status in CMV PCR–positive patients

Variable	Survived (n=23)	Deceased (n=7)	p-value
Fatigue / Exhaustion[a]	16 (69.6%)	6 (85.7%)	0.638
Fever[a]	9 (39.1%)	6 (85.7%)	0.080
Diarrhea / Colitis[a]	7 (30.4%)	1 (14.3%)	0.638
Pneumonia[a]	8 (34.8%)	6 (85.7%)	**0.031**
Anemia[a]	14 (60.9%)	5 (71.4%)	1.000
Thrombocytopenia[a]	6 (26.1%)	3 (42.9%)	0.640
Leukopenia[a]	6 (26.1%)	2 (28.6%)	1.000
Esophagitis[a]	1 (4.3%)	0 (0%)	1.000
Elevated Liver Enzymes[a]	5 (21.7%)	4 (57.1%)	0.153
Lymphocytes[b] (cells/mm³)	1180.0 ± 755.2	500.0 ± 383.0	**0.031**
ESR[b] (mm/h)	58.2 ± 34.8 (n=21)	66.7 ± 36.6 (n=6)	0.609
WBC[c] (cells/mm³)	7170 (2500–17920)	6400 (200–13750)	0.288
Neutrophils[c] (cells/mm³)	5000 (780–16220)	5900 (100–11200)	0.821
Hemoglobin[c] (g/dL)	10.2 (6.7–13.1)	9.3 (7.6–14.8)	0.103
Hematocrit[c] (%)	30.5 (13.1–38.5)	27.8 (23.4–43.2)	0.057
Platelets[c] (×10³/mm³)	153 (47–623)	109 (21–279)	0.213
CRP[c] (mg/L)	37.4 (2.4–260.8)	40.9 (0.4–289.5)	0.108
Creatinine[c] (mg/dL)	1.2 (0.5–5.8)	1.9 (0.7–3.6)	0.342
Ferritin[c] (ng/mL)	609.5 (12–7842) (n=16)	1100 (1094–1106) (n=2)	0.190
Albumin[c] (g/dL)	3.1 (2.1–4.3) (n=22)	2.7 (2.3–3.4) (n=7)	**0.010**
AST[c] (U/L)	15 (9–157)	35 (19–81)	0.167
ALT[c] (U/L)	18 (9–333)	24 (18–100)	0.123

Data are presented as mean±SD or median [IQR], as appropriate. [a]: Chi-square, [b]: Independent t-test, [c]: Mann–Whitney U, CRP: C- reactive protein, ESR: Erythrocyte Sedimentation Rate, WBC: White blood cell, AST:Aspartate aminotransferase, ALT:Alanine aminotransferase

Table 6. Multivariate logistic regression analysis for predictors of mortality in CMV PCR–positive patients

Variable	p-value	Odds Ratio (Exp(B))	95% Confidence Interval
Pneumonia	**0.042**	26.114	1.124 – 606.740
Lymphocyte	0.087	1.003	1.000 – 1.006
Albumin	0.258	6.218	0.263 – 147.183

DISCUSSION

Cytomegalovirus (CMV) reactivation is a well-established contributor to morbidity and mortality in immunocompromised groups, including transplant recipients and individuals living with HIV/AIDS; however, its clinical significance in patients with autoimmune rheumatic diseases (ARDs) has not been fully elucidated[5, 19]. Within this framework, the present study adds to the limited body of evidence by outlining the clinical characteristics and outcomes of CMV reactivation in ARD patients undergoing immunosuppressive treatment. To our knowledge, this represents one of the earliest reports from Türkiye specifically addressing CMV reactivation in this patient population.

CMV reactivation was identified in patients with a wide range of rheumatic conditions, with granulomatosis with polyangiitis and adult-onset Still's disease being the most frequently observed. Prior studies have suggested a heightened vulnerability to CMV reactivation among individuals with systemic lupus erythematosus, polymyositis, and dermatomyositis[20]. A substantial proportion of our patients had been exposed to high-dose pulse methylprednisolone and ongoing glucocorticoid therapy, highlighting the role of intensive immunosuppression in CMV reactivation[21, 22]. This finding is consistent with earlier reports identifying glucocorticoids as a major contributing factor[8]. In addition to cyclophosphamide and rituximab, which are well-established triggers[21], our results suggest that mycophenolate mofetil and anakinra may also be associated with CMV reactivation in selected patients.

At the time of CMV PCR positivity, patients commonly presented with nonspecific clinical manifestations, including fatigue, fever, pneumonia, and gastrointestinal symptoms. Coinfections were detected in nearly one-third of the cohort, further complicating the diagnostic process. These observations support previous reports indicating that overlapping infectious and autoimmune features may delay the recognition of CMV reactivation in patients with rheumatic diseases[7-10, 23, 24].

Patients who received ganciclovir generally exhibited more severe clinical and laboratory features, including higher CMV viral loads, lower lymphocyte and albumin levels, and elevated C-reactive protein levels. Fatigue was also more frequently observed in this group. While standardized management strategies for CMV infection are well established in transplantation medicine, no consensus-based approach currently exists for patients with ARDs[25, 26]. The need for hospitalization and intravenous antiviral therapy increases healthcare costs and the risk of nosocomial infections, underscoring the importance of identifying patients who may benefit from closer monitoring or earlier intervention[27].

In the present study, CMV-associated pneumonia was significantly associated with mortality in multivariable analysis, underscoring the clinical importance of pulmonary involvement. Although lymphopenia and hypoalbuminemia were associated with adverse outcomes in univariate analyses, only pneumonia remained significant after adjustment, likely reflecting the limited sample size. Consistent with previous studies[21, 22], pulmonary involvement emerged as a key determinant of prognosis. While hypoalbuminemia and renal dysfunction have been associated with CMV reactivation in other immunocompromised populations[28], their independent prognostic significance in patients with autoimmune rheumatic diseases remains uncertain.

CMV reactivation frequently coincided with active rheumatologic disease, posing a diagnostic challenge. Given that CMV infection may mimic or exacerbate autoimmune disease activity, distinguishing infection from disease flare remains difficult in clinical practice[23, 29]. Clinicians should maintain a high index of suspicion for CMV reactivation in patients with autoimmune rheumatic diseases who present with unexplained clinical deterioration, particularly in the presence of pneumonia or marked lymphopenia.

Larger, prospective studies with systematic viral surveillance are warranted to more accurately characterize the incidence, associated risk factors, and clinical impact of CMV reactivation in patients with autoimmune rheumatic diseases. In particular, future studies focusing on the role of pulmonary involvement, immunosuppressive treatment intensity, and immune status markers may help refine risk stratification and guide targeted monitoring strategies in clinical practice.

This study provides real-world data on CMV reactivation in patients with autoimmune rheumatic diseases, a population for which available evidence remains limited. The inclusion of diverse ARD subtypes, comprehensive clinical and laboratory data, and a detailed assessment of immunosuppressive

treatments enhances the clinical relevance of the findings. In addition, the absence of prior cohort-level publications from Türkiye on this topic highlights the contribution of our study to the regional literature.

Several limitations should be acknowledged. First, the retrospective, single-center design may limit generalizability and introduce selection bias. Second, CMV PCR testing was performed based on clinical suspicion rather than systematic screening, which may have led to an underestimation of asymptomatic CMV reactivation. Third, the relatively small sample size limited statistical power and resulted in wide confidence intervals. Fourth, the absence of a control group precluded direct comparison with patients with autoimmune rheumatic diseases without CMV reactivation. Finally, due to the retrospective nature of the study, CMV prophylaxis strategies and detailed viral load kinetics could not be evaluated. Despite these limitations, our findings emphasize the need for increased clinical awareness and structured surveillance of CMV reactivation in immunosuppressed patients with autoimmune rheumatic diseases.

In summary, CMV reactivation constitutes a clinically important complication among patients with autoimmune rheumatic diseases undergoing immunosuppressive treatment. It is frequently characterized by nonspecific systemic manifestations and typically arises in the context of intensive immunosuppression, particularly high-dose corticosteroid exposure. Despite the limitations imposed by the retrospective design and relatively small sample size, our findings indicate a strong association between CMV-related pneumonia and mortality. Collectively, these results highlight the need for heightened clinical awareness, prompt diagnostic evaluation, and further prospective investigations to optimize the care of this high-risk patient population.

Author Contributions: Concept/Design : MSÖ, ET, SY; Data acquisition: -; Data analysis and interpretation: MSÖ, ÖK, MNK; Drafting manuscript: MSÖ; Critical revision of manuscript: ET, SÇ, MÇ, SY; Final approval and accountability: MSÖ, ET, SÇ, ÖK, MNK, MÇ, SY; Technical or material support: ÖK, Supervision: ET, SÇ, ÖK, MNK, MÇ, SY; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained from the Medical Sciences University Gülhane Scientific Research Ethics Committee with the decision dated 28.05.2024 and numbered 2024-310.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Gandhi MK, Khanna R. Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. Lancet Infect Dis. 2004;4:725-38.
2. Griffiths P, Baraniak I, Reeves M. The pathogenesis of human cytomegalovirus. J Pathol. 2015;235:288-97.
3. Stéphan F, Méharzi D, Ricci S, Fajac A, Clergue F, Bernaudin JF. Evaluation by polymerase chain reaction of cytomegalovirus reactivation in intensive care patients under mechanical ventilation. Intensive Care Med. 1996;22:1244-9.
4. Cook CH, Yenchar JK, Kraner TO, Davies EA, Ferguson RM. Occult herpes family viruses may increase mortality in critically ill surgical patients. Am J Surg. 1998;176:357-60.
5. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013;96:333-60.
6. Nogalski MT, Collins-McMillen D, Yurochko AD. Overview of human cytomegalovirus pathogenesis. Methods Mol Biol. 2014;1119:15-28.
7. Ozaki T, Yamashita H, Kaneko S, Yorifuji H, Takahashi H, Ueda Y et al. Cytomegalovirus disease of the upper gastrointestinal tract in patients with rheumatic diseases: a case series and literature review. Clin Rheumatol. 2013;32:1683-90.
8. Takizawa Y, Inokuma S, Tanaka Y, Saito K, Atsumi T, Hirakata M et al. Clinical characteristics of cytomegalovirus infection in rheumatic diseases: multicentre survey in a large patient population. Rheumatology (Oxford). 2008;47:1373-8.
9. Mori T, Kameda H, Ogawa H, Iizuka A, Sekiguchi N, Takei H et al. Incidence of cytomegalovirus reactivation in patients with inflammatory connective tissue diseases under immunosuppressive therapy. J Rheumatol. 2004;31:1349-51.
10. Ramos-Casals M, Cuadrado MJ, Alba P, Sanna G, Brito-Zerón P, Bertolaccini L et al. Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature. Medicine (Baltimore). 2008;87:311-18.
11. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis, especially in the first 6 months of treatment. Rheumatology (Oxford). 2011;50:124-31.
12. Tsai WP, Chen MH, Lee MH, Yu KH, Wu MW, Liou LB. Cytomegalovirus infection causes morbidity and mortality in patients with autoimmune diseases, particularly systemic lupus erythematosus. Rheumatol Int. 2012;32:2901-8.

13. Berman N, Belmont HM. Disseminated cytomegalovirus infection complicating active treatment of systemic lupus erythematosus: an emerging problem. Lupus. 2017;26:431-4.
14. Choo HMC, Cher WQ, Kwan YH, Fong WWS. Risk factors for cytomegalovirus disease in systemic lupus erythematosus: a systematic review. Adv Rheumatol. 2019;59:12.
15. Yoon KH, Fong KY, Tambyah PA. Fatal cytomegalovirus infection in patients with systemic lupus erythematosus undergoing intensive immunosuppressive therapy. J Clin Rheumatol. 2002;8:217-22.
16. Lim CC, Tung YT, Tan BH, Lee PH, Mok I, Oon L et al. Epidemiology and risk factors for cytomegalovirus infection in glomerular diseases treated with immunosuppressive therapy. Nephrology (Carlton). 2018;23:676-81.
17. Mencarini J, Spinicci M, Bartalesi F. Risk of cytomegalovirus reactivation in patients with immune-mediated inflammatory diseases undergoing biologic treatment. Reumatismo. 2016;68:144-7.
18. Xue Y, Jiang L, Wan WG, Chen YM, Zhang J, Zhang ZC. Cytomegalovirus pneumonia in patients with rheumatic diseases after immunosuppressive therapy. Chin Med J (Engl). 2016;129:267-73.
19. Whitley RJ, Jacobson MA, Friedberg DN, Holland GN, Jabs DA, Dieterich DT et al. Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS. Arch Intern Med. 1998;158:957-69.
20. Fujimoto D, Matsushima A, Nagao M, Takakura S, Ichiyama S. Risk factors associated with elevated blood cytomegalovirus pp65 antigen levels in patients with autoimmune diseases. Mod Rheumatol. 2013;23:345-50.
21. Ota Y, Kaneko Y, Takeuchi T. Association between mortality and cytomegalovirus reactivation during remission induction therapy in patients with rheumatic diseases. Clin Exp Rheumatol. 2021;39:1324-30.
22. Kawamori K, Oguro N, Shimizu K, Kida T, Omura S, Nakagomi D et al. Risk factors for cytomegalovirus reactivation during the treatment of ANCA-associated vasculitis. Mod Rheumatol. 2025;35:691-6.
23. Hayashi T, Lee S, Ogasawara H, Sekigawa I, Iida N, Tomino Y et al. Exacerbation of systemic lupus erythematosus related to cytomegalovirus infection. Lupus. 1998;7:561-4.
24. Vasquez V, Barzaga RA, Cunha BA. Cytomegalovirus-induced flare of systemic lupus erythematosus. Heart Lung. 1992;21:407-8.
25. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients: guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33:e13512.
26. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation. Transplantation. 2018;102:900-31.
27. Tamura N, Itohara K, Ueda Y, Kitahiro Y, Yamamoto K, Omura T et al. Optimization of preemptive therapy for cytomegalovirus infections with valganciclovir. JMIR Res Protoc. 2025;14:e72549.
28. Shimada T, Higashida-Konishi M, Izumi K, Hama S, Oshige T, Oshima H et al. Risk factors associated with cytomegalovirus reactivation in patients receiving immunosuppressive therapy for rheumatic diseases. Sci Rep. 2022;12:20926.
29. Gardiner BJ, Haas EM, Bailey RC, Chow JK, Snydman DR. Reactivation of latent cytomegalovirus infection in patients with rheumatologic disease. Rheumatol Int. 2019;39:1229-40.
30. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F et al. 2012 revised international Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum. 2013;65:1-11.
31. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19:424-30.
32. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677-86.
33. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292:344-7.
34. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis. 2017;76:1955-64.
35. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome. Ann Rheum Dis. 2017;76:9-16.
36. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C et al. 2012 provisional classification criteria for polymyalgia rheumatica. Ann Rheum Dis. 2012;71:484-92.
37. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580-8.
38. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D et al. 2015 gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74:1789-98.