Clinical characteristics of active cytomegalovirus infection in patients with systemic lupus erythematosus of different sexes

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Abstract

Objective

To investigate the clinical characteristics of active cytomegalovirus (CMV) infection in patients with systemic lupus erythematosus (SLE) of different sexes.

Methods

SLE patients between September 2011 and March 2018 at Peking University Third Hospital were reviewed, and were followed up until the occurrence of active CMV infection, and their clinical data were collected. The clinical symptoms, laboratory tests, and follow-up data in patients of different sexes were analyzed statistically.

Results

Among 45 SLE patients with CMV active infection, 8 were male and 37 were female. The proportion of male patients with positive anticardiolipin antibody was higher than that of female patients (62.5% vs 8.1%, P = 0.002), and male patients had a higher proportion (50%) of abnormal liver function than female patients (50% vs 13.5%, P = 0.039). After 1:1 matching, active CMV infection occurred earlier in male patients (P = 0.041).

Conclusion

In our study, the proportion of positive anticardiolipin antibody and abnormal liver function were higher in male patients with SLE combined with active CMV infection. Active CMV infection occurred earlier in the course of SLE in male patients.

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease involving multiple systems. The prevalence in female patients is much higher than that in male patients, and male patients account for 7% – 20% of all patients[1]. At present, the pathogenesis of the disease is still not fully clear, but it is generally considered to be the result of both genetic predisposition and environmental factors (such as infection). Cytomegalovirus (CMV) infection is considered to be one of the environmental factors that may lead to systemic lupus erythematosus[2]. Cytomegalovirus is a herpesvirus that widely exists in nature and is commonly susceptible to human beings. It may initiate an autoimmune response through molecular simulation and epitope diffusion and then lead to the occurrence and development of SLE[3]. Cytomegalovirus (CMV) infection is one of the most common opportunistic infections in SLE patients and other immunocompromised patients and can lead to prolonged hospital stays, increased mortality, and increased medical costs[4]. The clinical manifestations of CMV infection vary, ranging from asymptomatic

infection to severe organ dysfunction. Sometimes it is difficult to differentiate SLE from active CMV infection because of similarities in their clinical manifestations.

In clinical practice, we found that male SLE patients often have CMV infection, but there are few studies on male SLE patients with CMV infection to guide our management. The goals of the study were to investigate the difference in clinical features of CMV infection between male SLE patients and female SLE patients and to determine when active CMV infection usually occurs in SLE patients.

Methods

Patient selection

The clinical data of 512 patients with SLE diagnosed between September 2011 and March 2018 at Peking University Third Hospital were reviewed. Finally, 45 patients were enrolled in our study; 8 of them were male, while 37 patients were female. A case–control matching approach was used to match two groups at a 1:1 ratio (male group: female group) according to age, hemoglobin, alanine aminotransferase, and SLEDAI score. The inclusion criteria and study flow chart of patients with SLE combined with active CMV infection are described in Fig. 1. All the patients fulfilled the 1997 American College of Rheumatology revised criteria for SLE. Our patients were followed up in the outpatient clinic.

The research complied with the Declaration of Helsinki. The design of this work was approved by the local ethical committees (384-02).

Clinical evaluation

The clinical disease activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The clinical data of all patients were collected and analyzed, including demographic data (sex, age), clinical manifestations (fever, skin involvement, arthritis, serositis, nervous system involvement, anemia, digestive system involvement, kidney involvement), laboratory examinations (white blood cell count, hemoglobin concentration, platelet count, alanine aminotransferase, serum creatinine, C3, C4, antinuclear antibodies, anti-double-stranded DNA antibodies, anti-SSA antibody, anti-SSB antibody, anti-RNP antibody, and anticardiolipin antibody) and treatment regimens (use of glucocorticoids and immunosuppressive agent).

Diagnosis of active CMV infection

The diagnosis of active CMV infection meets at least one of the following three criteria: CMV-pp65 antigen positive (at least 1 CMV pp65 antigen-positive cells per 2×10^5 white blood cells), CMV-IgM positive (> 30 U/ml), or CMV-DNA≥1×10^3 copies/ml.

Detection of CMV infection

Four milliliters of peripheral venous blood was collected, of which 2 ml was anticoagulated with heparin and 2 ml was not anticoagulated. CMV antibody (including IgG and IgM) was detected by chemiluminescence,

CMV-pp65 antigen was detected by indirect immunofluorescence, and CMV-DNA was detected by polymerase chain reaction.

Statistical Analysis

SPSS software package (version 22.0, SPSS Inc) was employed for statistical analysis. Continuous variables are presented as the mean ± standard deviation (SD) if they conformed to a normal distribution, and the median (range) was used for a nonnormal distribution. Categorical variables are presented as frequencies (percentages).

Continuous variables between groups were tested with t tests or nonparametric tests (for normally or nonnormally distributed data, respectively). Differences between categorical data were tested using the chi-square test. Kaplan–Meier survival curves and log-rank tests were used for survival analysis. Statistical significance was set at two-sided p values of less than 0.05.

Results

General Data of Patients with SLE Combined with Active CMV Infection

Among the 45 patients enrolled in the study, 8 were male and 37 were female, aged 31 (14–81) years old at presentation (Table 1). The clinical presentation and laboratory assessment of these patients are presented in Table 1. Regarding the treatment algorithm, all patients received oral prednisone therapy. A total of 22.2% (10/45) of patients completed treatment with monthly intravenous cyclophosphamide (600–800 mg/month). The other patients received mycophenolate mofetil (12/45) or leflunomide (2/45).

Comparisons of Clinical Data Between Male and Female SLE Patients with Active CMV Infection

The clinical features of the patients in the male and female groups are listed in Table 2. In our study, the age of the male group was 22 (18–81) years old, while the age of the female group was 34 (14–70) years old (P = 0.021). The proportion of abnormal liver function in male patients (50%) was higher than that in female patients (13.5%) (P = 0.039). The serum alanine aminotransferase of male patients was higher than that of female patients, but there was no significant difference between the two groups (P = 0.151). The hemoglobin levels in male and female patients were 124.5 ± 22.5 g/L and 104.9 ± 22.3 g/L, respectively (P = 0.029). The proportion of positive anticardiolipin antibody in male patients (62.5%) was higher than that in female patients (8.1%) (P = 0.002). There were no significant differences in other clinical manifestations, laboratory assessments, or SLEDAI scores between the male and female groups, as shown in Table 2. Table 2 also shows the comparison between the male and female groups after 1:1 matching according to age, hemoglobin, alanine aminotransferase, and SLEDAI score.

Active CMV infection-free survival rate

In our study, 60.0% (27/45) of patients experienced the first CMV active infection within the first year after the diagnosis of SLE, and the one-year CMV active infection-free rate was 40.0%. The 5- and 10-year CMV active

infection-free survival rates were 13.3% and 6.7%, respectively, as shown in Fig. 2.

There was no significant difference between male and female patients in the interval between the diagnosis of SLE and the diagnosis of CMV active infection ($P = 0.077$, Fig. 3). After matching according to the indicators mentioned above, CMV active infection occurred earlier in male patients than in female patients after the diagnosis of SLE. ($P = 0.041$, Fig. 4).

Discussion

Systemic lupus erythematosus (SLE) is an autoimmune disease with unknown etiology and multisystem involvement. It is common in women of childbearing age but relatively rare in men[1]. At present, the pathogenesis of the disease is not clear. Owing to the difference between men and women, most studies believe that sex hormones[5] are related to its pathogenesis. Meanwhile, the occurrence of SLE is also considered to be related to genetic predisposition and environmental factors (such as infection). Cytomegalovirus (CMV) infection is considered to be an environmental factor that may lead to SLE. CMV may initiate the autoimmune response through molecular simulation, epitope diffusion, and stimulation of the activation of polyclonal B cells to induce the onset of SLE and aggravate the condition of SLE[6, 7]. To control SLE, they need to use immunosuppressants and glucocorticoids. As a result, patients' immunity to various pathogens is reduced, and they are prone to infections. CMV is one of the most common opportunistic infections in SLE patients and one of the main causes of death in SLE patients.

Cytomegalovirus (CMV) is a double-stranded DNA virus and a member of the human herpesvirus family. Infection with CMV is ubiquitous and generally asymptomatic in healthy people. However, immunocompromised individuals are at risk of developing life-threatening results[8–11]. The clinical manifestations of CMV infection are similar to SLE, and the use of glucocorticoids and immunosuppressants can inhibit the immune response, which makes the inflammatory reaction and fever in CMV infection not typical, leading to the difficulty in the differential diagnosis of the two diseases.

In previous studies, it was often reported that there were differences in clinical characteristics, laboratory assessments, and mortality between male SLE patients and female SLE patients, but the results of different studies were different[12–16]. Few studies have reported male SLE with CMV infection. This study is based on a retrospective analysis of SLE patients with CMV infection in our hospital to investigate the clinical characteristics of SLE patients with CMV infection of different sexes.

In our study, we found that the proportion of positive anticardiolipin antibody and abnormal liver function were higher in male SLE patients than in female SLE patients with CMV active infection; after 1:1 matching, CMV active infection occurred at an earlier stage in male SLE patients than in female SLE patients.

In terms of autoantibodies, the results of our study showed that the proportion of positive anticardiolipin antibodies in male SLE patients with CMV infection was higher than that in these female patients. This was similar to the results of previous studies[12, 17–20], but it was not clear whether these patients were complicated with CMV infection. Anticardiolipin antibodies can cause hypercoagulability and hemolytic anemia and are closely related to antiphospholipid antibody syndrome (APS). Some previous studies found

that male patients are more likely to experience thrombotic events[20], but the correlation between positive anticardiolipin antibody and thrombosis has not been confirmed[17]. Some studies have shown that CMV infection can promote the production of antiphospholipid antibodies[21], and the proportion of positive anticardiolipin antibody SLE patients with CMV seropositivity was higher than those with CMV-seronegative antibodies[22]. CMV infection in SLE patients may cause secondary APS and Raynaud's phenomenon[21, 23, 24]. CMV infection may also lead to thromboembolic complications[25–27]. Thus, SLE patients complicated with CMV infection may be more prone to thrombotic events and APS. There were no serious thromboembolic events in our patients, but we should be cautious about such complications.

Regarding liver function, our study found that in SLE patients with CMV active infection, the proportion of abnormal liver function in male patients was higher. This may be related to the fact that CMV infection in male patients is more severe than that in female patients. Although SLE can involve various organs, liver damage is relatively rare in SLE. When SLE patients present abnormal liver function and elevated transaminase, CMV infection should be considered[28]. At the same time, active infection with CMV can aggravate SLE. When the disease activity of SLE is high, the inflammatory state in patients is more severe, which may result in more CMV replication; CMV replication is also affected by the immune function of T cells[29]. In our study, the level of alanine aminotransferase in male patients was slightly higher than that in female patients, but the difference was not statistically significant ($P = 0.151$), which may be due to the small sample size of this study.

Our study also found that CMV active infection occurred at an earlier stage in male SLE patients than in female patients after 1:1 matching. In SLE patients, the risk factors for CMV infection often include impaired immune function, glucocorticoid and immunosuppressant use, lymphocytopenia, and a high SLEDAI score[30–33]. The relationship between CMV infection and SLE is complex. Active CMV infection in SLE patients may be a primary infection or reactivation with latent CMV infection. In clinical practice, it is difficult to distinguish the two cases and determine the source of CMV active infection. Whether this is related to CMV infection at an earlier stage remains to be clarified. After 1:1 matching, the effects of age, SLEDAI score, glucocorticoid and immunosuppressant use were eliminated, and CMV active infection in male patients occurred at an earlier stage, which suggested that this result may be related to sex differences. First, the role of sex hormones is worth noting. The effect of sex hormones in SLE has been demonstrated. Estrogen can promote the immune response, enhance Th2 cell function, activate B cells, and induce antibody production[34, 35], and estrogen can also activate T cells[36]; androgens may have immunosuppressive and anti-inflammatory effects, and they can promote $CD8^+$ T cells[35]. In some studies, it was found that estradiol levels increased while testosterone levels decreased in female SLE patients[36]; some male SLE patients have hypoandrogenia[37]. The imbalanced state of estrogen versus androgen in SLE males also increases susceptibility to disease activity[36]. For CMV, anti-CMV immunity is highly complex and includes humoral immunity, cellular immunity, innate immunity, and adaptive immunity, among which adaptive immunity plays the most important role. Many studies have shown that CMV-specific T cells, especially CMV-specific $CD8^+$ T cells, are the key to controlling CMV infection[38–40]. Therefore, in male SLE patients, low androgen levels and an imbalance of sex hormones may affect $CD8^+$ T-cell immunity, which leads to the occurrence of a CMV active infection. And for only CMV infection, some studies suggest the CMV-specific T-cell response in men

was larger and more pro-inflammatory than in women[41]. So the difference of sex may play an important role in male SLE patients with CMV infection. But some other studies found CMV + males carried lower numbers of total $CD4^+$, $CD4^+$ central memory (CM) and follicular helper T cells than females and CMV^- males. Moreover, CMV + males had significantly lower numbers of regulatory T (Treg)-cells and memory B cells than CMV + females[42]. Similar to the only CMV infection, there is abnormal activation of CD8, a decrease in CD4 cells, and an inversion of the CD4:CD8 ratio[2, 43] in SLE patients with CMV active infection. The effect of sex hormones on CMV immunity remains to be explored. Second, some previous studies found that hematological involvement is more prominent in male SLE patients, and lymphocytopenia is more common in male patients[44, 45], which may be one of the reasons why male SLE patients are more likely to be infected with CMV. Just like our studies, the prevalence of CMV infection was higher in male SLE patients than in female SLE patients (15.9% vs. 8%). However, some contrary results showed that sex is not related to the occurrence of lymphocytopenia[15] or that lymphocytopenia is less common in male patients than in female patients[16, 46, 47].

The results of this study show that CMV active infection occurs at an earlier stage in male SLE patients, which suggests that we should be alert to the occurrence of CMV infection if the male patient is diagnosed with SLE. Regular monitoring, evaluation of CMV activity, and even preventative therapy are suggested in high-risk groups. Meanwhile, it is worth mentioning that the relationship between CMV infection and SLE activity. A recent CMV infection might trigger the development of SLE or a flare of SLE[48]. Patients with SLE have an elevated prevalence and concentrations of antibodies against CMV[49], and the presence of CMV-Ag was associated with severe illness and a higher risk of death [50]. CMV-DNA loading can predict clinical progression to disease or clinical relapse[51].

There are some disadvantages to our research. First, this study is a single-center retrospective study, so whether the results can be extended to other ethnic groups and regions remains to be explored. Second, the sample size of this study is small. The results need to be confirmed in a larger sample, multicenter cohort, and follow-up study.

In conclusion, we investigated the clinical characteristics of SLE patients with active CMV infection in different sexes. It was found that in SLE patients with CMV active infection, the proportion of positive anticardiolipin antibody and abnormal liver function were higher in male patients, and CMV infection occurred earlier in the course of SLE. This suggests that we should be alert to the occurrence of CMV infection in male patients first diagnosed with SLE and regularly monitor the related indicators of CMV and liver function from an early stage.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Nini Dai wrote the original draft and revised it. Qiuyu Li had made contributions to the design of the work. Nini Dai, Qiuyu Li, Rong Zhou and Xin Li had made the acquisition, and the analysis. Qiuyu Li and Jinxia Zhao had made contributions to the revision of the draft. Qiuyu Li was the corresponding author of this article. All authors read and approved the final version of the manuscript.

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Tables

Table 1. General data of patients with systemic lupus erythematosus combined with active CMV infection.

Clinical evaluation		Laboratory assessment	
Number of patients	45	Number of patients	45
Gender (male/female)	8/37	Hemoglobin (mean ± SD) (g/L)	108.36±23.32
Age (median, range) (years)	31(14-81)	Serum creatinine (median, range) (μmol/L)	69.0 (42.0-297.0)
Follow-up time (months, median, range)	7.5(3,195)	alanine aminotransferase (median, range) (IU/L)	22.5(5,260)
Fever (noninfectious) No. (%)	25(55.6)	C4 (median, range) (g/l)	0.06(0.017-0.28)
Skin involvement, No. (%)	22(48.9)	C3 (median, range) (g/l)	0.37(0.12-0.96)
Photosensitivity, no. (%)	4(9)	Anti-nuclear antibody (+) No. (%)	45(100)
Oral ulcer, no. (%)	13(28.9)	Anti-double stranded DNA antibody (+) No. (%)	34(75.6)
Alopecia, no. (%)	10(22.2)	Anti-SSA antibody (+) No. (%)	31(68.9)
Arthralgia No. (%)	28(62.2)	Anti-SSB antibody (+) No. (%)	8(17.8)
Serositis No. (%)	12(26.7)	Anti-Smith antibody(Sm) (+) No. (%)	16(35.6)
Neurologic disorder No. (%)	5(11.1)	Anti-ribonucleoprotein antibody (+) No. (%)	19(42.2)
Anemia No. (%)	24(53.3)	Anti-cardiolipin antibody (+) No. (%)	8(17.8)
Kidney involvement No. (%)	26(57.8)		
Digestive system involvement No. (%)	4(9)	Treatment, No. (%)	
SLEDAI (mean ± s.d.)	15.4±8.5	P	45(100)
Leukocytopenia No. (%)	19(42.2)	CYC	10(22.2)
Anemia No. (%)	24(53.3)	LEF	2(4.4)
Thrombocytopenia No. (%)	16(35.6)	MMF	12(26.7)
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index. P =oral prednisone, CYC =cyclophosphamide, LEF= Leflunomide MMF= Mycophenolate Mofetil			

Table 2. Comparisons of clinical data between male and female SLE patients with active CMV infection.

	Unmatched			Matched		
	Male	Female	*P*	Male	Female	*P*
Number of patients	8	37	-	8	8	-
Age, y, median (range)	22(18-81)	34(14-70)	0.021	22(18-81)	23(20-64)	0.672
Number of fever (%)	5(62.5)	20(54.1)	0.716	5(62.5)	7(87.5)	0.569
Number of neurologic disorder (%)	0(0)	5(13.5)	-	0(0)	0(0)	-
Number of anemia (%)	4(50)	20(54.1)	1.000	4(50)	6(75)	0.608
Number of thrombocytopenia (%)	5(62.5)	11(29.7)	0.111	5(62.5)	0(0)	-
Number of abnormal liver function (%)	4(50)	5(13.5)	0.039	4(50)	2(25)	0.608
Hemoglobin, g/L (mean±SD)	124.5±22.5	104.9±22.3	0.029	124.5±22.5	103.9±23.9	0.098
Platelet count, $\times 10^9$ cells/L	113.61±79.9	131.2±72.7	0.545	113.61±79.9	147.8±36.2	0.325
alanine aminotransferase median (range) (IU/L)	45.5(5-260.0)	21.5(0-146.0)	0.151	124.5(5-279)	26.5(13-52)	0.505
Number of positive anti-cardiolipin antibody (%)	5(62.5)	3(8.1)	0.002	5(62.5)	1(12.5)	0.119
SLEDAI	13(9-33)	13□0-27□	0.308	13(9-33)	11.5(6-26)	0.336
Treatment, No. (%)						
P	8(100)	37(100)	1	8(100)	8(100)	1
CYC	3(37.5)	7(18.9)	0.349	3(37.5)	1(12.5)	0.569
LEF	0(0)	2(5.4)	-	0(0)	1(12.5)	-
MMF	3(37.5)	9(24.3)	0.661	3(37.5)	3(37.5)	1
P =oral prednisone, CYC =cyclophosphamide, LEF= Leflunomide□ MMF= Mycophenolate Mofetil						

Figures

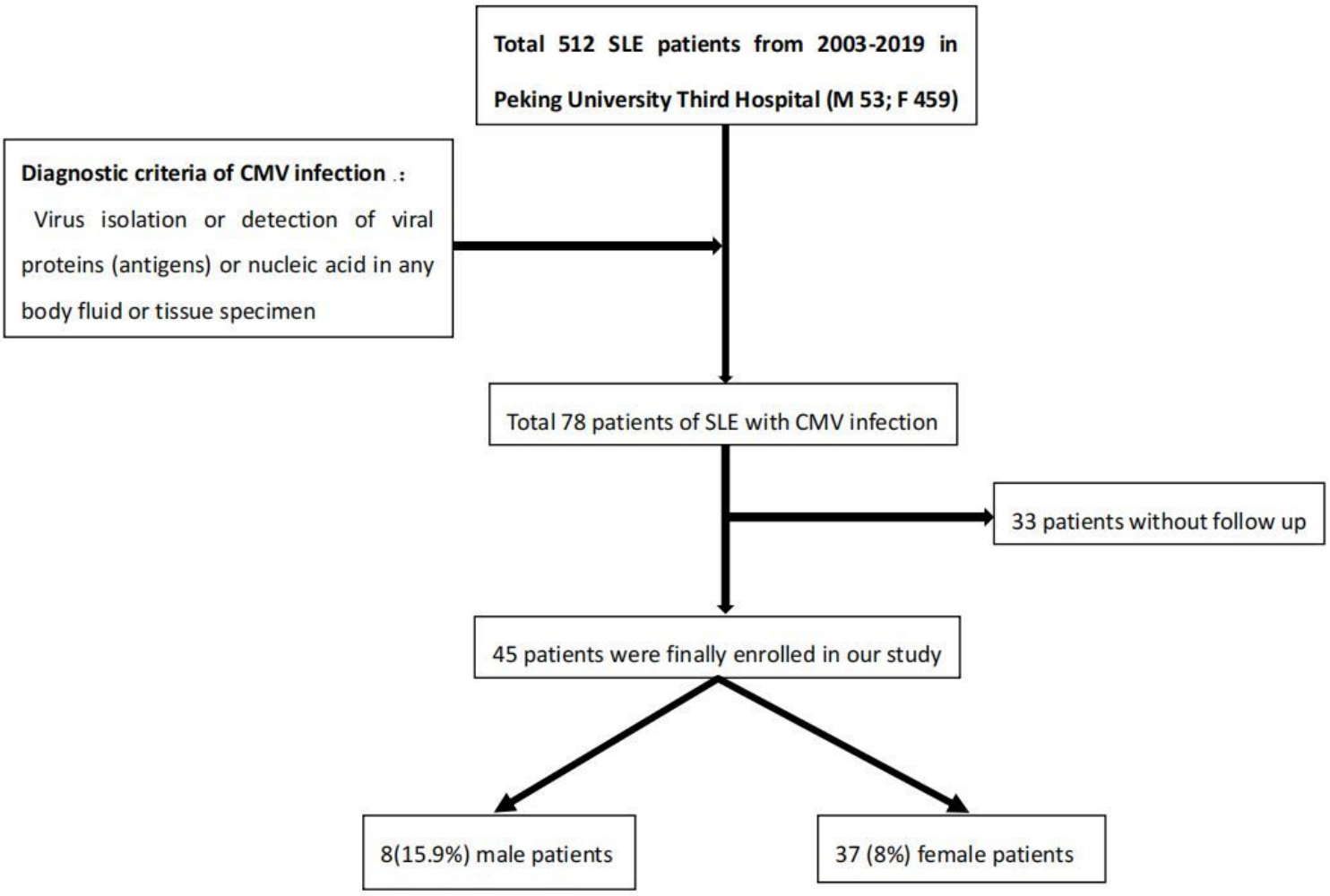

Figure 1

Inclusion criteria of SLE combined with CMV infection and the design of the study

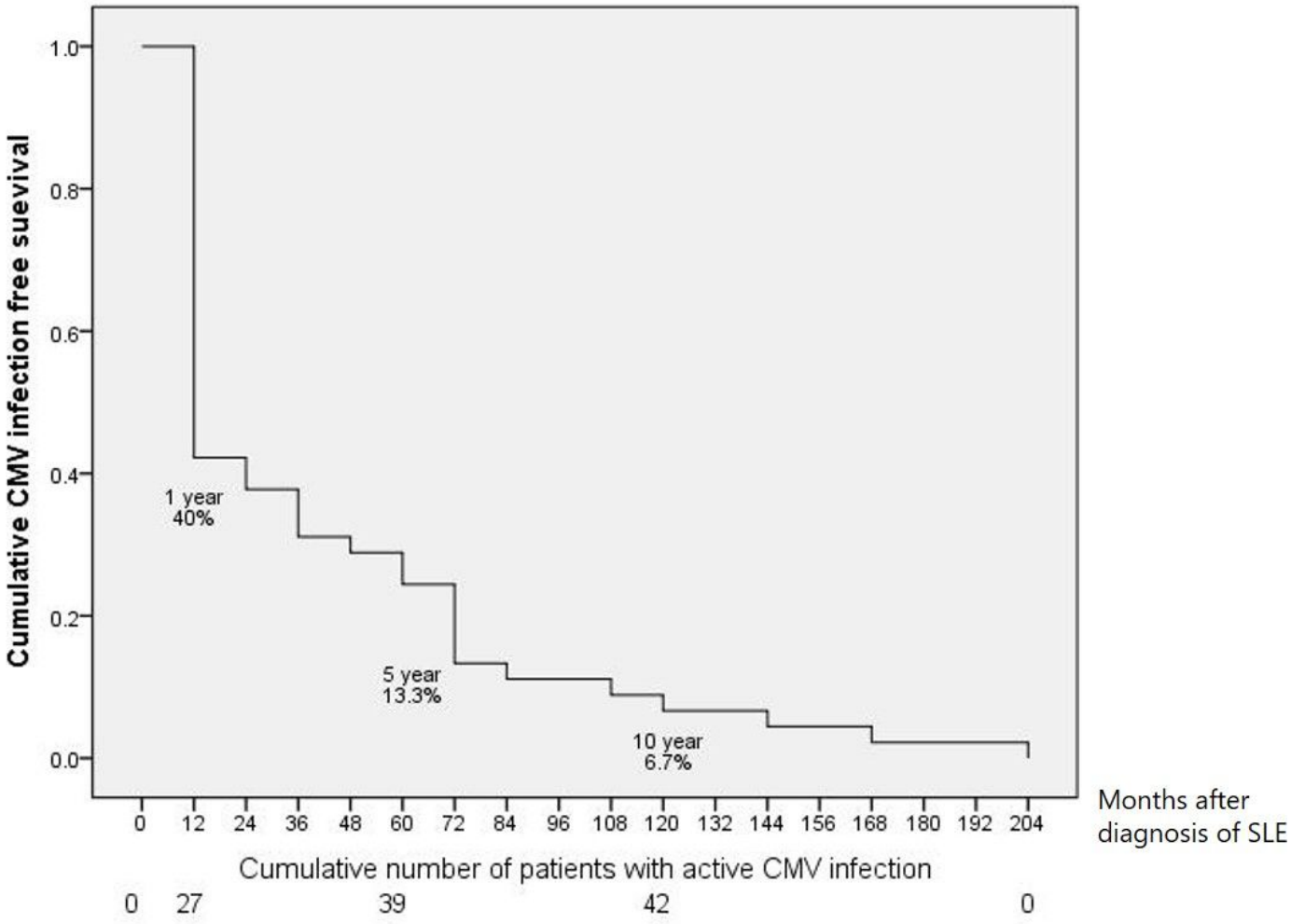

Figure 2

Cumulative CMV active infection-free survival

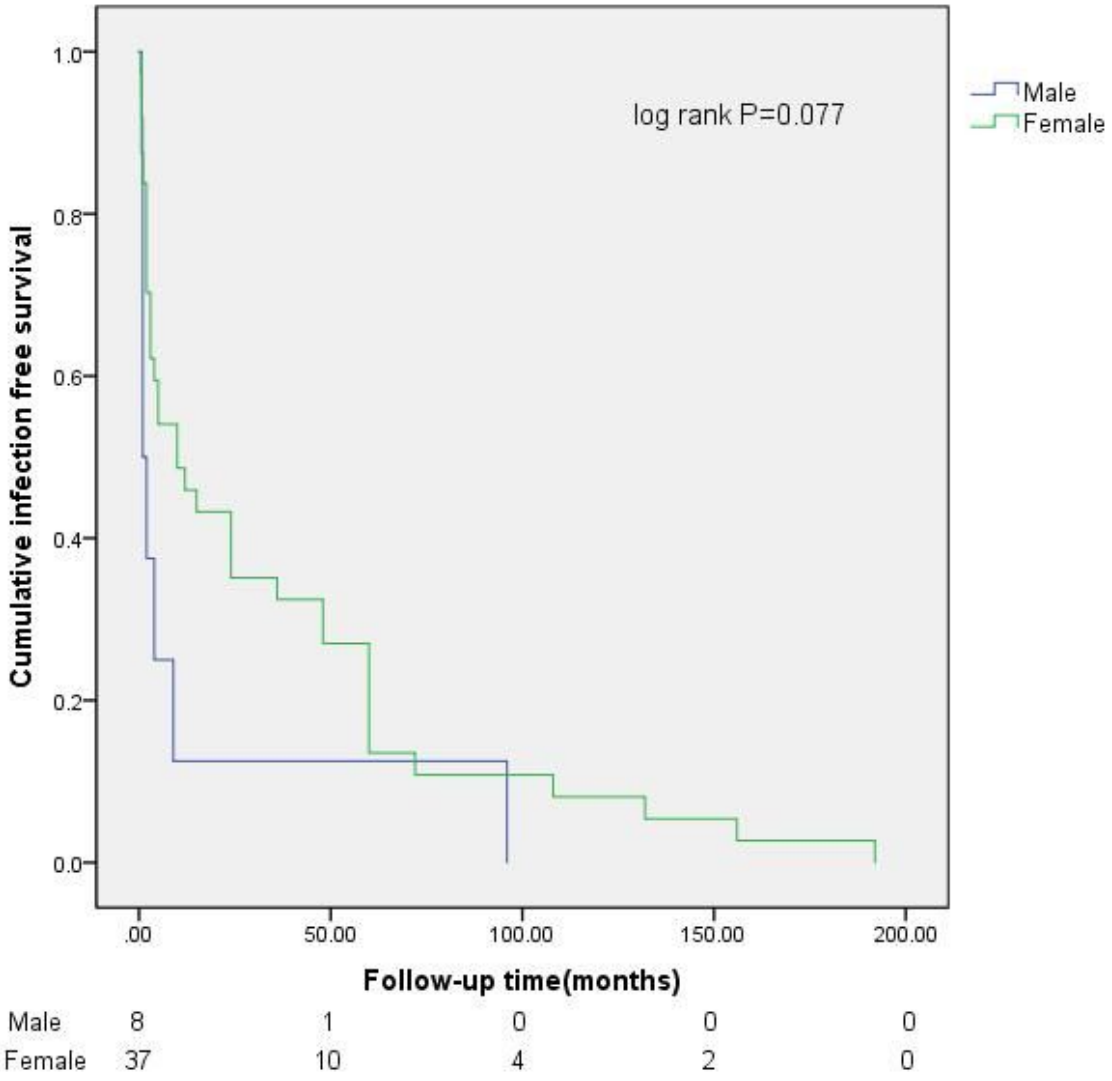

Figure 3

Comparison of cumulative CMV active infection-free survival between male and female SLE patients (unmatched)

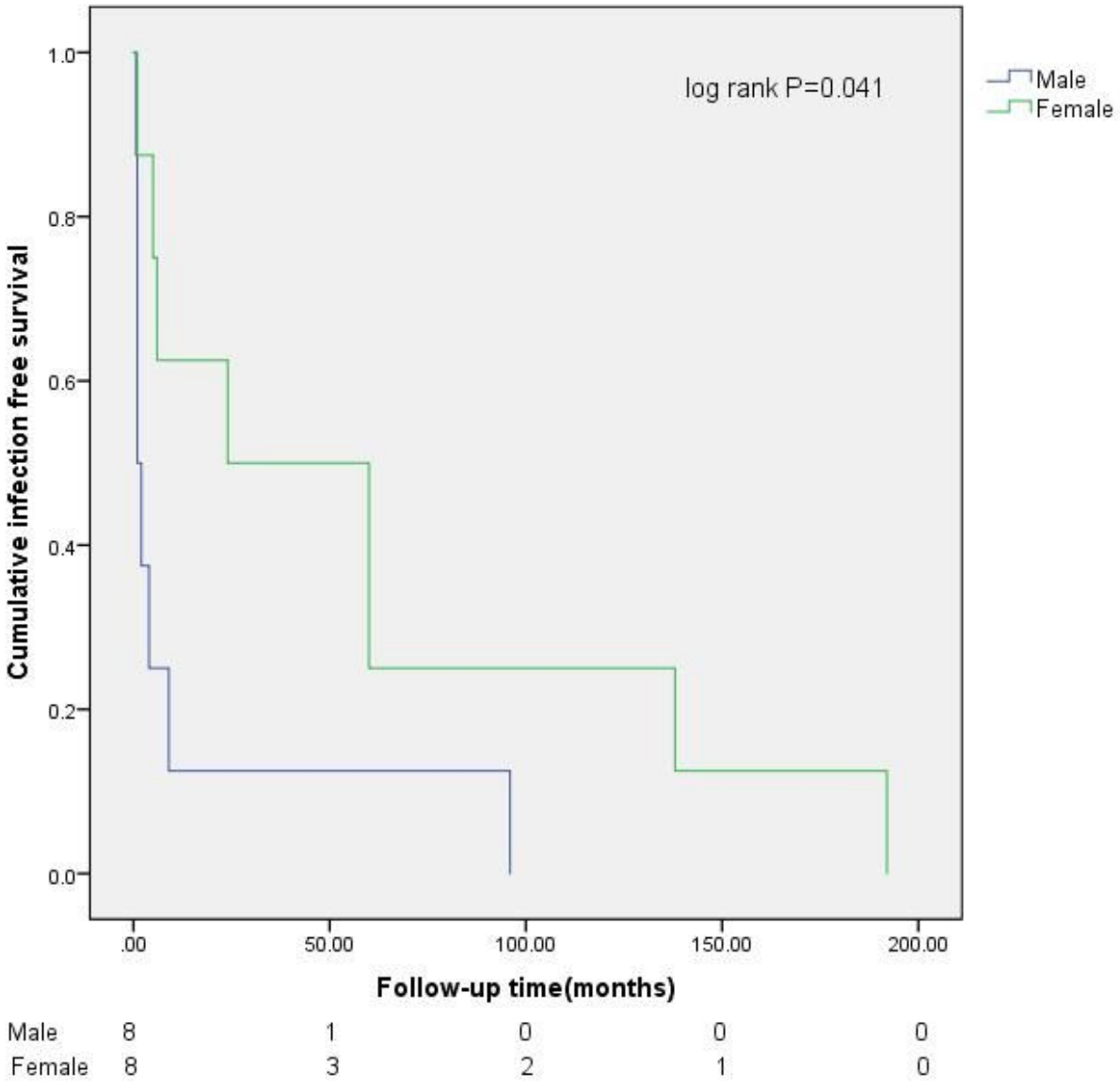

Figure 4

Comparison of cumulative CMV active infection-free survival between male and female SLE patients (1:1 matched)