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Original Article

The clinical features and mortality risk factors of cytomegalovirus infection in patients with systemic lupus erythematosus

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Systemic lupus erythematosus;
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Abstract *Background:* The clinical features and outcomes of cytomegalovirus (CMV) diseases in patients with systemic lupus erythematosus (SLE) are unknown. We analyzed such data from a medical center in Taiwan.
Methods: We retrospectively reviewed the medical records of patients with SLE who were diagnosed with CMV diseases between 2006 and 2016 in Taipei Veterans General Hospital Taiwan. Clinical and laboratory parameters and treatment outcomes were analyzed.
Results: The study enrolled 56 eligible patients with CMV diseases and separated them into survival (n = 24) and mortality (n = 32) groups. All cases showed a significantly high incidence of pneumonitis (71.43%). The patients in the mortality group had a higher SLE disease activity index (SLEDAI)-2000 ($p = 0.009$), more cases of recent methylprednisolone pulse therapy ($p = 0.013$) and pancytopenia ($p = 0.001$), stronger evidence of CMV infection demonstrated by polymerase chain reaction (PCR) in blood ($p < 0.001$) and bronchoalveolar lavage ($p = 0.021$), and more concurrent infections (bacteremia $p = 0.026$; fungemia $p < 0.001$).
Conclusions: Recent pulse therapy, pancytopenia, and concurrent infections constituted risk factors for mortality in patients with SLE and CMV infection. Among mortality patients, PCR rather than serological tests (IgM antibodies) helped to arrive at an earlier diagnosis.
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Introduction

Cytomegalovirus (CMV) is a major cause of life-threatening complications in immunocompromised hosts, including allogeneic bone marrow transplant patients, solid organ transplant patients, and patients with acquired immunodeficiency syndrome (AIDS).[1–4] The reactivation of CMV depends on the immune status of the hosts.[2,3] Systemic lupus erythematosus (SLE) is an autoimmune disease where the immune system is dysregulated, which often requires steroid and immunosuppressive agents to induce remission or decrease disease activity. It is widely accepted that lupus patients are prone to opportunistic infections, which constitute a leading cause of morbidity and mortality in cases of the disease. It is unknown whether the incidence and severity of CMV diseases fluctuate with the course of various immunosuppressive therapies, including conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologics in the treatment of autoimmune diseases such as SLE.

CMV encephalitis, colitis, hepatitis, and pneumonitis have been reported in the context of pulse steroids, cyclophosphamide, mycophenolate mofetil (MMF),[5] tocilizumab,[6] and rituximab (RTX)[7] treatments. Some studies show a higher corticosteroid dosage (mean 26.3 mg/day) and higher frequency of azathioprine (AZA) use in patients with CMV infections.[8] However, only a few studies have examined the clinical outcomes and mortality risk factors of CMV diseases in SLE patients who are being treated with immunosuppressive agents,[9–12] and the clinical significance remains inconclusive. This investigation presents the clinical presentations, laboratory characteristics, treatment profiles (including steroid, immunosuppressive agents, and biological agents), and clinical outcomes in SLE patients with CMV diseases. Furthermore, the mortality risk factors among these patients were analyzed.

Methods

Study design and patient selection

This retrospective observational study was conducted over an 11-year period (from January 1, 2006 to December 31, 2016) at Taipei Veterans General Hospital to identify the mortality risk factors associated with CMV diseases in patients with SLE. Patients were excluded if they were younger than 18 years old at the beginning of the study. All of the patients fulfilled the 1982 American College of Rheumatology SLE classification criteria with the 1997 update[13,14] or the 2012 Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus (SLICC Criteria).[15] All of the patients were admitted to the hospital during the index period due to complications of SLE.

The medical records of 56 admitted patients indicated CMV diseases. These patients were further stratified into mortality and survival groups. The study was approved by the Institutional Review Board at Taipei Veterans General Hospital (2017-01-002BC) and was conducted in accordance with the principles set forth in the Declaration of Helsinki. The requirement to obtain informed consent was waived because the data retrieved were encrypted, and the study was retrospective in nature.

CMV viremia, retinitis and disease

CMV viremia was defined by the yield of CMV DNA by polymerase chain reaction (PCR) in peripheral venous blood. CMV retinitis was defined by the presence of cotton wool lesion in the retina according to indirect ophthalmoscopy. CMV disease was defined by the presence of relevant clinical syndromes caused by CMV, including fever, malaise, leukopenia, diarrhea, retinitis, pneumonitis, and hepatitis, along with the presence of IgM antibodies against CMV in serum and CMV-DNA copies in circulation (peripheral blood), sputum, urine, or other tissues. These samples were obtained by biopsies or bronchoalveolar lavage (BAL). The results were detected by PCR; the culture yield of CMV from biopsied tissue, sputum, urine, or vitreous fluid; or immunohistochemical evidence of CMV invasion in various tissue or in BAL fluid.

Concurrent pulse corticosteroid therapy and recent rituximab therapy

We defined concurrent pulse corticosteroid therapy as the use of 500—1000 mg/day of methylprednisolone (or equivalent) for no more than 3 days during the hospital course due to CMV diseases or other indications of pulse therapy, such as induction therapy for lupus nephritis (LN), autoimmune hemolytic anemia, and rapidly progressive glomerulonephritis (RPGN) within three months. The RTX therapies for SLE patients were initiated by the physician and were not based on reimbursement. The indications included refractory LN, autoimmune hemolytic anemia, and other catastrophic lupus complications. Recent RTX therapy was defined as having received the therapy within 6 months, which conformed to the standard protocol of 500—1000 mg of RTX two weeks apart for one course and two courses 6 months apart every year, which is the same course prescribed for rheumatoid arthritis.[16]

SLE disease activity index

Disease activity of SLE was calculated according to the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K).[17,18]

Statistical analysis

The software IBM Statistical Package for Social Sciences (SPSS) version 22 was used for all data analyses. Non-normal-distributed data are presented as the mean (standard deviation (SD)), and categorical variables are expressed as counts (%). To analyze differences between the mortality and survival groups, an independent *t* test was used to compare numerical data, and the chi-squared test was used to compare categorical data. Risk factors for in-hospital mortality in patients with SLE and CMV diseases were identified using binary logistic regression analyses, and the hazard ratios (HRs) are listed along with the 95% confidence intervals (CIs). In all statistical analyses,

the two-tailed *p*-value was interpreted as significant when it was less than 0.05.

Results

Comparison of baseline characteristic and immunosuppressive treatments in the mortality and survival groups

There was no difference between patients in the mortality and survival groups in terms of age, gender, organs involved in lupus, and comorbidity. However, all patients receiving renal transplantation were in the survival group ($p = 0.008$). The mortality group had significantly higher mean SLEDAI-2K scores indicating the active status of CMV diseases than the survival group ($p = 0.009$, HR1.154, 95% CI 1.037—1.285) (Table 1).

There were no significant differences in the mean daily steroid dose used by the mortality and the survival groups (17.08 *vs.* 12.97 mg/day, $p = 0.325$). Compared with those in the survival group, the mortality group had higher rates of recent pulse therapy ($p = 0.013$, HR 4.569, 95% CI 1.313—15.902) and plasmapheresis ($p = 0.005$, HR6.905, 95% CI 1.637—29.122) during the hospital course. The mortality group did not receive any treatments with tacrolimus, sirolimus, or anti-thymocyte globulin (Table 1). There were no statistical differences between the two groups in the mean daily doses of prednisolone, AZA, MMF, or equivalent mycophenolic acid (MPA), and cyclosporine. There were also no statistical differences in the percentage of patients receiving AZA, MMF, cyclosporine, cyclophosphamide, and recent RTX therapy (Table 1). In addition, the mortality group had a significantly higher rate of pancytopenia ($p = 0.001$, HR9.667, 95% CI 2.307—40.511, Table 1) than the survival group.

Clinical features of CMV infections and their differences between the mortality and survival groups

End-organ diseases of CMV included pneumonitis, retinitis, gastroenteritis, and hepatitis. Among them, 83.33% of the mortality group and 25% of the survival group had CMV end-organ diseases combined with viremia, which was significantly different ($p \leq 0.001$, HR15.000, 95% CI 3.932—57.223) (Table 2). There was no difference in organ involvement of CMV diseases between groups, and the most common was pneumonitis (71.43% of total patients, 83.33% of the mortality group, and 62.5% of the survival group).

The positive rate of CMV IgM antibodies was significantly lower in the mortality group than the survival group ($p = 0.010$, HR0.228, 95% CI 0.071—0.729). In contrast, the yielding rates of PCR from blood or BAL fluid among the mortality group was higher than the survival group (blood: $p < 0.001$, HR15.000, 95% CI 3.932—57.223, BAL fluid: $p = 0.021$, HR6.176, 95% CI 1.151—33.151). The mortality group had higher rates of CMV-positive culture, CMV-positive cytology, and biopsy specimens that had positive immunohistochemical stains than the survival group ($p = 0.013$, HR4.333, 95% CI 1.312—14.317, Table 2).

Co-morbidities with bacteremia and other opportunistic infections

There were significant differences in bacteremia ($p = 0.026$, HR4.833, 95% CI 1.122—20.824) and fungal

Table 1 Demographic data of CMV diseases in SLE patients.

Parameters	Total (n = 56)	Mortality group (n = 24)	Survival group (n = 32)	*P* value
Patient Characteristics				
Age (years, mean ± SD)	43.32 ± 16.52	45.17 ± 17.89	41.94 ± 15.83	0.471
SLEDAI-2K	12.36 ± 8.70	16.08 ± 11.44	9.56 ± 4.303	**0.009**
Gender (Female,%)	49 (87.5)	20 (83.3)	29 (90.6)	0.414
MTP pulse therapy within 6 months (%)	16 (28.6)	11 (45.8)	5 (15.6)	**0.013**
Plasmapheresis (%)	13 (23.21)	10 (41.67)	3 (9.38)	**0.005**
Prednisolone (mg/day)[a]	14.73 ± 15.22	17.08 ± 17.69	12.97 ± 13.09	0.325
RTX within 6 months (%)	15 (26.79)	9 (37.5)	6 (18.75)	0.117
Pancytopenia (%)	15 (26.79)	12 (50)	3 (9.38)	**0.001**
Proteinuria (g/d) or urine protein/creatinine ratio	2.51 ± 3.56	2.86 ± 3.89	2.25 ± 3.33	0.521
Concurrent infections				
No coinfection	16 (28.57%)	2 (14.3%)	14 (43.75%)	**0.004**
Bacteremia[b]	11 (19.64%)	8 (33.33%)	3 (9.38%)	**0.026**
PJP	14 (25%)	9 (37.5%)	5 (15.63%)	0.061
Other fungal infection	16 (28.57%)	13 (54.17%)	3 (9.38%)	**0.001**

[a] The daily dose of prednisolone is simplified with equivalent dose.
[b] The microorganism of bacteremia: *methicillin-susceptible Staphylococcus aureus, vancomycin-resistant Enterococci, bacillus cereus, carbapenem-resistant Acinetobacter baumannii, Escherichia coli, Enterobacter cloacae, Salmonella spp., Stenotrophomonas maltophilia.*
MTP, methylprednisolone; RTX, rituximab; PJP, *Pneumocystis jiroveci* pneumonia.
Bold represents $P < 0.05$.

Table 2 The involved organ, serologic data, culture evidence of CMV diseases in SLE patients.

	Total (n = 56)	Mortality group (n = 24)	Survival group (n = 32)	*P* value	HR	95% CI
Viremia (%)[a]	28 (50)	20 (83.33)	8 (25)	**0.001**	**15.000**	**3.932–57.223**
Pneumonitis (%)	40 (71.43)	20 (83.33)	20 (62.5)	0.088	3.000	0.826–10.901
Hepatitis (%)	5 (8.93)	1 (4.17)	4 (12.5)	0.279	0.304	0.032–2.916
Gastroenteritis (%)	6 (10.71)	1 (4.17)	5 (15.63)	0.170	0.235	0.026–2.157
Retinitis (%)	5 (8.93)	1 (4.17)	4 (12.5)	0.279	0.304	0.032–2.916
Laboratory diagnosis of CMV (+) culture/pathology (%)	18 (32.14)	12 (50)	6 (18.75)	**0.013**	**4.333**	**1.312–14.317**
CMV IgM Positive (%)	25 (44.64)	6 (25)	19 (59.38)	**0.010**	**0.228**	**0.071–0.729**
CMV PCR (+) in BAL fluid (%)	9 (16.07)	7 (29.17)	2 (6.25)	**0.021**	**6.176**	**1.151–33.151**

Bold represents $P < 0.05$.

[a] Viremia was defined as a positive finding of CMV DNA PCR in blood.

infections other than *Pneumocystis jiroveci* infections ($p < 0.001$, HR11.424, 95% CI 2.722–47.952) between the two groups (Table 1). *P. jiroveci* pneumonia (PJP) was twice as common in the mortality group as in the survival group, although the difference was not statistically significant.

Concurrent infection with other pathogens might be one of the risk factors for mortality in CMV diseases ($p = 0.004$, HR0.117, 95% CI 0.023–0.583).

All-cause in-hospital mortality group and mortality group risk factors in CMV diseases

Septic shock (n = 10, 41.2% of the mortality group) was the most common cause of mortality in CMV diseases, and multiple organ dysfunction was the second (n = 5, 20.9% of the mortality group). Other etiologies are listed in Fig. 1. We utilized univariate and logistic regression analyses to determine clinical features that correlated with increased mortality in cases of CMV diseases. As shown in Fig. 2, except for the absence of co-infections or the presence of IgM antibodies against CMV, all other studied factors increased the risk of mortality, with the highest increase observed for CMV viremia.

Subgroup analysis and all-cause mortality in CMV pneumonitis

As shown in Table 3, the mortality group had more cases of recent steroid pulse therapy ($p = 0.008$, HR 6.926, 95% CI 1.529–31.377), more mechanical ventilations ($p < 0.001$, HR 4.333, 95% CI 2.148–8.742), more cases of pulmonary hemorrhage ($p = 0.028$, HR6.000, 95% CI 1.082–33.274), more acute respiratory distress syndromes (ARDS, $p = 0.002$, HR1.667, 95% CI 1.165–2.384), and more cases of plasmapheresis ($p = 0.018$, HR5.667, 95% CI 1.254–25.606) during the hospital course. On the other hand, there was no significant difference in the mean daily dose and frequency of prednisolone or immunosuppressive agents in both groups (data not shown). The presence or absence of antibodies against CMV in serum did not predict the outcome of the diseases in both CMV pneumonitis and CMV diseases. The mortality group had more cases that showed an absence of CMV IgM antibodies accompanied by the presence of CMV DNA in blood as detected by PCR was than the survival group (Table 3).

The presence of CMV DNA in BAL fluid was four times more common in the mortality group than in the survival group, although it did not reach statistical significance. There was no significant difference in the frequency of CMV DNA detected by PCR in BAL fluid in the survival group (Table 3). Excluding PJP, concurrent infections with fungi were one of the risks leading to death in both CMV pneumonitis and CMV diseases ($p = 0.001$, HR23.222, 95% CI 2.585–208.615). The two leading direct causes of mortality were septic shock (n = 10, 50% of the mortality group) and multiple organ dysfunction (n = 4, 20% of the mortality group). Other risk factors are listed in Fig. 1.

Discussion

CMV belongs to the β-herpes virus subfamily and infects epithelial cells, endothelial cells, fibroblasts, peripheral blood mononuclear cells, and nerve cells. Latent CMV infection is usually asymptomatic in healthy individuals,[19] and some studies have demonstrated that CMV infection might be a trigger for SLE.[20] CMV infection may lead to severe or even fatal illnesses in immunocompromised hosts, but few studies have investigated the association between CMV diseases and mortality in patients with SLE.

In the present investigation, pneumonitis was the most common CMV disease associated with SLE and was an unequivocal risk factor for the mortality of SLE patients with an immunocompromised condition. However, it is difficult to identify the exact direct cause of death in SLE patients with CMV diseases. Patients with SLE often have multiple and complicated medical conditions, including systemic inflammation, associated chronic renal diseases, and other concurrent infections.[21] These factors obscure the identification of the cause of fatality in cases of CMV.

Steroid and immunosuppressive agents

It has been reported that most patients with an autoimmune condition who suffer from CMV diseases are treated with high doses of corticosteroids, including pulse methylprednisolone, in addition to immunosuppressive agents.[5–7,9–11] The CMV diseases in patients with SLE may be precipitated

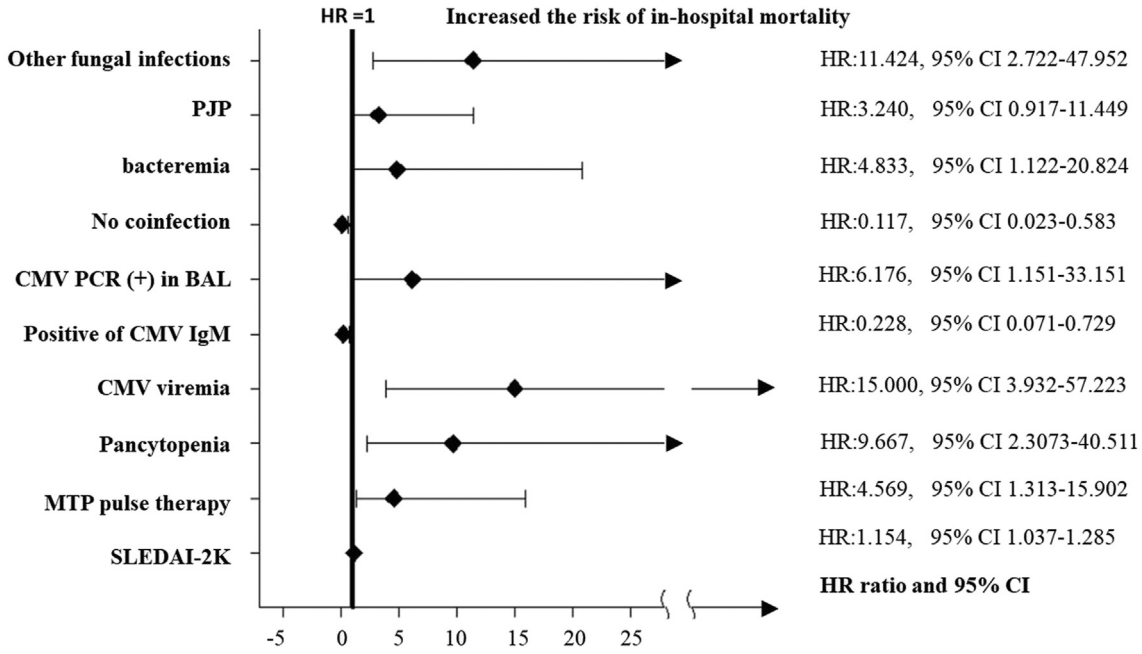

Fig. 1. Forest plot for mortality risk factors in SLE patients with CMV diseases.

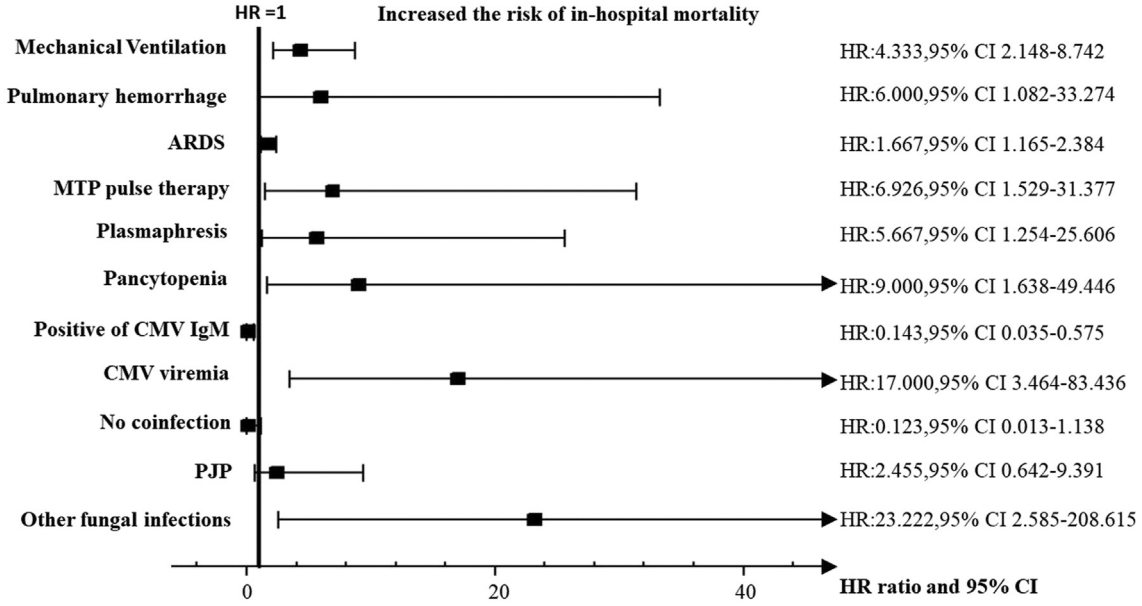

Fig. 2. Forest plot for mortality risk factors among SLE patients with CMV pneumonitis.

immunosuppressive treatments in combination with daily oral or pulse steroid therapy, AZA, MMF, cyclosporine, cyclophosphamide, anti-thymoglobulin, and RTX. However, the mean dose of steroid as well as how often our patients used it did not influence the mortality rate of CMV diseases and CMV pneumonitis in this cohort, except for recent methylprednisolone pulse therapy (Fig. 2).

Leukopenia and pancytopenia

An effective immune response is crucial for controlling CMV replication.[22] The role of natural killer (NK) cells in the clearance of virus infection and T cell responses in the control of virus replication has been understood recently.[23,24] Hence, Tsai et al.[8] reported that lymphopenia predicted mortality or morbidity in 54 Chinese patients with autoimmune diseases, especially in patients with SLE.

In the present investigation, the patients were subclassified into groups of pancytopenia, leukopenia only, or thrombocytopenia only. Leukopenia only or thrombocytopenia only was not a risk factor for mortality in cases of CMV diseases (Table 3) and CMV pneumonitis (data not shown). However, pancytopenia in association with CMV

Table 3 Characteristics of CMV pneumonitis in SLE patients.

	Total (n = 40)	Mortality group (n = 20)	Survival group (n = 20)	*P* value
Age (years, mean ± SD)	43.32 ± 16.98	42.35 ± 17.39	44.30 ± 17.39	0.717
SLEDAI-2K	13.33 ± 9.725	16.35 ± 12.21	10.30 ± 5.07	0.064
Gender (Female,%)	34 (85)	17 (85)	17 (85)	1.000
BAL (%)	24 (60)	15 (75)	9 (45)	0.053
MTP pulse therapy within 6 months (%)	14 (35)	11 (55)	3 (15)	**0.008**
Prednisolone (mg/d)	16.91 ± 17.14	19.00 ± 18.68	14.81 ± 15.65	0.442
Plasmapheresis (%)	13 (32.5)	10 (50)	3 (15)	**0.018**
Pancytopenia (%)	12 (30)	10 (50)	2 (10)	**0.006**
Mechanical ventilation (%)	26 (65)	20 (100)	6 (30)	**0.001**
Pulmonary Hemorrhage (%)	10 (25)	8 (40)	2 (10)	**0.028**
ARDS (%)	8 (20)	8 (40)	0 (0)	**0.002**
Serologic data, CMV PCR, and coinfections				
CMV (+) of culture/pathology (%)	16 (40)	10 (50)	6 (30)	0.197
CMV IgM Positive (%)	19 (47.5)	5 (25)	14 (70)	**0.004**
CMV viremia (%)	22 (55)	17 (85)	5 (25)	**0.001**
CMV PCR (+) in BAL fluid (%)	9 (22.5)	7 (35)	2 (10)	0.058
No coinfection (%)	7 (17.5)	1 (5)	6 (30)	**0.037**
Bacteremia (%)	8 (20)	6 (30)	2 (10)	0.114
PJP (%)	14 (35)	9 (45)	5 (25)	0.185
Other Fungal infection (%)	12 (30)	11 (55)	1 (5)	**0.001**

Bold represents $P < 0.05$.

diseases or CMV pneumonitis did constitute a risk factor for in-hospital mortality.

Serologic and PCR tests for CMV detection and diagnosis

The negative results of CMV-IgM antibodies accompanied by a positive finding of CMV DNA PCR in our study could originate from the different laboratory features at different phases of the viral diseases. Similar characteristics have been found in cases of human immunodeficiency virus (HIV).[25] In a such scenario, CMV DNA viremia might be present prior to the sero-conversion phase of CMV-IgM antibodies.

Given the findings of serological antibodies and CMV DNA PCR, it is reasonable to carry out both tests simultaneously in order to improve the diagnosis rate. A logical alternative to empirical antiviral therapy may be biomarker-driven/preemptive antiviral therapy using serum CMV IgM antibodies, CMV PCR, or both as monitoring guides. The CMV-DNA copy number is a useful marker for predicting the progression of CMV infection[26] that has been used to monitor the response of treatment and to identify patients at risk of CMV disease after transplantation.[27–29] In the present investigation, we found that the detection rate of CMV DNA was significantly higher in the mortality group than in the survival group (Fig. 2), and an increasing CMV-DNA PCR copy number was observed in progressively uncontrolled CMV diseases.

Co-infection

Concurrent infections with bacteria, PJP, and other fungi may make the situation more complex in febrile patients with autoimmune diseases, especially SLE, who are diagnosed with CMV diseases and CMV pneumonitis. The different antibiotics used against different microbes may interact with each other to enhance or offset the drug effects and thus increase the failure rate of treatment or mortality. In addition, the microorganisms themselves may enhance or inhibit each other by nature. As shown in the present investigation, concurrent infections with bacteria, PJP, and other fungi were risk factors for mortality (Fig. 2). Accordingly, in SLE patients with febrile episodes, we suggest that vigorous efforts might be necessary to find out any possible pathogens, including bacteria, fungi, and viruses, and to prescribe the correct antibiotic agents in a timely manner.

Sub-classification of CMV pneumonitis

CMV pneumonitis is the most common destructive complication of CMV diseases, as shown in the present study. However, there have been little data about the relationship between SLE and CMV pneumonitis and the outcomes. We therefore present the clinical features and outcomes in CMV pneumonitis with concurrent SLE.

Severe CMV pneumonitis was associated with a higher intubation rate (100% in the mortality group *vs.*30% in the survival group, $p < 0.001$, Table 3). This might originate from the more frequent presentations of hypoxemia and acute respiratory failure in cases of CMV pneumonitis rather than in overall CMV disease. The other factors contributing to the high mortality in CMV pneumonitis included pulmonary hemorrhage and ARDS ($p = 0.028$ and 0.002, respectively). Among the patients with pulmonary hemorrhage, as much as 80% (n = 10) of them developed ARDS, and the combination was universally fatal.

The benefit of intensive clinical follow-up

There were no cases of mortality from catastrophic complications originating from LN in eight patients who had undergone renal transplantation. All of them had been placed under careful scrutiny with a high index of suspicion and could hence be recognized to have CMV diseases earlier.

Limitations of the present investigation

The present study has several shortcomings or limitations. The sample size was relatively small since the data were only retrieved from a single medical center, which has an accommodation capacity of about 3000 inpatients. This implies that the conclusions may not be applicable to all of Taiwan, let alone the whole world. Furthermore, the serological data of CMV IgM antibodies were not complete because of the unavailability or absence of records from before 2009. The methods used to detect CMV IgM antibodies were variable from 2006 to 2016. Thus, we could not evaluate the relationship between CMV IgM antibody titers and the severity of the CMV diseases.

BAL procedures were not always timely in this hospital because acute respiratory illness in CMV pneumonitis has been so prevalent that our facilities could not provide interventions in time. For this, the confounding factors for decision making about the procedure might have also included critical illness status, extremely high PaO2/FiO2 ratio of ventilation, and coagulopathy that obviously increases the risk of BAL-related complications. These dilemmas led to insufficient PCR data from lavage fluid and thus compromised the comparison of the most severe and complicated presentations. Finally, the present investigation lacked of histopathologic evaluation of the liver damage caused by CMV. Nevertheless, the present investigation has still provided pertinent information for use in the recognition of CMV infections in SLE patients and potential therapeutic strategies.

Conflicts of interest

There were no conflicts of interests among all of the coauthors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2018.12.002.