

A Prospective Epidemiological and Immunological Study of CMV Infection in Systemic Lupus Erythematosus Patients Receiving Immunosuppressant

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Background

- Cytomegalovirus (CMV) infection could cause morbidity and mortality among SLE patients, especially those receiving immunosuppressant
- To investigate for an epidemiology, risk factors especially immunological factors and outcome of CMV infection in SLE patients receiving immunosuppressant

Methods

- A prospective study of adult SLE patients who received immunosuppressant (Nov 2017 to Jan 2020) at Ramathibodi hospital
- Clinical characteristics and risk factors of clinically significant CMV infection (CsCMVI) were extracted and analyzed
- **CsCMVI : plasma CMV DNA loads > 1,000 IU/mL either with (CMV disease) or without symptoms**
- Plasma CMV DNA loads was measured by quantitative real-time PCR (Abbott RealTime CMV assay)
- CMV-specific cellular immune responses were measured by an enzyme-linked immunosorbent assay (QuantiFERON-CMV®, QFT-CMV) and intracellular cytokine assay

Results

- A total of 39 active SLE patients, 36 (92%) were female with a median age of 28 (IQR 24-44) years
- Median SLEDAI score was 16 (IQR 9-20)
- 74% had renal involvement and 94% received methylprednisolone
- Thirty-six (92%) patients were CMV-seropositive
- CsCMVI occurred in 6 (15.4%) patients included CMV syndrome (66.6%), tissue invasive disease (16.7%) and asymptomatic CMV infection (16.7%)
- Among 197 blood samplings, 16 (8.1%) episodes were defined as CsCMVI
- The percentage of CMV-IE1-specific NKT cells in those with CsCMVI were lower than those without CsCMVI (0.18% vs. 1.93%, p = 0.03)
- In multivariate analysis, neurological involvement was associated with CsCMVI (OR 7.9; 95% CI 1.5-41.9, [p = 0.015])

Table 1 Characteristics of 39 SLE recipients

| Variables | N (%) |
|----------------------------|------------|
| Age (yrs), median (IQR) | 28 (24-44) |
| Female sex | 36 (92) |
| SLEDAI score, median (IQR) | 16 (9-20) |
| Organ involvement | |
| Skin | 19 (51) |
| Arthritis | 8 (21) |
| Serositis | 5 (13) |
| Renal | 29 (74) |
| Neurology | 8 (21) |
| Hematology | 19 (49) |
| CMV IgG | |
| Positive | 36 (92) |
| Negative | 3 (8) |
| QuantiFERON-CMV | |
| Reactive | 11 (42) |
| Non-reactive | 7 (27) |
| Indeterminate | 8 (31) |
| Immunosuppressant | |
| Methylprednisolone | 37 (94) |
| Cyclophosphamide | 12 (31) |
| Mycophenolic acid | 12 (31) |
| Tacrolimus | 4 (10) |
| Cyclosporine | 4 (10) |
| Rituximab | 6 (15) |

Figure 1 Incidence of CsCMVI in SLE patients

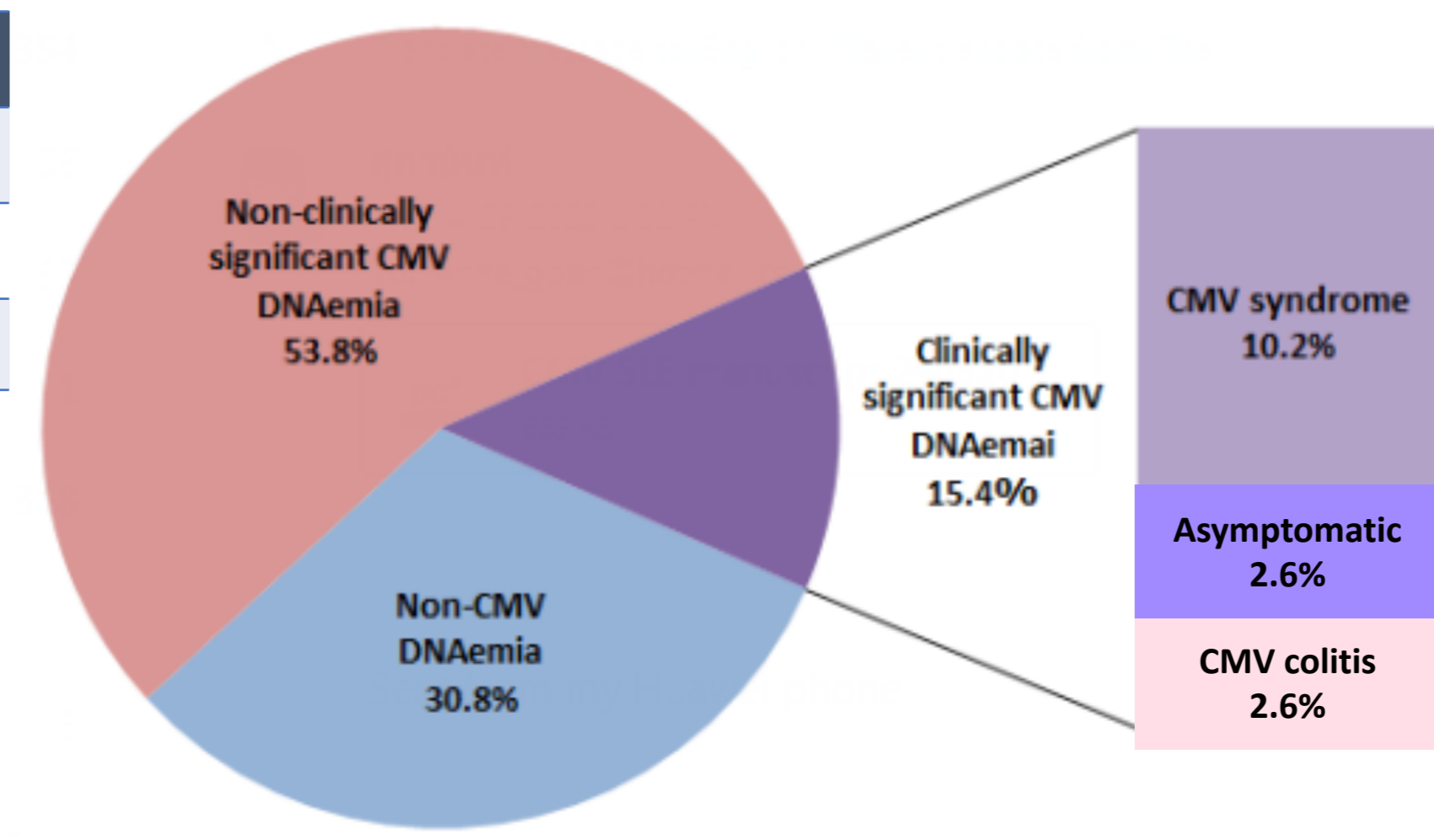


Figure 2 Kaplan Meier plot of CsCMVI in patients with/without neurological involvement

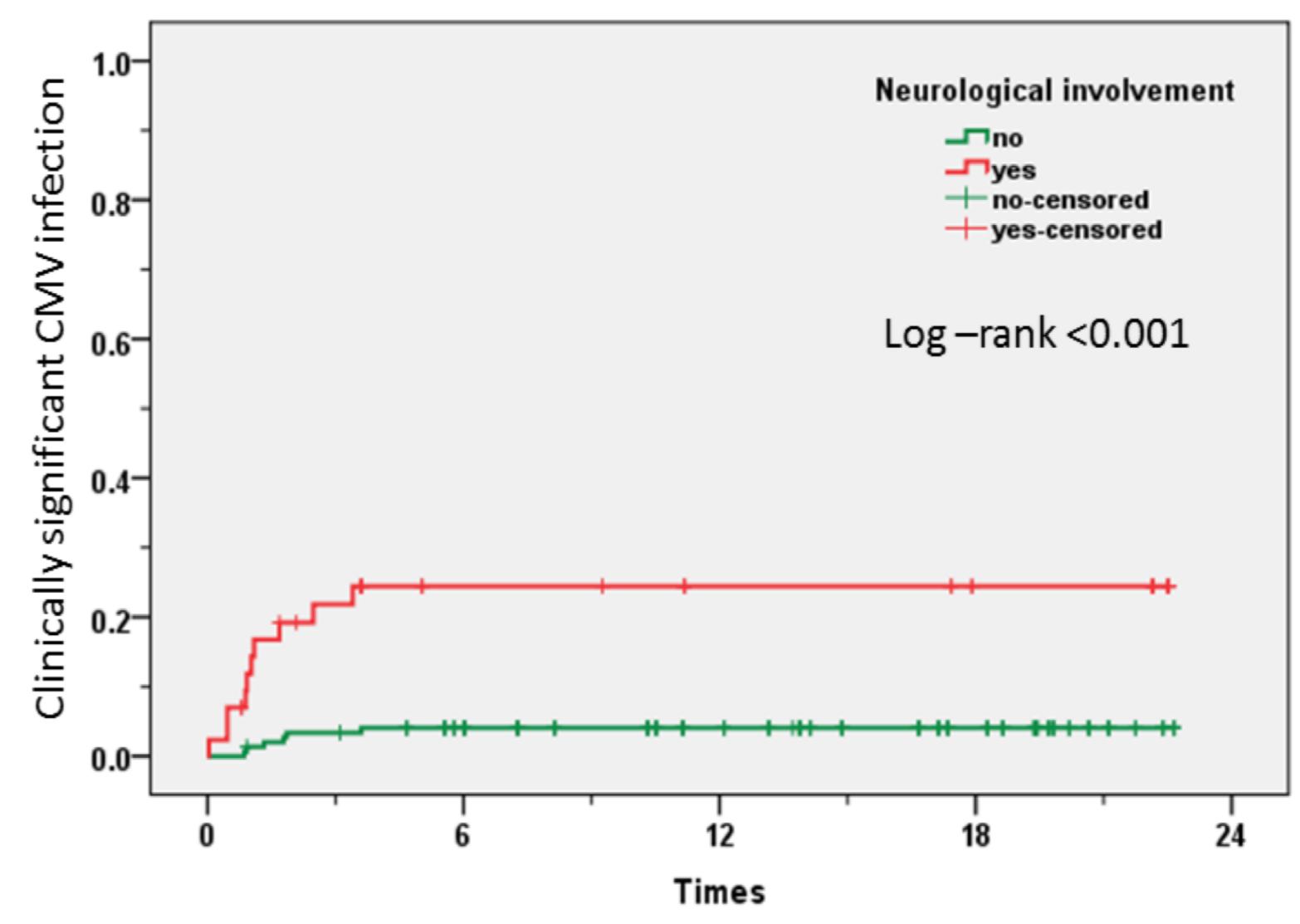


Table 3 Logistic regression analysis for risk factors of CsCMVI

| Risk factors | Univariate | | Multivariate | |
|---------------------------------|--------------------------|------------------|--------------------------|--------------|
| | OR (95%CI) | P value | OR (95%CI) | P value |
| Creatinine | 0.01 (0.00-0.34) | 0.009 | | |
| % CMV-IE1-specific NKT cells | 0.49 (0.13-1.80) | 0.280 | | |
| Renal involvement | 0.24 (0.09-0.69) | 0.080 | 0.26 (0.22-5.87) | 0.887 |
| Neurological involvement | 7.22 (2.45-21.28) | <0.001 | 7.92 (1.50-41.85) | 0.015 |

Table 2 Immunological responses in 197 blood samples

| Variables Mean (SD) | CsCMVI N = 16 | No CsCMVI N = 181 | P-value |
|--------------------------------|--------------------|--------------------|--------------|
| CMV-specific CD4 T cell | | | |
| %Total CD4 cell | 22.97 (10.81) | 20.83 (10.48) | 0.801 |
| Total CD4 cell | 268 (306) | 216 (180) | 0.086 |
| %IE-1 CD4 cell | 0.01 (0.02) | 0.22 (0.05) | 0.269 |
| Total IE-1 CD4 cell | 0.02 (0.03) | 0.04 (0.11) | 0.290 |
| %pp65 CD4 cell | 0.02 (0.02) | 0.05 (0.12) | 0.131 |
| Total pp65 CD4 cell | 0.03 (0.03) | 0.08 (0.19) | 0.161 |
| % Whole lysate CD4 cell | 0.01 (0.03) | 0.03 (0.06) | 0.314 |
| Total Whole lysate CD4 cell | 0.01 (0.01) | 0.04 (0.09) | 0.199 |
| CMV-specific CD8 T cell | | | |
| % CD8 cell | 35.61 (12.66) | 32.73 (13.16) | 0.842 |
| Total CD8 cell | 368 (352) | 354 (281) | 0.415 |
| % IE-1 CD8 cell | 0.01 (0.01) | 0.04 (0.11) | 0.159 |
| Total IE-1 CD8 cell | 0.02 (0.02) | 0.17 (0.57) | 0.204 |
| % pp65 CD8 cell | 0.03 (0.04) | 0.12 (0.27) | 0.148 |
| Total pp65 CD8 cell | 0.15 (0.28) | 0.36 (0.85) | 0.250 |
| % Whole lysate CD8 cell | 0.01 (0.02) | 0.01 (0.03) | 0.726 |
| Total Whole lysate CD8 cell | 0.09 (0.18) | 0.04 (0.15) | 0.194 |
| CMV-specific NK cell | | | |
| % NK cell | 0.33 (0.23) | 0.77 (0.86) | 0.061 |
| Total NK cell | 277 (237) | 663 (759) | 0.063 |
| % IE-1 NK cell | 0.19 (0.55) | 2.74 (8.27) | 0.181 |
| Total IE-1 NK cell | 0.15 (0.43) | 14.93 (55.50) | 0.205 |
| % pp65 NK cell | 0.81 (1.31) | 4.34 (10.02) | 0.092 |
| Total pp65 NK cell | 0.86 (1.22) | 23.41 (68.71) | 0.116 |
| % Whole lysate NK cell | 0.38 (1.06) | 1.04 (2.31) | 0.280 |
| Total Whole lysate NK cell | 0.70 (1.98) | 3.52 (9.72) | 0.260 |
| CMV-specific NKT cell | | | |
| %NKT cell | 0.14 (0.10) | 0.15 (0.42) | 0.695 |
| Total NKT cell | 0.37 (0.65) | 1.80 (8.96) | 0.497 |
| %IE-1 NKT cell | 0.18 (0.52) | 1.93 (3.96) | 0.031 |
| Total IE-1 NKT cell | 0.15 (0.41) | 12.48 (34.90) | 0.086 |
| %pp65 NKT cell | 0.14 (0.39) | 3.23 (8.20) | 0.110 |
| Total pp65 NKT cell | 0.26 (0.73) | 21.01 (53.37) | 0.071 |
| % Whole lysate NKT cell | 1.43 (3.13) | 1.83 (5.19) | 0.774 |
| Total Whole lysate NKT cell | 6.47 (16.38) | 8.92 (31.46) | 0.755 |

Conclusions

- ❖ Active SLE patients with neurological involvement who received immunosuppressant are at risk of CMV infection
- ❖ Lack of CMV-specific NKT cell response tends to be associated with CMV infection