

## Original Article



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
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# Changes in Cytomegalovirus Seroprevalence in Korea for 21 Years: a Single Center Study

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## ABSTRACT

**Purpose:** Cytomegalovirus (CMV) infection is mostly asymptomatic but can be detrimental to certain hosts. We investigated changes of CMV seroprevalence in Koreans before and after the year 2000.

**Methods:** We reviewed laboratory values of patients who were tested for CMV immunoglobulin G (IgG) at Samsung Medical Center, Seoul, Korea, from January 1995 to December 2015. Changes in seroprevalence were analyzed by gender, age, region, and tested year period (period 1, 1995–2005 vs. period 2, 2006–2015).


**Results:** Overall CMV seropositivity was 94.1% (10,900/11,584). There was no significant difference for CMV seropositivity among the two periods (94.2% vs. 94.1%) ( $P=0.862$ ). CMV seropositivity in the 11 to 20-year age group in period 2 (78.8%) was significantly lower than that of period 1 (89.9%) ( $P=0.001$ ). The seropositivity of individuals aged 31–40 years (97.4%) was significantly higher than that of younger age groups ( $P<0.001$ ) and lower than that of older age groups ( $P<0.001$ ). Of 2,441 females of reproductive age (from 15 to 49), CMV seropositivity was 97% (2,467/2,441). The seropositivity in women aged 20–24-years was higher than that of men in the same age group (97.6% vs. 85.6%,  $P=0.003$ ). No significant difference was observed among different regions.

**Conclusions:** Overall CMV seropositivity of Koreans was estimated to be 94% and the average seropositivity of reproductive women was 97%. Monitoring of the changes in seroprevalence including the reproductive age group is needed in the future.


**Keywords:** Cytomegalovirus; Seroprevalence; Korea

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#### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

#### Author Contributions

Conceptualization: Kim YJ; Data curation: Choi SR, Kim KR; Formal analysis: Kang JM, Kim SJ, Kim JM; Investigation: Kim DS, Kim KR; Methodology: Kim YJ; Project administration: Kim YJ; Resources: Kang ES, Oh SY; Software: Choi SR; Supervision: Kim YJ, Peck KR, Chung DR, Kang CI; Validation: Kim YJ, Kang ES, Oh SY; Visualization: Kim YJ; Writing - original draft: Choi SR; Writing - review & editing: Choi SR, Kim YJ.

## INTRODUCTION

Cytomegalovirus (CMV) infections are usually asymptomatic but can be detrimental in immunocompromised patients or fetuses. CMV infection is the most common viral cause of congenital infection in the United States and in Western European countries.<sup>1-3)</sup> The intrauterine transmission rate is approximately 40% in primary CMV infection in pregnancy, which poses the main risk of congenital infection and disease. CMV immunoglobulin G (IgG) seropositivity is highly influenced by socioeconomic status and lifestyle. CMV IgG seropositivity of adults ranges from 40% in industrialized countries to nearly 100% in developing countries. In recent studies, CMV IgG seropositivity was 42.3% in Germany,<sup>4)</sup> 41.9% in France,<sup>5)</sup> 85% in Bulgaria,<sup>6)</sup> 95% in China,<sup>7)</sup> and 100% in Thailand.<sup>8)</sup> However, there are industrialized countries in Asia with high seroprevalence, such as Singapore 87%,<sup>9)</sup> Japan 69.7%,<sup>10)</sup> and Taiwan 91.1%.<sup>11)</sup> In South Korea, several studies have reported high seroprevalence of CMV since the early 1980s. Positive CMV IgG was found in over 99% of females over 20 years of age in 1984, and the prevalence was still over 98% in pregnant women in 2006.<sup>12,14)</sup> A high seroprevalence of CMV, approximately 97%, was observed in Koreans over 7 years of age before the year 2000, and was 100% in females of reproductive potential, over 30 years old, in the early 1990s.<sup>15)</sup>

Some studies have examined chronologic changes in CMV seroprevalence. A comparison of CMV seroprevalence in women in Spain between 1993 and 1999 showed a statistically significant decrease in IgG positivity in two age groups; 6 to 10 years old (56.7% vs. 43.7%) and 31 to 40 years old (90.3% vs. 79.1%).<sup>16)</sup> Another study in Japan also compared the changes in IgG seropositivity of umbilical cords between 2001 and 2013. The results demonstrated a decrease in the seropositivity from 75.7 to 67.2%.<sup>17)</sup>

There are a limited number of studies on CMV seroprevalence available in South Korea and no reports have been published with data for the last two decades. We performed this study to investigate the chronological changes of CMV seroprevalence among Koreans in all age groups.

## MATERIALS AND METHODS

### 1. Data collection and analysis

Laboratory values of all patients who underwent anti-CMV IgG tests during clinical care at Samsung Medical Center, Seoul, Korea, from January 1995 to December 2015 were retrospectively reviewed. Only the first laboratory value was reviewed if the patient underwent multiple tests. Study years were divided into two periods: period 1 from 1995 to 2005 and period 2 from 2006 to 2015. Changes in seropositivity were analyzed by sex, age, region, and tested year period. Age group was analyzed into interval of 10 years of age. We performed additional analyses for females in the reproductive age group (15–49) divided into interval of 5 years of age. CMV seropositivity was also examined at 25 to 30 years of age which was the median first childbearing age group (throughout 21 years, according to the Korean statistical database, the median 1st childbearing age was between the age group).<sup>18)</sup> Samsung Medical Center is one of the major tertiary referral centers which allowed the study to recruit patients from all regions across the country. Therefore, we were able to analyze seropositivity by sex, age, and region, which included seven metropolitan cities and six major provinces. CMV IgG were detected by using commercial immunoassays (VIDAS CMV IgG; Biomerieux, Marcy-l'Étoile, France) used since 2008. Information on commercial kit used before 2008 was not available.

## 2. Statistical methods

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analysis. Clinical characteristics are presented as mean, odds ratio (OR) and 95% confidence interval (CI). The association of potential risk factors for having CMV IgG seropositivity was tested by logistic regression analysis. *P*-values and 95% CIs were corrected using Bonferroni's method in cases of multiple testing or subgroup analysis. A *P*-value <0.05 was considered statistically significant. Statistical analysis was supported by the Department of Biostatistics of Samsung Medical Center.

## RESULTS

CMV IgG was tested in 11,584 patients and the proportion of male patients was 58% (6,743/11,584). The overall CMV IgG seropositivity was 94.1% (10,900/11,584) and demographic distributions are shown in **Table 1**.

### 1. Overall CMV seropositivity in two periods

The seropositivity was over 90% throughout the study period. There was no significant difference for CMV seropositivity among the two periods (94.2% vs. 94.1%, *P*=0.861) (**Table 1**).

### 2. CMV seropositivity by age groups

Significant differences in seropositivity were observed by age (**Table 1**). Compared to the seropositivity in individuals aged 31–40 years (97.4%), seropositivity was significantly lower in younger age groups (*P*<0.001; OR<1) and higher in older age groups (*P*<0.001; OR>1).

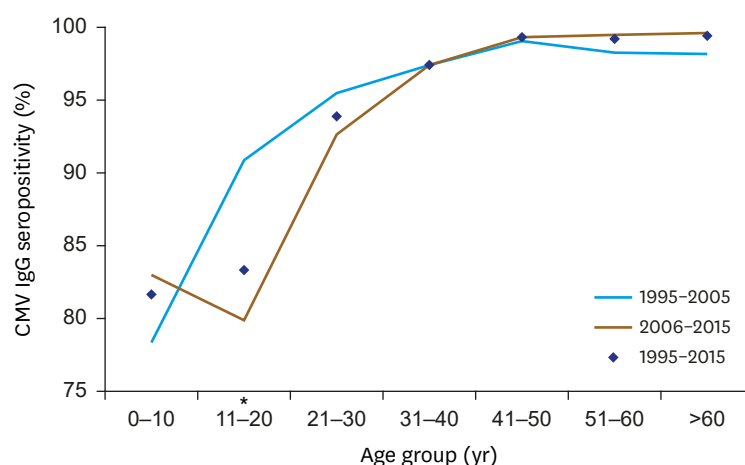
### 3. CMV seropositivity by age groups in two periods

In period 1, a steep and continuous rise in CMV seropositivity was observed in each age group until the age reaching 40s. In period 2, there was a delayed rise in CMV seropositivity after the 20s (**Fig. 1**). When comparing CMV seropositivity in each age group between periods, CMV seropositivity in the 11–20-year age group in period 2 (78.8%) was significantly lower than that of period 1 (89.9%) (*P*=0.001; OR, 0.42; 95% CI, 0.23–0.79).

**Table 1.** Demographic characteristics of CMV IgG seropositivity

Demographic factor	Category	Total tested	CMV IgG		Univariable		Multivariable	
			Positive	Prevalence (%)	OR	95% CI	OR	95% CI
Sex	Male	6,743	6,340	94.0	Ref.		Ref.	
	Female	4,841	4,560	94.2	1.03	0.88–1.21	1.17	0.99–1.38
Age (median age, yr)	0–10 (1.8)	1,602	1,311	81.7	0.12	0.08–0.19	0.13	0.08–0.19
	11–20 (13.8)	858	715	83.3	0.12	0.08–0.20	0.13	0.08–0.20
	21–30 (27.6)	1,170	1,099	93.9	0.36	0.22–0.59	0.36	0.22–0.59
	31–40 (36.0)	1,810	1,765	97.5	Ref.		Ref.	
	41–50 (46.3)	2,122	2,107	99.3	3.76	1.72–8.25	3.82	1.74–8.38
	51–60 (55.6)	2,327	2,308	99.2	3.75	1.77–7.93	3.83	1.81–8.12
	≥61 (65.0)	1,196	1,189	99.4	3.78	1.50–9.50	3.85	1.53–9.72
Period								
1	1995–2005	3,842	3,618	94.2	Ref.			
2	2006–2015	7,742	7,282	94.1	0.98	0.83–1.16	1.02	0.85–1.21
Total		11,584	10,900	94.1				

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; OR, odd ratio; CI, confidence interval; Ref., reference.



**Fig. 1.** CMV IgG seropositivity in each age group by year period.  
\*Age group with statistical significance between the two periods.  
Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G.

#### 4. CMV seropositivity in women at reproductive age

Data from 2,441 females in the reproductive age (15 to 49 years old) were further analyzed. CMV IgG positivity was 97% (2,467/2,441) and the average seropositivity in each age group (every 5 years; 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, and 45–49) was 83.8%, 97.6%, 97.2%, 97.2%, 98.6%, 99.5%, and 99.5%, respectively (**Fig. 2A**). Although there was lower seropositivity in period 2 (79.8%) compared to that of period 1 (93.9%), in the 15–19 year old age group, this result was not statistically significant ( $P=0.258$ ) (**Fig. 2A**).

Comparison of CMV seropositivity between women of reproductive age and men in the same age group is shown in **Fig. 2B**. CMV seropositivity in women in the 20–24-year age group was higher than that of men in the same age group (97.6% vs. 85.6%, OR, 6.78; 95% CI, 1.59–28.97;  $P=0.003$ ).

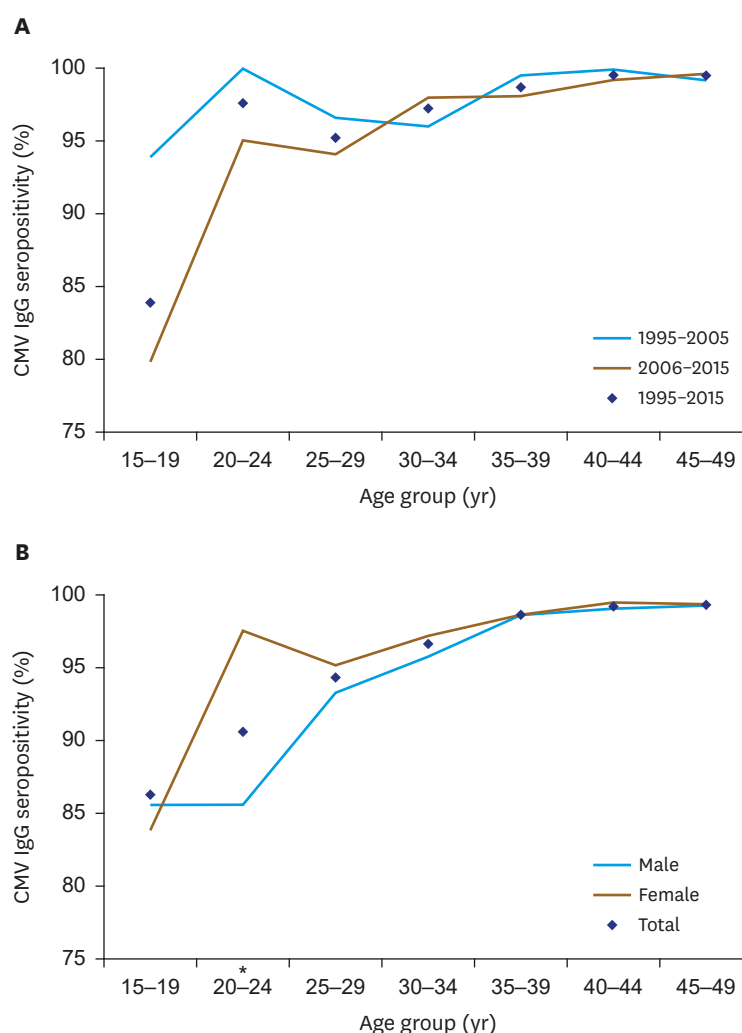
The overall CMV IgG positivity in the first child bearing age group (25–30 years of age)<sup>18)</sup> was 96.1%. There was no difference in seropositivity between period 1 (97%, 192/198) and period 2 (95.4%, 272/285) ( $P=0.482$ ).

#### 5. CMV seropositivity by region

Among 10,900 patients who were CMV IgG positive, 89.2% (9,718/10,900) had residential region identified by medical records (**Fig. 3**). The CMV seropositivity of all regions was over 90% in all metropolitan cities and provinces with no statistical significance.

## DISCUSSION

This is the first study in Korea that examined CMV seropositivity in all ages. This study showed that CMV seroprevalence was 94.1% among Koreans in all population and 97% among reproductive women during 21-year period. There was no significant difference in overall CMV seropositivity between the period 1 and period 2. However, of interest, decrease of the CMV seropositivity in 11–20 year group was observed in the period 2 when compared to that of period 1.

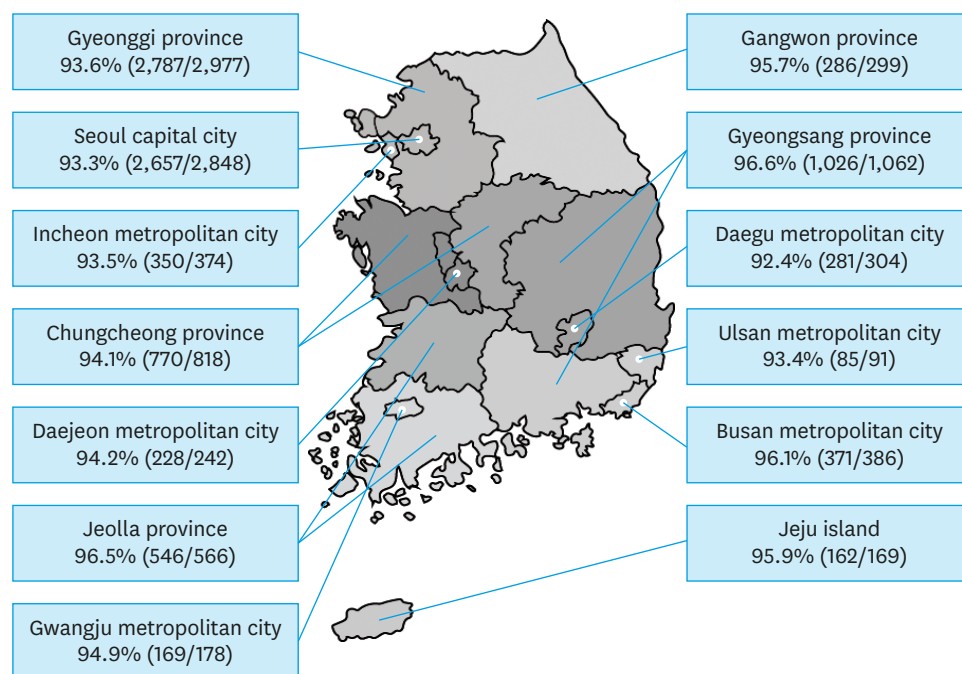


**Fig. 2.** Analysis of CMV IgG seropositivity by age and year period. (A) CMV IgG seropositivity of women in the reproductive age group by period. (B) Difference in CMV seropositivity of women in the reproductive age group, compared to men in the same age group.

\*Age group with statistical significance between men and women.

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G.

CMV seroprevalence is an important epidemiology data that should be considered when estimating the risk of congenital CMV infection in newborns.<sup>3,7,19,20</sup> In addition, assessing CMV seroprevalence of women in the reproductive age group is also important to understand the mechanism of CMV infection during pregnancy (primary infection vs. reinfection/reactivation) in each community. CMV IgG seropositivity is highly influenced by socioeconomic status and lifestyle. There were several studies on seroprevalence of Koreans in various age groups over the past decades (**Supplementary Table 1**) which still showed high CMV seropositivity. However, improvement in hygiene and socioeconomic status of Korea over the past several decades led the authors to generate a hypothesis on potential changes in CMV IgG seropositivity. We also hypothesized that the changes in CMV seropositivity could be different in various age groups if it occurs. Therefore, we reviewed CMV seropositivity data in all ages which was not performed in previous Korean studies. Although, overall CMV IgG seropositivity in Koreans was maintained at 94% from 1995 to 2015, there was clear evidence that individuals in the 11–20-year-old age group in period 2 had significantly lower CMV



**Fig. 3.** CMV IgG seropositivity by region of South Korea. No statistical significance shown in regions. Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G.

seropositivity compared to that in period 1. This group was the only age group that showed significant decrease in CMV seropositivity among the two periods.

CMV IgG positivity in young children is low in Western countries; and has been reported as 20.7% in the United States,<sup>2)</sup> and 27.4% in Germany.<sup>21)</sup> However, in Korea, primary CMV infection typically occurs around 12 months of age, according to the study in 1996.<sup>15)</sup> A 3-year seroprevalence study revealed that 92.9% of patients up to 3 months old demonstrated CMV IgG positivity, which declined to 20% in 7 to 9-month-olds, and increased again to 83.9% at 24 months. In another study by Seo et al.,<sup>14)</sup> 217 patients younger than 60 months of age had 84% CMV IgG positivity (182/217). In our study, the seropositivity was also around 82% in the 0–10-year age group. Our data show that significant CMV infection still occurs in children 0–10 year age group but additional infection in 11–20 year age group seems stunned in period 2.

Several studies in other countries have examined differences in CMV seroprevalence among the reproductive age groups (**Table 2**). The studies in Japan, Spain, and Germany<sup>4,16,17,22)</sup> reported decreased CMV seropositivity in recent years. Unlike those countries, no statistically significant difference between the two periods was observed in our study (**Fig. 2A**); overall CMV seropositivity was 97% in reproductive women and 96% in the first childbearing age group during the 21-year period. Such a high female CMV seropositivity in reproductive age implies that the Korean congenital CMV infection would be mostly caused by re-infection or re-activation rather than by primary infection. Of note, although not significant, CMV seropositivity of 15–19-years old age group among reproductive women was 79.8% in period 2 and 93.9% in period 1. Additional longer duration follow-up in future years is needed to see if there is any significant drop in CMV seropositivity in this population.



**Table 2.** Changes in CMV IgG seroprevalence in other countries

Country	Study period	Size (n)	Age/study group	Average seropositivity (%)
Germany <sup>4)</sup>	1996–2010	40,324	Pregnant women	1996–2000: 44.3
				2001–2005: 42.8
				2006–2010: 40.9
Japan <sup>22)</sup>	2003–2012	15,616	Pregnant women	2003: 69.9 2012: 65.2
Thailand <sup>8)</sup>	1984	966	Children	59.0
	1989	927		46.0
Japan <sup>17)</sup>	2001–2002	378	Umbilical cord	75.7
	2013	561		67.2
Spain <sup>16)</sup>	1993	312	Women	6–10 yr: 56.7 31–40 yr: 90.3
				6–10 yr: 43.7 31–40 yr: 79.1
	1999	288		

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; n, number of study size.

There are some limitations to this study. First, CMV seropositivity of infants reflects IgG transmission from their mother through the placenta at birth, which may result in inaccurate overall average positivity. Second, this was a single-center study, which has limitations for interpreting the results of overall seroprevalence in the Korean population. However, we analyzed the values from over 11,000 individuals of seven metropolitan cities and six provinces, which we consider representative of national data. In addition, unlike previous studies which only investigated CMV seroprevalence data from certain age groups, we included all individuals from 0 year to adults older than 60 years.

In conclusion, this study was the first report to investigate CMV seroprevalence in Korea of all ages and the overall CMV IgG seropositivity was estimated to be 94%. Consistent monitoring of changes in seroprevalence, including those of reproductive age, is essential for further studies of congenital CMV infection among pregnant women.

## SUPPLEMENTARY MATERIAL

### Supplementary Table 1

Summary of CMV seroprevalence studies in Korea

[Click here to view](#)

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## 요약

**목적:** 거대세포바이러스(Cytomegalovirus [CMV])는 정상 면역을 가진 사람에서는 대부분 불현성 감염이지만, 면역저하자 또는 태아의 선천 감염의 경우 위중한 합병증을 유발한다. 본 연구는 21년 동안의 시기 및 연령에 따른 CMV 항체 양성률을 조사하였다.

**방법:** 1995년 1월부터 2015년 12월까지 성균관대학교 의과대학, 삼성서울병원에서 CMV immunoglobulin G (IgG) 검사를 시행한 환자를 대상으로 하였다. 검사 결과는 성별, 연령별, 전국 지역별로 분석하였고, 두 시기에 따른 (1995–2005년; 1기, 2006–2015년; 2기) 항체 양성률의 변화를 분석하였다.

**결과:** 총 11,584명의 환자 중 CMV IgG 양성결과를 보인 총 환자는 10,900명 (94.1%)이었다. 전체 환자에서 두 시기에 따른 CMV 양성률의 차이는 없었다 (94.2% vs. 94.1%) ( $P=0.86$ ). 10년 간격으로 비교를 했을 때 다른 연령군은 유의하지 않았으나 11–20세의 연령군의 CMV 양성률은 1기에 비해 2기에 더 낮았다 ( $P<0.001$ ). 이 연령에 따른 항체 양성률 분석에서 31–40세 연령군의 항체 양성률 (97.4%)은 이보다 어린 연령군에 비하여 유의하게 높았으며 ( $P<0.001$ , odds ratio [OR]<1), 더 높은 연령군에 비하여 유의하게 낮았다 ( $P<0.001$ , OR>1). 가임기 여성은 총 2,441명이었으며 (15–49세) 이 중 CMV IgG 양성률은 2,367 (97%)명이었다. 해당 연령군의 시기별 항체 양성률의 유의한 차이는 없었다. 가임기 여성 중 20–24세의 연령군은 해당 연령의 남자에 비하여 유의한 높은 항체 양성률을 보였다 (97.6% vs. 85.6%, OR, 6.78; 95% CI, 1.585–28.968;  $P=0.0028$ ). 지역별 항체 양성률의 큰 차이는 보이지 않았다.

**결론:** 본 논문은 한국인의 전 연령의 CMV 항체 양성률 변화에 대한 조사를 시행한 최초 논문이며 전체적으로 약 94%의 높은 CMV 항체 양성률과 가임기 여성은 97%의 항체 양성률을 보이는 것으로 관찰되었다. 향후, 가임기 여성을 포함한 한국인의 CMV 항체 양성률의 변화 추세에 대한 모니터링과 국내 임신부에서의 CMV 감염에 대한 연구가 필요할 것으로 사료된다.