

Predictors of CMV Infection in CMV-Seropositive Kidney Transplant Recipients: Impact of Pretransplant CMV-Specific Humoral Immunity

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Background. Although cytomegalovirus (CMV)-seropositive solid organ transplant recipients have a relatively lower risk of CMV infection than CMV-seronegative recipients who receive allograft from CMV-seropositive donors, some patients remain at risk of CMV infection after transplant. We investigated the pretransplant CMV-specific humoral immunity (CHI) and other CMV infection predictors in CMV-seropositive kidney transplant (KT) recipients.

Methods. This retrospective study was conducted on adult CMV-seropositive KT recipients during 2017 and 2018. The cumulative incidence of CMV infection was estimated using the Kaplan-Meier method. CHI, measured with an enzyme-linked fluorescent immunoassay and other predictors for CMV infection, was analyzed using Cox proportional hazards models.

Results. Of the 340 CMV-seropositive KT recipients (37% female; mean \pm SD age, 43 \pm 11 years), 69% received deceased-donor allograft and 64% received induction therapy. During a mean follow-up of 14 months, the cumulative incidence of CMV infection was 14.8%. In multivariate analysis, low pretransplant CHI (defined as anti-CMV immunoglobulin [IgG] titer <20 AU/mL) was significantly associated with CMV infection (hazard ratio [HR], 2.98; 95% CI, 1.31–6.77; $P = .009$). Other significant predictors of CMV infection included older donor age (HR, 1.03; 95% CI, 1.01–1.06; $P = .005$), antithymocyte induction therapy (HR, 2.90; 95% CI, 1.09–7.74; $P = .033$), and prolonged cold ischemic time (HR, 1.06; 95% CI, 1.02–1.10; $P = .002$).

Conclusions. A low pretransplant CHI is independently associated with post-transplant CMV infection in CMV-seropositive KT recipients. A quantitative anti-CMV IgG assay could potentially stratify CMV-seropositive patients at risk of CMV infection after KT.

Keywords. anti-CMV immunoglobulin G titer; CMV infection; humoral immunity; kidney transplantation; viral-specific immunity.

Kidney transplantation (KT) is a well-established strategy to improve the quality of life and survival of patients with end-stage renal disease [1]. However, these patients are at increased risk of infectious complications due to an immunocompromised state acquired from immunosuppressive therapy. Among the many pathogens that commonly infect KT recipients, cytomegalovirus (CMV) is a leading cause of substantial morbidity [2, 3]. Previous retrospective studies

conducted among CMV-seropositive KT recipients revealed a prevalence rate of CMV infection ranging from 4% to 25% [4, 5]. CMV infection was found to be associated with kidney allograft failure after adjusting for other risk factors. Thus, to reduce allograft failure and CMV-associated morbidity, it is critical to take steps before organ transplantation to prevent the occurrence of CMV infection. Pretransplant qualitative CMV-specific humoral immunity (CHI), defined by anti-CMV immunoglobulin G (IgG), is universally recommended to stratify the risk of infection after transplant [2]. Although CMV-seropositive KT recipients are considered to have a relatively lower risk of post-transplant CMV infection than those with CMV seronegativity, a subgroup of these patients remains at risk of CMV infection after transplant [6]. The independent risk factors identified in the aforementioned cohort study are older donor age and the occurrence of acute cellular rejection, especially those requiring antithymocyte globulin therapy [4, 5]. Lately, immunological factors have been investigated as markers to predict post-transplant CMV infection. Candidate markers have included components of

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both nonspecific and viral-specific immunity [7]. To date, the research and associated clinical studies on CMV-specific cellular immunity (CMI) have mostly focused on its potential role to guide management in solid organ transplant (SOT) recipients [8]. However, the financial incompatibility of utilizing these tests in a resource-limited setting remains a barrier to their implementation [9]. Instead, the anti-CMV immunoglobulin G (IgG) titer has been reported to have a potential role in predicting CMV infection among CMV-seropositive liver transplant recipients, especially those with severe CMV infection [10, 11]. The guidelines for prophylaxis and treatment of CMV infection in SOT recipients recommended by the Study Group on Infection in Transplantation (GESITRA) of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) suggest that pretransplant CMI may be used together with CHI to better stratify the risk of CMV infection after transplantation in CMV-seropositive liver transplant recipients [12]. A previous study of CMV-seropositive heart transplant recipients reported a low pretransplant anti-CMV IgG titer associated with the risk of CMV infection after transplantation [13]. However, the possibility of a similar association in CMV-seropositive KT recipients has not been explored. Therefore, we aimed to assess the association between the anti-CMV IgG titer and the risk of post-transplant CMV infection among CMV-seropositive KT recipients.

METHODS

We conducted a retrospective study of all adult (ie, aged ≥ 18 years) KT recipients with CMV seropositivity during 2017–2018 at a single transplant center. Clinical characteristics, risk factors, and outcomes were extracted from patient medical records. The majority of recipients were monitored for CMV infection, and plasma CMV quantitative polymerase chain reaction (qPCR) was measured when clinically indicated. Only those receiving antithymocyte globulin (ATG) for induction therapy or steroid-refractory rejection were provided intravenous ganciclovir or oral valganciclovir for anti-CMV prophylaxis for a total of 3 months or switched to preemptive CMV monitoring by plasma CMV qPCR if clinically indicated (if they could not complete the course of therapy). Trimethoprim/sulfamethoxazole (1 year) for *Pneumocystis jirovecii* prophylaxis, acyclovir (6 months) for herpes simplex virus prophylaxis, and isoniazid (9 months) for latent tuberculous infection therapy were prescribed to all KT recipients.

CMV-Specific Humoral Immunity

CMV-specific humoral immunity was assessed by anti-CMV IgG titer. Pretransplant anti-CMV IgG antibody titers were measured with a semiquantitative enzyme-linked fluorescent immunoassay performed on the VIDAS (bioMérieux, Durham,

NC, USA), reported as numeric values, and interpreted as follows: negative (<4 arbitrary units [AU]/mL), equivocal (4–5 AU/mL), or positive (≥ 6 AU/mL). Low CHI and high CHI were defined as anti-CMV IgG titer <20 AU/mL and ≥ 20 AU/mL, respectively.

CMV Infection

CMV infection was defined as the presence of CMV DNA in plasma regardless of symptoms. Plasma CMV DNA load was measured via quantitative real-time polymerase chain reaction performed on a Roche COBAS AmpliPrep/COBAS Taqman (Branchburg, NJ, USA). The DNA load was reported in IU/mL. The lower limit of quantification was <137 IU/mL. All patients with CMV infection were classified as follows: asymptomatic CMV infection (CMV infection without signs and symptoms) or CMV disease (CMV infection accompanied by compatible clinical signs and symptoms). CMV disease was further categorized as CMV syndrome (eg, fever and/or malaise, leukopenia, or thrombocytopenia) or tissue-invasive CMV disease (eg, gastrointestinal disease, pneumonitis, and hepatitis) [2].

Statistical Analyses

The cumulative incidence of CMV infection after transplant was estimated using the Kaplan-Meier method. Descriptive analysis was used for reporting baseline characteristics. Continuous variables were summarized as the mean and SD and compared by the Student *t* test or Mann-Whitney *U* test. Categorical variables were summarized as frequencies and percentages and were compared by the χ^2 test or Fisher exact test. Multivariate Cox proportional hazards models were used to analyze for independent predictors of CMV infection including anti-CMV IgG titer by cutoff value. *P* values $<.05$ were considered significant. Statistical analyses were performed with Stata statistical software, version 15 (StataCorp, LLC, College Station, TX, USA). A dot plot of pretransplant anti-CMV IgG titer distributions between KT recipients with and without CMV infection was performed with GraphPad Prism 6.0 (GraphPad Software, Inc, San Diego, CA, USA).

RESULTS

Patient Population

The medical records of a total of 362 KT patients whose surgeries occurred during 2017–2018 were retrieved; 22 of these patients were excluded from our analysis because they were younger than 18 years old (17 patients) or were CMV seronegative (5 patients) (Figure 1). Our study included 340 CMV-seropositive KT recipients, 37% of whom were female. Their mean \pm SD age was 43 ± 11 years. Among these, 69% received deceased-donor allograft, and 64% received induction therapy. Pretransplant anti-CMV IgG titer distributions in KT recipients with and without CMV infection are shown in Figure 2.

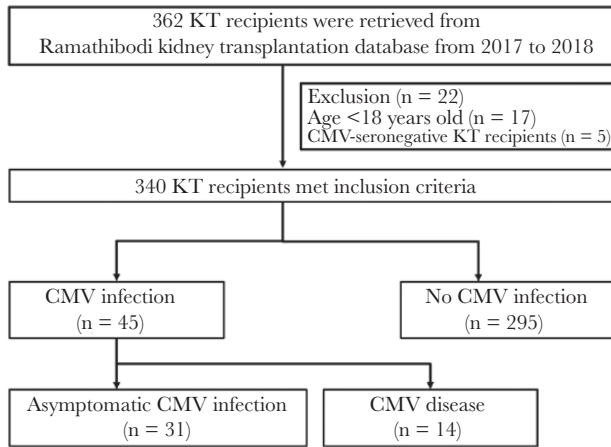


Figure 1. Study flowchart. Abbreviations: CMV, cytomegalovirus; KT, kidney transplant.

There were 7.1% patients classified as having low pretransplant CHI, while the remaining 92.9% had high pretransplant CHI. The baseline characteristics of the 340 patients (45 of whom developed post-transplant CMV infection) are compared in Table 1. Recipient age, sex, body mass index (BMI), and surgical time were not significantly different between patients with or without post-transplant CMV infection. The following variables were statistically different between KT recipients with or without post-transplant CMV infection: mean \pm SD donor age (45 ± 12 vs 39 ± 14 years, respectively), receipt of an allograft from a deceased donor ($41/45$ [91.1%] vs $191/295$ [64.7%], respectively), and mean \pm SD cold ischemic time (16.41 ± 5.95 hours vs 11.38 ± 8.86 hours, respectively). Additionally, a low pretransplant CHI was significantly associated with post-transplant CMV infection: $7/45$ (15.6%) vs $17/295$ (5.8%).

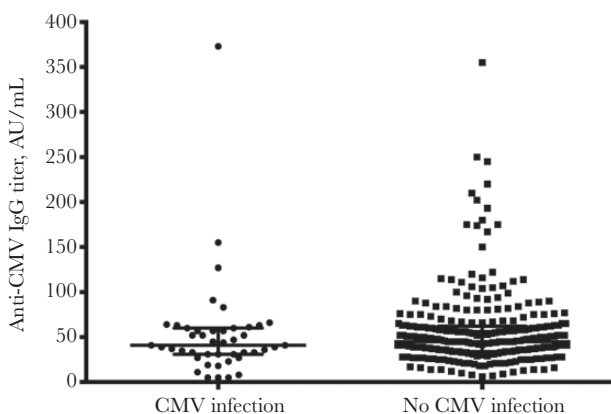


Figure 2. Anti-CMV IgG titer distributions between kidney transplant recipients with and without CMV infection. Abbreviations: AU, arbitrary units; CMV, cytomegalovirus; IgG, immunoglobulin G.

CMV Infection

During a mean follow-up of 14 months, the cumulative incidence of CMV infection was 14.8%. Of the KT recipients with post-transplant CMV, 31 (69%) had asymptomatic CMV infection and 14 (31%) had tissue-invasive disease, including gastrointestinal disease (15.5%) and pneumonia (15.5%). The time to CMV infection stratified by CHI up to 1 year after transplant is presented in Figure 3 by a Kaplan-Meier curve.

Risk Factors of CMV Infection

The variables potentially related to CMV infection are described in Table 2. In our univariate analysis, a low pretransplant CHI was significantly associated with post-transplant CMV infection (HR, 2.70; 95% CI, 1.21–6.05; $P = .02$). Other significant risk factors of post-transplant CMV infection included older donor age per 1-year increase (HR, 1.03; 95% CI, 1.01–1.06; $P = .008$), deceased donor (HR, 5.17; 95% CI, 1.85–14.45; $P = .002$), prolonged cold ischemic time per 1-hour increase (HR, 1.07; 95% CI, 1.03–1.12; $P = .001$), pretransplant double filtration plasmapheresis (DFPP; HR, 5.30; 95% CI, 1.28–21.91; $P = .021$), antithymocyte globulin (ATG) induction therapy (HR, 3.08; 95% CI, 1.20–7.95; $P = .020$), and cyclosporin A maintenance therapy (HR, 1.84; 95% CI, 1.00–3.40; $P = .049$).

In multivariate analysis, a pretransplant CHI remained significantly associated with post-transplant CMV infection (HR, 2.98; 95% CI, 1.31–6.77; $P = .009$). Other significant risk factors of post-transplant CMV infection included older donor age per 1-year increase (HR, 1.03; 95% CI, 1.0–1.06; $P = .005$), ATG induction therapy (HR, 2.90; 95% CI, 1.09–7.74; $P = .033$), and prolonged cold ischemic time per 1-hour increase (HR, 1.06; 95% CI, 1.02–1.10; $P = .002$).

OUTCOME

The outcomes of KT recipients with and without CMV infection were compared (Table 3). All the patients without a post-transplant CMV infection survived. The numbers of patients with graft loss were 6 (13.3%) and 5 (1.7%) in the CMV infection and non-CMV infection groups, respectively ($P = .001$).

DISCUSSION

Here, we report the first study investigating a potential role for quantitative measurement of CHI as a predictor of post-transplant CMV infection in CMV-seropositive KT recipients. We observed that a lower pretransplant anti-CMV IgG titer is associated with an increased risk of post-transplant CMV infection among CMV-seropositive KT recipients. This association remained significant after adjustments for other variables. We further identified other independent risk factors for post-transplant CMV infection, such as older donor age, prolonged cold ischemic time, and use of ATG for induction therapy.

Table 1. Baseline Characteristics of Kidney Transplant Recipients With and Without Post-transplant CMV Infection

Baseline Characteristics, No. (%)	CMV Infection (n = 45)	No CMV Infection (n = 295)	P Value
Recipient variables			
Age, mean ± SD, y	44 ± 10	43 ± 11	.794
Sex			
Male	27 (60)	189 (64.1)	.597
Female	18 (40)	106 (35.9)	
BMI, mean ± SD, kg/m ²	23.18 ± 3.92	22.66 ± 3.93	.412
Pretransplant anti-CMV IgG titer			
Low (<20 AU/mL)	7 (15.6)	17 (5.8)	.027
High (≥20 AU/mL)	38 (84.4)	278 (94.2)	
Donor variables			
Age, mean (SD), y	45 ± 12	39 ± 14	.005
Donor status			
Living donor	4 (8.9)	104 (35.3)	<.001
Deceased donor	41 (91.1)	191 (64.7)	
Transplant variables			
Cold ischemic time, mean ± SD, h	16.41 ± 5.95	11.38 ± 8.86	<.001
Surgical time, mean ± SD, h	5.03 ± 1.80	4.68 ± 1.29	.215
No. of KTs			
First KT	45 (100)	290 (98.3)	>.999
Second KT	0 (0)	5 (1.7)	
HLA mismatch			
≥3	16 (35.6)	111 (37.6)	.789
PRA			
≥51	5 (11.1)	24 (8.1)	.564
Pretransplant DFPP	2 (4.4)	2 (0.7)	.086
Pretransplant IVIG	1 (2.2)	2 (0.7)	.348
Induction therapy			
No	15 (33.4)	107 (36.3)	.052
ATG	6 (13.3)	13 (4.4)	
Anti-IL2 receptor antagonist	24 (53.3)	175 (59.3)	
Post-transplant variables			
Maintenance therapy			
Prednisolone	45 (100)	295 (100)	>.999
Tacrolimus	29 (64.4)	230 (78)	.047
Cyclosporin A	16 (35.6)	64 (21.7)	.041
Mycophenolate mofetil	38 (84.4)	243 (82.4)	.732
Mycophenolate sodium	7 (15.6)	50 (16.9)	.816
Reoperation	0 (0)	11 (3.7)	.371

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ATG, antithymocyte globulin; AU, arbitrary unit; BMI, body mass index; CMV, cytomegalovirus; DFPP, double-filtration plasmapheresis; HLA, human leukocyte antigen; IgG, immunoglobulin G; IL, interleukin; IVIG, intravenous immunoglobulin; KT, kidney transplant; PRA, panel reactive antibody.

Global nonspecific and CMV-specific immunity is essential in controlling viral replication. Lack of either global innate or CMV-specific adaptive immunity has been described as a poor prognostic factor for CMV reactivation after SOT [14]. The restoration of viral-specific cell-mediated immunity is associated with viral clearance, and, conversely, the failure of this immunity is associated with uncontrolled infection by viruses such as adenovirus, BK polyomavirus, and CMV [8, 15, 16]. However, the measurement of viral-specific cell-mediated immunity is not universally available, and its

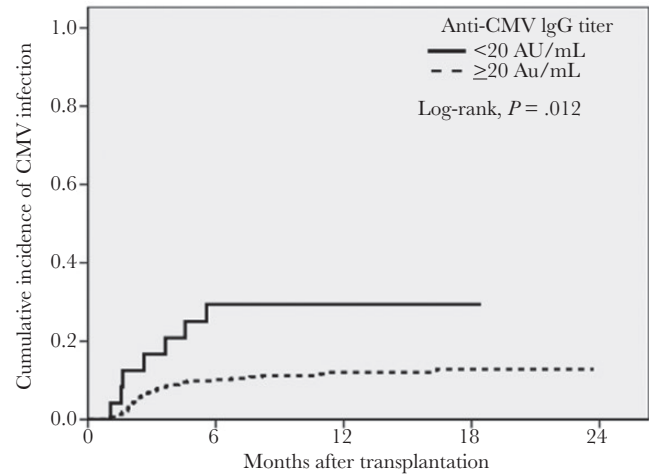


Figure 3. Kaplan-Meier plot for cumulative incidence of CMV infection after kidney transplantation. Abbreviations: AU, arbitrary units; CMV, cytomegalovirus; IgG, immunoglobulin G.

accessibility is low compared with the measurement of anti-CMV IgG titer. Previous studies have indicated that measuring the anti-CMV IgG titer has promise as a predictive tool for post-transplant CMV infection in liver and heart transplant recipients [10, 11, 17]. This universally available and relatively affordable test could be used as a simple tool to better classify those at risk of infection among CMV-seropositive SOT recipients. We confirmed this association in CMV-seropositive KT recipients. It is hypothesized that the low IgG titer may reflect weaker pretransplant immunity, which could then be aggravated by pharmacologic immunosuppression, thereby leading to a higher post-transplant CMV risk. A lower pretransplant non-CMV (BK) virus IgG titer is also affirmed to be associated with early BK viremia in pediatric KT recipients, especially in those paired with high BK virus IgG titer in donors [18]. Additionally, a pretransplant BK virus antibody level was significantly higher in KT recipients who did not develop BK viremia than those who developed BK viremia [19].

In addition to extending the association of CMV infection and antibody titers in KT recipients, our study also confirmed several identified risk factors of post-transplant CMV infection among CMV-seropositive KT recipients. Older donor age, prolonged cold ischemic time, and use of ATG for induction therapy were also described as independent risk factors in 2 retrospective studies conducted in transplant centers with a high prevalence of CMV seropositivity [4, 5].

Due to the nature of retrospective studies, some data may be affected by recall bias. Furthermore, the lack of a standardized protocol for preemptive monitoring of CMV in our center may have underestimated the true prevalence of CMV infection, especially in patients without symptoms. Additionally,

Table 2. Univariate and Multivariate Analysis Cox Proportional Hazard Models for Risk Factors of Post-transplant CMV Infection

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	PValue	HR (95% CI)	PValue
Recipient age (per year)	1.00 (0.98–1.03)	.798		
Male	0.85 (0.47–1.53)	.580		
BMI (per unit), kg/m ²	1.03 (0.96–1.10)	.401		
Low pretransplant CMV-specific humoral immunity (anti-CMV IgG titer <20 AU/mL)	2.70 (1.21–6.05)	.016	2.98 (1.31–6.77)	.009
Donor age (per year)	1.03 (1.01–1.06)	.008	1.03 (1.01–1.06)	.005
Deceased donor	5.17 (1.85–14.45)	.002		
Cold ischemic time (per hour)	1.07 (1.03–1.12)	.001	1.06 (1.02–1.10)	.002
Surgical time (per hour)	1.14 (0.97–1.33)	.104		
Second KT	0.05 (<0.001–1734)	.572		
HLA mismatch of ≥3	0.92 (0.50–1.70)	.800		
PRA of ≥51 %	1.40 (0.55–3.54)	.482		
Pretransplant DFPP	5.30 (1.28–21.91)	.021		
Pretransplant IVIG	3.48 (0.48–25.27)	.218		
Induction therapy				
ATG	3.08 (1.20–7.95)	.020	2.90 (1.09–7.74)	.033
Anti-IL-2 receptor antagonist	0.99 (0.52–1.88)	.970		
Maintenance therapy				
Tacrolimus	0.55 (0.30–1.02)	.056		
Cyclosporin A	1.84 (1.00–3.40)	.049		
Mycophenolate mofetil	1.45 (0.51–2.56)	.742		
Reoperation	0.47 (<0.001–65.39)	.408		

Abbreviations: ATG, antithymocyte globulin; AU, arbitrary unit; BMI, body mass index; CMV, cytomegalovirus; DFPP, double-filtration plasmapheresis; HLA, human leukocyte antigen; IgG, immunoglobulin G; IL, interleukin; IVIG, intravenous immunoglobulin; KT, kidney transplant; PRA, panel reactive antibody.

there is a lack of standardization among semiquantitative and quantitative CMV serologic assays. This precludes accurate direct comparison because of inter- and sometimes intralaboratory test variations in cutoffs. While our study was conducted using a single CMV serologic assay with a single cutoff value, which offered a standardized assessment in our study, we suggest caution in comparing studies using different assays. We also encourage further studies using more standardized serologic tests to better generalize this potential predictor in clinical practice.

In summary, a low level of pretransplant CHI is independently associated with post-transplant CMV infection in CMV-seropositive KT recipients. The universally available test for anti-CMV IgG titer could potentially stratify individuals at risk and target them to receive a more specific preventive strategy.

Table 3. Outcome of Kidney Transplant Recipients With and Without Post-transplant CMV Infection

Outcome	CMV Infection (n = 45), No. (%)	Non-CMV Infection (n = 295), No. (%)	P Value
Mortality	3 (6.7)	0 (0)	.002
Graft failure	6 (13.3)	5 (1.7)	.001

Abbreviation: CMV, cytomegalovirus.

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Patient consent. The patient's written consent was obtained. The study protocol was reviewed and approved by the Institutional Review Board of the Faculty of Medicine at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (approval number: ID 06-61-34).

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