Associations of high anti-CMV IgG titer with renal function decline and allograft rejection in kidney transplant patients

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Abstract

Background: An anti-cytomegalovirus (CMV) immunoglobulin G (IgG) antibody is produced after primary CMV infection and generally persists after the primary infection. However, it is not well-known about the relationship between anti-CMV IgG titer and outcomes in kidney transplant recipients. We, therefore, aimed to explore the role of anti-CMV IgG titer on the risks of CMV disease development, allograft rejection, renal function decline, and mortality.

Methods: In a hospital-based study, we identified 179 CMV-seropositive kidney transplant recipients between January 2013 and December 2017. These patients were divided into low and high anti-CMV IgG titer groups, respectively. The cutoff level of anti-CMV IgG titer was determined by receiver operating characteristic curve analysis. The outcomes evaluated included CMV disease, decrease of ≥15% in estimated glomerular filtration rate (eGFR), biopsy-proven allograft rejection, and all-cause mortality.

Results: The high anti-CMV IgG titer group (≥846.2 AU/mL) exhibited a higher risk of CMV disease (adjusted hazard ratio [aHR], 3.77; 95% CI, 1.47–9.68; $p = 0.006$), eGFR decline ≥15% (aHR, 2.00; 95% CI, 1.19–3.35; $p = 0.009$), and renal allograft rejection (aHR, 2.95; 95% CI, 1.11–7.87; $p = 0.030$) than the low titer group (<846.2 AU/mL).

Conclusion: In kidney transplant recipients, a high anti-CMV IgG titer was associated with higher risks for developing CMV disease, undergoing allograft rejection, and eGFR decline.

Keywords: Allografts; Biopsy; Cytomegalovirus; Kidney; ROC curve

1. INTRODUCTION

For patients with end-stage kidney disease who underwent maintenance dialysis, kidney transplantation is the treatment of choice, and it is associated with prolonged survival and improved quality of life.[1] However, kidney transplant recipients are more susceptible to opportunistic pathogens compared with the general population since a complex immunosuppressive regimen is needed to maintain the transplant. Consequently, high-risk transplant recipients need to be closely monitored and/or receive antimicrobial prophylaxis.

Cytomegalovirus (CMV) is one of the most common viral pathogens that affect kidney transplant recipients. Prior to effective CMV prevention, approximately 60% of kidney transplant recipients developed an active infection.[2,3] CMV infection has been associated with an increased risk of renal allograft rejection, graft loss, and mortality.[4–6] Therefore, early identification of CMV infection and administration of appropriate CMV therapy in kidney transplant recipients at risk for CMV infection are important. Currently, a diagnosis of CMV infection is dependent on a positive CMV antigenemia test or a positive quantitative polymerase chain reaction (PCR) assay for CMV DNA. However, these testing materials are expensive and are often only checked when a CMV infection is clinically suspected. In addition, negative PCR detection of CMV DNA has been reported in a patient with documented CMV disease.[7]

Approximately 6 to 8 weeks after a primary CMV infection develops, an anti-CMV immunoglobulin G (IgG) antibody can be detected in blood.[8] Moreover, production of this antibody usually persists indefinitely after the primary infection event. In the clinic, detection of this antibody is used to determine the serological status of both kidney transplant donors and recipients. It has been observed that kidney transplantation between a positive donor and a negative recipient (CMV D+/R−) is

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associated with the highest risk of developing CMV disease.[9] Therefore, consensus guidelines recommended a 3- to 6-month CMV prophylaxis with oral valganciclovir for CMV D+/R– and CMV R+ patients.[10]

It has been observed that titers of anti-CMV IgG usually correlated with the CD4+ T lymphocyte response to CMV.[11] In elderly patients with a high titer of anti-CMV IgG, a higher risk of mortality has been observed.[12] Therefore, it has been suggested that anti-CMV IgG titer levels may represent a marker of chronic inflammation and viral reactivation, thereby leading to higher risks of arterial atherosclerosis and postcoronary angioplasty restenosis.[13–15] In addition, levels of circulating anti-CMV IgG may predict risk of atrial fibrillation recurrence after catheter ablation.[16] In kidney transplant recipients, a positive correlation between CMV reactivation and anti-CMV IgG titers has also been reported.[15]

To date, an association between anti-CMV IgG titer and allograft outcome has not been investigated. Therefore, to the best of our knowledge, this is the first study to examine the role of anti-CMV IgG titer in relation to risks of graft rejection, renal function decline, and mortality. In addition, quantitative CMV PCR was assessed in our analysis as a time-dependent covariate.

2. METHODS

2.1. Study design

We conducted a hospital-based cohort study using medical records in a tertiary medical center. A total of 179 CMV-seropositive kidney transplant recipients aged 20 years or older were identified at the Taipei Veterans General Hospital between January 1, 2013, and December 31, 2017. Index day was defined as the first date when an anti-CMV IgG titer was recorded. Patients who received anti-CMV therapy within 30 days before their index day were excluded. All participants were divided into high and low anti-CMV IgG titer groups, respectively. The study was approved by the institution's review board (2017-09-002BC).

2.2. CMV disease

CMV disease was defined based on the detection of CMV DNA or viral isolation in clinical specimens concomitant with attributable symptoms or signs. Symptoms and signs included fever, malaise, leukopenia, neutropenia, atypical lymphocytosis, thrombocytopenia, or tissue invasive disease such as retinitis, hepatitis, or pneumonitis. Leukopenia was defined based on a leukocyte count of <4000/μL in peripheral blood. Thrombocytopenia was defined based on a platelet count <100 000/uL. Kidney transplant recipients who had a CMV infection were treated with ganciclovir intravenously, followed by oral administration of valganciclovir.

2.3. CMV prevention and detection strategies

Universal prophylaxis with valganciclovir or valacyclovir was given for all recipients in the early posttransplant period for 6 months. All recipients underwent serologic testing with anti-CMV IgG and IgM before transplant, and additional testing was performed among recipients who present with signs or symptoms of suspected CMV disease, such as fever, malaise, leukopenia, colitis, or pneumonitis after transplant.

2.4. Outcomes

The outcomes included developing CMV disease, an estimated GFR (eGFR) decline of ≥15%, biopsy-proven allograft rejection, and all-cause mortality. All cases of renal allograft rejection were diagnosed by renal biopsy, and these were interpreted and reviewed by experienced renal pathologists. Outcomes were defined based on time to first occurrence, censoring for death when it occurred. Percentage change in eGFR ≥15% was identified during the follow-up period and was calculated according to the creatinine equation proposed by investigators in the Chronic Kidney Disease Epidemiology Collaboration (mL/min per 1.73 m^2).[17] Patients were followed until death or until the end of the study period (December 31, 2013), whichever occurred first.

2.5. Statistical analysis

For continuous data, we calculated the mean ± SD for data exhibiting normal distribution. For data that did not follow normal distribution, median and interquartile range (IQR) values were calculated to characterize the study population at baseline. Among the baseline characteristics, Pearson's chi-square tests were used to compare categorical variables, while the independent *t* test and Mann-Whitney *U* test were used to compare parametric and nonparametric continuous variables, respectively. We assessed the anti-CMV IgG titer cutoff levels associated with CMV disease using the receiver operating characteristic (ROC) analysis.

Kaplan-Meier analysis was used to test the effect of anti-CMV IgG titer on CMV disease, renal function decline, and allograft rejection. Statistical significance was estimated by using the log-rank test. For multivariate analyses, a Cox proportional hazard model was used to estimate the effect of anti-CMV IgG titer on risks of CMV disease, eGFR decline, biopsy-proven allograft rejection, and all-cause mortality. In time-dependent analyses, serum level of CMV DNA was considered a time-varying covariate. In subgroup analyses, Cox regression was performed according to age, gender, body mass index, albumin, glucose, hemoglobin, diabetes mellitus, dyslipidemia, use of calcium channel blockers, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and use of β-blockers. Interactions between associations according to likelihood ratio tests were also examined. Data were analyzed with the SAS software (version 9.4; SAS Institute Inc, Cary, NC, USA) and R software (version 3.1.1) for Windows. *p* values <0.05 were considered to indicate statistical significance.

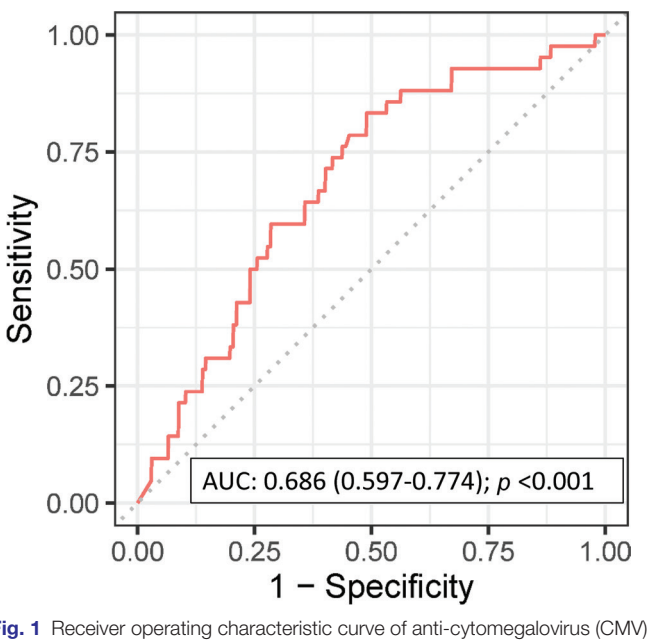

Fig. 1 Receiver operating characteristic curve of anti-cytomegalovirus (CMV) immunoglobulin G (IgG) titer for the prediction of CMV disease. AUC = area under the curve.

3. RESULTS

The ROC curve analysis for anti-CMV IgG titer is shown in Fig. 1. The area under the curve for the prediction of CMV disease was 0.686 ($p < 0.001$) and the cutoff level was <846.2 AU/mL. Among 179 kidney transplant recipients, 121 patients had high anti-CMV IgG titers (≥846.2 AU/mL) and 58 patients had low anti-CMV IgG titers (<846.2 AU/mL). Baseline characteristics of these two groups are listed in Table 1. These baseline characteristics were similar between the high and low anti-CMV IgG titers groups, except that the low anti-CMV IgG titer group had a higher level of serum triglyceride and a lower proportion of use of steroids and mammalian target of rapamycin inhibitors.

During the follow-up period, there were 34 cases of newly diagnosed biopsy-proven rejection. Twenty-nine of these cases were in the high CMV IgG titer group, and 5 of these cases were in the low titer group. Of note, the patients with high anti-CMV IgG titers had a higher proportion of antibody-mediated rejection events compared with those with low anti-CMV IgG titers (58.6% vs 40.0%, respectively). In contrast, those with low CMV IgG titers had a greater proportion of T-cell–mediated rejection events compared with patients with high CMV IgG titers (80% vs 48.3%, respectively). In addition, a higher proportion of microvascular inflammation events was observed in patients with a high CMV IgG titer compared with those with a low CMV IgG titer (64.3% vs 40%, respectively). Detailed pathology characteristics are shown in Fig. 2.

The median duration of follow-up for the entire cohort was 33.3 months (IQR, 22.9–40.6). The results of Kaplan-Meier survival analysis log-rank test for CMV disease, eGFR decline, biopsy-proven allograft rejection, and mortality are shown in Fig. 3. Patients with a high anti-CMV IgG titer exhibited significantly higher risks of CMV disease (log-rank test, $p = 0.001$), ≥15% decrease in eGFR ($p = 0.018$), and allograft rejection ($p = 0.022$) compared with the low anti-CMV IgG titer group during the follow-up period.

In a multivariate Cox regression analysis adjusted for potentially confounding factors, the high anti-CMV IgG titer group exhibited greater risks for CMV disease (adjusted hazard ratio [aHR], 3.77; 95% CI, 1.47–9.68; $p = 0.006$), eGFR decline ≥15% (aHR, 2.00; 95% CI, 1.19–3.35; $p = 0.009$), and renal allograft rejection (aHR, 2.95; 95% CI, 1.11–7.87; $p = 0.030$; Table 2). In contrast, the risk for all-cause mortality did not significantly differ between the two groups. Similar results were obtained after considering CMV DNA levels in serum as detected by PCR as a time-dependent covariate.

Table 1

Baseline demographic data

Characteristics	All patients (n = 179)	Anti-CMV IgG low titer (n = 58)	Anti-CMV IgG high titer (n = 121)	*p*
Demographic				
Age, years	54.8 ± 11.1	54.5 ± 10.7	54.9 ± 11.3	0.840
Male	94 (52.5)	32 (55.2)	62 (51.2)	0.739
BMI, kg/m^2	23.5 ± 4.0	23.8 ± 3.6	23.4 ± 4.1	0.536
SBP, mm Hg	117.3 ± 16.9	116.7 ± 17.2	117.5 ± 16.9	0.774
DBP, mm Hg	70.9 ± 12.3	70.7 ± 12.9	71.0 ± 12.1	0.872
Comorbidities				
Diabetes mellitus	81 (45.3)	24 (41.4)	57 (47.1)	0.575
Hypertension	167 (93.3)	54 (93.1)	113 (93.4)	0.999
Dyslipidemiaa	39 (21.8)	18 (31.0)	21 (17.4)	0.060
Laboratory data				
Albumin, g/dL	3.8 ± 0.5	3.8 ± 0.5	3.9 ± 0.5	0.511
Fasting glucose, mg/dL	123.4 ± 49.8	122.2 ± 41.8	123.9 ± 53.4	0.834
Total cholesterol, mg/dL	178.4 ± 37.1	180.8 ± 41.5	177.2 ± 34.9	0.552
Triglyceride, mg/dL	122.6 ± 68.3	137.3 ± 91.9	115.6 ± 52.4	0.046
LDL cholesterol, mg/dL	110.2 ± 34.4	112.1 ± 38.6	109.2 ± 32.3	0.616
HDL cholesterol, mg/dL	50.0 ± 16.2	47.0 ± 14.0	51.3 ± 17.0	0.137
Ca, mg/dL	9.3 ± 0.8	9.2 ± 0.8	9.3 ± 0.8	0.546
IP, mg/dL	3.0 ± 0.8	3.1 ± 0.8	3.0 ± 0.7	0.229
Hgb, g/dL	12.0 ± 1.9	11.8 ± 1.9	12.0 ± 1.9	0.471
eGFR, mL/min per 1.73 m^2	57.3 ± 22.4	59.3 ± 24.1	56.4 ± 21.7	0.418
Concomitant medications				
α-Blocker	96 (53.6)	27 (46.6)	69 (57.0)	0.248
ACEI/ARB	111 (62.0)	39 (67.2)	72 (59.5)	0.404
β-Blocker	118 (65.9)	38 (65.5)	80 (66.1)	0.999
Calcium channel blocker	138 (77.1)	43 (74.1)	95 (78.5)	0.644
Oral antihypoglycemic drugs	44 (24.6)	13 (22.4)	31 (25.6)	0.779
Insulin	61 (34.1)	18 (31.0)	43 (35.5)	0.670
Immunosuppressants				
Steroids	159 (88.8)	47 (81.0)	112 (92.6)	0.042
CNI	171 (95.5)	53 (91.4)	118 (97.5)	0.140
MMF	17 (95.0)	53 (91.4)	117 (96.7)	0.247
mTOR inhibitors	57 (31.8)	12 (20.7)	45 (37.2)	0.041

Values for categorical variables are given as numbers (percentages); values for continuous variables are given as means ± SD.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; Ca = calcium; CMV = cytomegalovirus; CNI = calcineurin inhibitors; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; Hgb = hemoglobin; IgG = immunoglobulin G; IP = phosphate; LDL = low-density lipoprotein; LDL-C = low density lipoprotein-cholesterol; MMF = mycophenolate mofetil; mTOR = mammalian target of rapamycin; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

aDefinition for dyslipidemia: TC ≥240 mg/dL or LDL-C ≥160 mg/dL or TG ≥200 mg/dL.

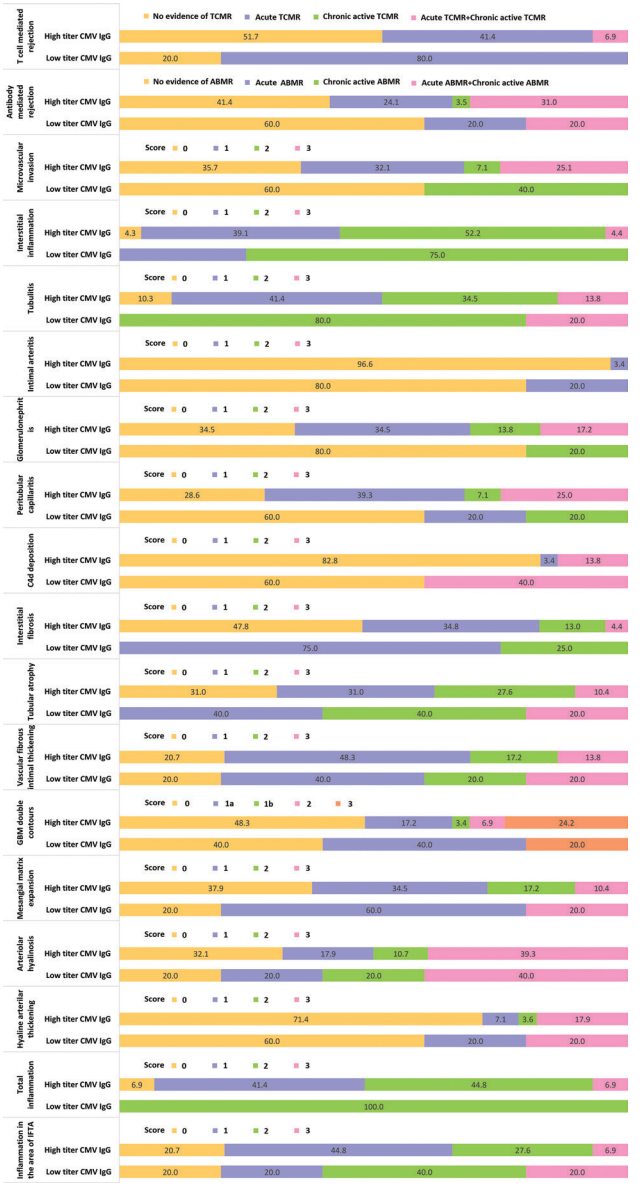

Fig. 2 Characterization of the pathologic results in high anti-cytomegalovirus (CMV) immunoglobulin G (IgG) titer group versus low anti-CMV IgG titer group. ABMR = antibody-mediated rejection; GBM = glomerular basement membrane; IFTA = interstitial fibrosis and tubular atrophy; TCMR = T cell-mediated rejection.

Subgroup analyses showed the results remained consistent between CMV disease, ≥15% decrease in eGFR, and allograft rejection (Supplementary Tables 1–3, http://links.lww.com/JCMA/A121).

4. DISCUSSION

To the best of our knowledge, this is the first study to examine the relationship between the levels of anti-CMV IgG titer and renal allograft outcome in kidney transplant recipients. A retrospective analysis of kidney transplant recipients with high anti-CMV IgG titers showed that this group exhibited higher risks of developing CMV disease, of undergoing allograft rejection, and experiencing renal function decline compared with recipients with low anti-CMV IgG titers.

In a previous study,[18] high anti-CMV IgG titers in serum have been shown to be a marker of long-standing immunological reactions and chronic inflammation. In addition, patients with higher anti-CMV IgG titers had higher levels of tumor necrosis factor, IL (interleukin)-6, and C-reactive protein.[18] A prospective study that enrolled 187 patients and 93 age-matched volunteers also demonstrated that high anti-CMV IgG titer antibody titers (≥1:800) could be an early predictor of atherosclerosis.[14] Intriguingly, in a hospital-based study comprised of 58 kidney transplant recipients, kidney transplant recipients who experienced CMV reactivation had increased levels of CMV-specific antibodies.[15] It implies that high anti-CMV IgG titers may represent a risk marker for CMV reactivation. However, the relationship between anti-CMV IgG titer and future risk of allograft outcome in kidney transplant recipients has not well been investigated.

CMV infection is characterized by a broad spectrum of organ damage, including CMV retinitis, pneumonitis, colitis, hepatitis, and meningoencephalitis. To our knowledge, the present study is the first to show a positive correlation between high anti-CMV IgG titer and CMV disease. Moreover, our results remained consistent by adjusting other confounding factors and further using the serum level of CMV DNA detected by PCR as a time-dependent variable. Thus, anti-CMV IgG titer may represent a clinically valuable predictor of CMV disease, as well as a guidance for CMV prophylaxis.

CMV infection and reactivation has previously been identified as a risk factor for acute allograft rejection in kidney transplant recipients.[19–21] In addition to allograft rejection, direct invasion of CMV into a graft kidney can induce a cytopathic effect in glomerular and tubular epithelial cells.[22] The term "CMV nephropathy" has been reported previously, and this condition is often characterized by tubulointerstitial nephritis with nuclear and cytoplasmic inclusions in tubules.[20,23,24] In a retrospective hospital-based study that included 207 kidney transplant recipients, those with CMV infection/disease were associated with higher risks of early acute rejection and impaired renal function compared with patients who were not infected with CMV.[25] In another study that enrolled 264 kidney transplant recipients, a higher CMV peak viral load was related to a more pronounced posttransplantation eGFR decline during the 3-year study period examined.[26] Similarly, in the present study, a high anti-CMV IgG titer was associated with higher risks of eGFR decline and allograft rejection.

Distinct rejection patterns were observed in the two groups of our cohort. The patients in the high anti-CMV IgG titer group had a higher proportion of antibody-mediated rejection, whereas the low titer group had a higher proportion of T-cell–mediated rejection. A higher risk of microvascular inflammation was also observed in the former group. In a previous study, microvascular inflammation was associated with decreased allograft survival.[27] This finding might partly explain the higher risk of renal function decline we observed in our patients with high CMV IgG titers.

Mechanistic details regarding the association between a higher CMV IgG titer and a higher risk of allograft rejection remain unknown. However, it has been observed that kidney transplant recipients who experienced an episode of CMV reactivation during a follow-up period had higher levels of CMV antibodies.[15] In contrast, CMV antibody levels in the recipients without CMV reactivation were decreased. This association is probably due to the administration of immunosuppressant agents following kidney transplantation. CMV-mediated upregulation of adhesion molecules can trigger the inflammatory process, thereby resulting in higher serum levels of inflammatory cytokines and infiltration of the allograft parenchyma by polymorphonuclear leukocytes. Moreover, it has been demonstrated that lymphocytes negatively affect renal allograft rejection and survival.[21,28,29] In a previous study that investigated cytokine patterns at the time of acute rejection, during chronic

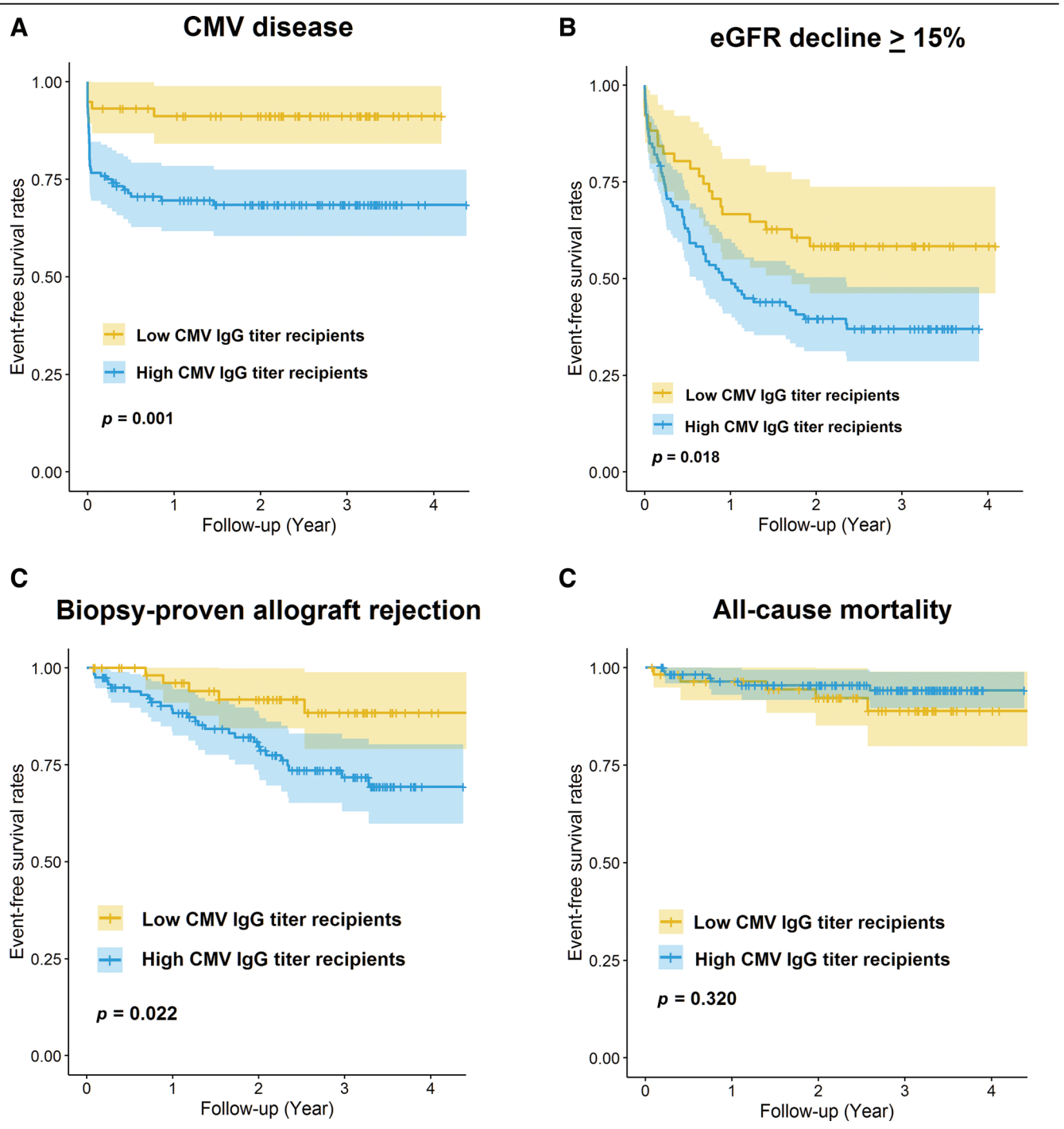

Fig. 3 Kaplan-Meier curves for the risks of (A) cytomegalovirus (CMV) disease, (B) estimated glomerular filtration rate (eGFR) decline ≥15%, (C) biopsy-proven allograft rejection, and (D) all-cause mortality in high anti-CMV immunoglobulin G (IgG) titer group versus low anti-CMV IgG titer group.

rejection, and during a stable condition, upregulated production of interferon-γ and IL-10 was detected in the serum of a patient undergoing acute rejection.[30] It should also be considered that CMV infection with concurrent alloantigens may activate cytotoxic T cells to trigger acute rejection.[31]

Our study was the first one with a relatively long follow-up period to investigate the effects of anti-CMV IgG titer as an independent predictor of CMV disease, renal function decline, and renal allograft outcome. In addition, patients with biopsy-proven rejection were analyzed to establish the specific pathologic features of this population. When underlying comorbidities, laboratory data, and contaminant drugs were considered, and possible confounding factors and their interactions were controlled for, anti-CMV IgG titers were found to be a clinically useful marker for predicting renal allograft outcome and risk of developing CMV disease.

Some limitations in this study should be acknowledged. First, since we performed a retrospective, observational study rather than an interventional study, the correlation between anti-CMV IgG titer and outcome does not imply causality. Second,

Table 2

Risks of CMV disease, eGFR decline ≥15%, allograft rejection, and all-cause mortality in kidney transplant recipients with high anti-CMV IgG titer versus low anti-CMV IgG titer

	Cox regression analysis Crude HR (95% CI)	*p*	Cox regression analysis Adjusted HR (95% CI)	*p*	Cox regression with time-dependent covariates Adjusted HR (95% CI)	*p*
CMV disease						
Low CMV IgG titer	Reference		Reference		Reference	
High CMV IgG titer	4.04 (1.59–10.29)	0.003	3.77 (1.47–9.68)	0.006	3.82 (1.64–11.15)	0.005
eGFR decline ≥15%						
Low CMV IgG titer	Reference		Reference		Reference	
High CMV IgG titer	1.79 (1.09–2.93)	0.020	2.00 (1.19–3.35)	0.009	1.70 (1.05–2.85)	0.037
Allograft rejection						
Low CMV IgG titer	Reference		Reference		Reference	
High CMV IgG titer	2.89 (1.12–7.48)	0.029	2.95 (1.11–7.87)	0.030	3.05 (1.29–8.98)	0.021
All-cause mortality						
Low CMV IgG titer	Reference		Reference		Reference	
High CMV IgG titer	0.55 (0.17–1.82)	0.331	0.60 (0.17–2.07)	0.414	0.38 (0.09–1.43)	0.147

Crude model was an unadjusted crude hazard ratio. Adjusted model was adjusted for covariates listed in Table 1. Cox regression with time-dependent covariates was taken the levels of CMV PCR as time-dependent covariates.

CMV = cytomegalovirus; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IgG = immunoglobulin G.

the degree of immunosuppression in each patient is difficult to quantify, and this could also represent a confounding factor. However, different types of immunosuppressive agents were included as covariates for adjustment in our analysis. Third, HLA matching of our patients was not analyzed in this study, and this might be a prognostic impact factor for allograft rejection. Finally, this study included only kidney transplant recipients in Taiwan; thus, the external validity to other ethnicity and other populations is uncertain.

In conclusion, kidney transplant recipients in our cohort with high anti-CMV IgG titers were associated with higher risks of developing CMV disease, undergoing allograft rejection, and eGFR decline than those with low anti-CMV IgG titers. Measurement of serum antibody titers might be potential for identifying kidney transplant recipients who are at high risk for CMV infection. However, further studies are required to validate this association.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A121.

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