Cause of End-Stage Renal Disease Is Not a Risk Factor for Cytomegalovirus Infection After Kidney Transplant

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ABSTRACT

Background. Cytomegalovirus infection (CMV) after kidney transplantation leads to increased morbidity and mortality. Whether the cause of end-stage renal disease (ESRD) influences the risk of CMV infection post-transplant is not known.

Methods. We analyzed data from 2741 adult kidney transplant recipients from January 1993 through December 2014. The causes of ESRD included diabetes mellitus (n = 947), hypertension (n = 442), polycystic kidney disease (n = 549), and glomerulonephritis (GN) (n = 803). The primary outcome was incidence of CMV infection, defined as the first episode of detectable CMV DNA in the blood following transplant.

Results. Three hundred and thirty patients developed a CMV infection over a median follow-up of 4.5 years. Patients with diabetes mellitus (DM) as the cause of ESRD had a higher incidence of CMV infection post-transplant compared to patients with GN (2.37 vs 1.58/100 person-years, $P < .005$) whereas hypertension (HTN) and autosomal dominant polycystic kidney disease (PKD) were similar (2.17 and 2.07/100 person-years). DM was associated with a 35% higher risk of CMV infection compared to GN in unadjusted analyses [hazard ratio=1.35 [95% confidence interval 1.02–1.78], $P = .04$). However, after adjustment for age, the risk of CMV infection was similar in all groups (DM: age-adjusted hazard ratio 1.02 [0.78–1.39]; HTN: 0.96 (0.67–1.36); PKD: 1.08 [0.78–1.48]; compared to GN). The risk of CMV infection increased with age (adjusted hazard ratio=1.32 [1.18–1.47] for every decade of life, $P < .001$).

Conclusions. Our study demonstrates that the cause of ESRD is not a significant risk factor for CMV infection in kidney transplant recipients once adjusted for age. Future studies are needed to identify risk factors for CMV infection to define patient-centered monitoring and prevention.

IN the United States, the seropositivity of cytomegalovirus (CMV) is general population ranges from 50% to 90% [1]. Immunocompromised patients including kidney transplant recipients are at risk of reactivation of CMV infection. CMV infection post-transplant is associated with increased risk of allograft loss, increased morbidity, and mortality in kidney transplant recipients [2,3]. The primary risk factor associated with reactivation of CMV infection post-transplant is the serostatus of recipient and donor. CMV seronegative recipients receiving the organ from CMV seropositive donor (R-/D+) are at the highest risk of developing CMV infection post-transplant [4]. Pharmacotherapy is very commonly used for prevention of reactivation of CMV, known as CMV prophylaxis, in the early post-transplant

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period [5]. CMV prophylaxis is associated with a significant cost of the drug as well as side effects of the medications. Thus, it is prudent to identify kidney transplant recipients who are at the highest risk of reactivation of CMV and use CMV prophylaxis in high-risk patients.

The use of lymphocyte depleting agents for induction and mycophenolate for maintenance immunosuppression have been shown to increase rate of CMV infection post-transplant [6–8]. Other risk factors have been associated with increased risk of CMV reactivation such as T-cell mediated immunity, age of recipient, and pretransplant dialysis [9]. However, there is no study in literature examining the cause of end-stage renal disease (ESRD) prior to transplant as a risk factor for reactivation of CMV post-transplant. There are reasons to assess the cause of ESRD as a risk factor for CMV infection post-transplant. Many patients with glomerulonephritis (GN) as a cause of ESRD have an autoimmune disease and have a large immunosuppressive exposure burden prior to transplant. These factors alter their immunity against CMV and could increase the risk of CMV reactivation post-transplant. In addition, patients with diabetes mellitus (DM) are in a relatively immunocompromised state, which may put these patients at increased risk of opportunistic infections post-transplant. The goal of this study is to determine whether the cause of ESRD is associated with higher risk of CMV reactivation post-transplant.

METHODS

Study Population

The University of Wisconsin Madison Institutional Review Board and Human Subjects Committee approved this study. Data were obtained from Organ Procurement and Transplantation Network registry from the United Network for Organ Sharing and the Wisconsin Allograft Recipient Database. All consecutive adult (> 18 years) renal transplant recipients who underwent kidney transplant at the University of Wisconsin Hospital and Clinics between January 1, 1993, and December 31, 2014, were included. The cohort included primary transplant only. Retransplant patients or patients with any other organ transplant prior to kidney transplant were excluded. The 4 major types of cause of kidney disease causing ESRD in the study were GN, hypertension (HTN), DM, and polycystic kidney disease (PKD). Patients were followed up for a mean of 4.5 years. The primary outcome was CMV infection, defined as the first episode of detectable CMV DNA in blood following transplant. CMV prophylaxis after transplant was the standard of care at our center from the start of the study from 1994 until the current time [4]. From 1994 to 1998, all patients (except low-risk D-/R-) received acyclovir 800 mg 4 times daily for 12 weeks. Since 1998, all patients except low-risk patients receive ganciclovir based on creatinine clearance for 6 months. Low-risk patients (D-/R-) receive acyclovir for 3 months. After treatment for acute rejection, patients are given ganciclovir for 3 months as prophylaxis for CMV prevention.

Statistical Analysis

Continuous variables were compared between groups with Student *t* tests and Kruskal-Wallis tests. Categorical variables were compared between groups with χ^2 tests. Univariable and multivariable Cox proportional hazards were used to assess independent associations between baseline characteristics and CMV infection rates in different groups of cause of ESRD as well as subtypes of glomerulonephritis. Multivariable hazard ratio was calculated after adjusting for age, sex, race, dialysis pretransplant, duration of dialysis, panel reactive antibody, donor status, donor age, donor sex, prior transplant, delayed graft function, calcineurin use, and human leukocyte antigen mismatch. Time to event data were analyzed with Kaplan-Meier curves and log-rank tests. All analyses were performed using SAS statistical software version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Baseline Demographics

A total of 2741 adult patients underwent kidney transplantation at our center between January 1993 and December 2014. The causes of ESRD in kidney transplant recipients included diabetes mellitus (DM, n = 947, 34%), hypertension (HTN, n = 442, 16%), polycystic kidney disease (PKD, n = 549, 20%), or glomerulonephritis (GN, n = 803, 29%). The mean age of recipients was significantly lower for GN group at 45.3 (± 13.2) ($P < .05$) years compared to DM at 54.8 (± 10.1) years, HTN at 53.2 (± 12.4) years, and PKD at 52.7 (± 9.1) years (Table 1). The proportion of women was significantly lower in the HTN (28%) and DM (34%) groups compared to the GN (42%) and PKD (47%) groups ($P < .05$). The proportion of patients as well as the duration of pretransplant dialysis was significantly higher in the DM and HTN groups compared to the GN subgroup. Patients with positive panel reactive antibody (panel-reactive antibody>10%) were similar in all 4 subgroups. Patients with DM (66%) and HTN (74%) as the cause of ESRD had significantly higher deceased donor transplant compared to the GN (53%) and PKD (55%) groups. Recipients with DM (24%) and HTN (26%) also had significantly higher rates of delayed graft function in comparison to GN (14%) and PKD (13%). Induction immunosuppression was similar in all subgroups. Maintenance immunosuppression was similar in all subgroups except the PKD group, which had significantly higher use of mycophenolate than the rest of the subgroups. The DM (33%) and HTN (37%) groups had a significantly higher number of CMV seropositive donors and recipients in comparison to the GN (26%) and PKD (26%) groups (Table 1). Incidence rates of acute rejection were similar in all groups. The incidence of acute rejection in GN was 4.2 per 100 person years, HTN was 5.6 per 100 person years ($P = .19$ compared to GN), DM was 4.1 per 100 person years ($P = .18$ compared to GN), and PKD was 3.9 per 100 person years ($P = .49$ compared to GN).

Risk of CMV Infection Stratified by Cause of ESRD

Three hundred and thirty patients developed CMV infection over a median follow-up time of 4.5 years. Kidney transplant recipients with DM as the cause of ESRD had a significantly higher incidence of CMV infection at 2.27 per hundred person years in comparison to GN at 1.58 per

Table 1. Patient Characteristics

	GN (n = 803)	HTN (n = 442)	DM (n = 947)	PKD (n = 549)
Age (years), mean	45.3 ± 13.2	53.2 ± 12.4*	54.8 ± 10.1*	52.7 ± 9.1*
Sex, n (%)				
Female	340 (42%)	125 (28%)*	322 (34%)*	256 (47%)
Race, n (%)				
Caucasian	646 (80%)	275 (62%)*	788 (83%)	510 (93%)*
BMI (kg/m^2), mean	27.1 ± 5.2	27.7 ± 5.1	29.2 ± 5.4	27.9 ± 5.1
Pre-transplant dialysis, n (%)	592 (74%)	378 (86%)*	804 (85%)*	324 (59%)*
HD duration prior to transplant (months), median	20	24	20	16
PRA positive, n	372	220	474	263
>10%, n (%)	71 (19%)	37 (17%)	82 (17%)	50 (19%)
Donor type, n (%)				
Deceased	422 (53%)	327 (74%)*	623 (66%)*	301 (55%)
Donor age (years), mean	41.8 ± 14.3	43.7 ± 15.1*	43.9 ± 14.8*	43.6 ± 14.3*
HLA mismatch > 2, n (%)	568 (71%)	352 (80%)*	675 (71%)	427 (78%)*
Induction, n (%)				
Alemtuzumab	114 (14%)	64 (15%)	168 (18%)	82 (15%)
Basiliximab	414 (52%)	226 (51%)	459 (48%)	323 (59%)
Thymoglobulin	131 (16%)	92 (21%)	200 (21%)	84 (15%)
None	144 (18%)	60 (14%)	120 (13%)	60 (11%)
Maintenance IS, n (%)				
Prednisone	801 (100%)	442 (100%)	947 (100%)	549 (100%)
CNI	730 (91%)	397 (90%)	844 (89%)	495 (90%)
Mycophenolate	709 (88%)	394 (89%)	857 (90%)	506 (92%)*
DGF, n (%)	111 (14%)	115 (26%)*	227 (24%)*	74 (13%)
CMV seropositivity				
D-/R-	237 (30%)	91 (21%)	230 (24%)	150 (27%)
D-/R+	187 (23%)	119 (27%)	212 (22%)	116 (21%)
D+/R+	208 (26%)	164 (37%)*	311	142 (26%)
D+/R-	164 (20%)	65 (15%)*	(33%)*	138 (25%)
Unknown	7 (1%)	3 (0.6%)	190 (20%)	3 (0.5%)
			4 (0.4%)	

P value: compared to GN group.
Abbreviations: BMI, body mass index; CMV, cytomegalovirus; CNI, calcineurin inhibitor; DGF, delayed graft function; DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; IS, immunosuppressive; PKD, polycystic kidney disease; PRA, panel-reactive antibody.
*$P < .05$.

hundred person years ($P < .005$) (Table 2). The HTN (2.17 per 100 person years) and PKD (2.07 per 100 person years) groups also had a higher incidence of CMV infection post-transplant in comparison to the GN group, but the difference was not statistically significant. The proportion of patients with CMV infection post-transplant were higher in the DM group compared to the GN group (Fig 1). The time to CMV infection was similar in all subgroups at 7.25 months post-transplant. In the unadjusted model, patients with DM as cause of ESRD had 35% higher risk of

Table 2. Native Kidney Disease Is Not Associated With Increased Risk of CMV Infection Post-Transplant

	GN (n = 803)	HTN (n = 442)	DM (n = 947)	PKD (n = 549)
CMV infection events (n)	82	52	122	74
Incidence rate (per 100 person-years)	1.58	2.17	2.37†	2.07
Time of follow-up (median, years)	5.4	3.8	4.5	5.8
Time to event (median, months)	6.8	6.6	7.8	7.8
Unadjusted relative hazard ratio (95% CI)	1.00 (Reference)	1.24 (0.88–1.75)	1.35* (1.02–1.78)	1.32 (0.97–1.81)
Age-adjusted relative hazard ratio‡ (95% CI)	1.00 (Reference)	0.96 (0.67–1.36)	1.02 (0.77–1.37)	1.08 (0.79–1.48)
Fully adjusted relative hazard ratio§ (95% CI)	1.00 (Reference)	0.92 (0.64–1.33)	1.00 (0.74–1.34)	0.89 (0.64–1.23)

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; DGF, delayed graft function; GN, glomerulonephritis; HTN, hypertension; PKD, polycystic kidney disease.
*$P < .05$ compared to GN.
†$P < .005$ compared to GN.
‡Adjusted for age.
§Adjusted for age, sex, race, dialysis pre-transplant, duration of dialysis, donor status, donor age, DGF, HLA mismatch > 2, induction immunosuppression use, and serostatus (of donor and recipient).

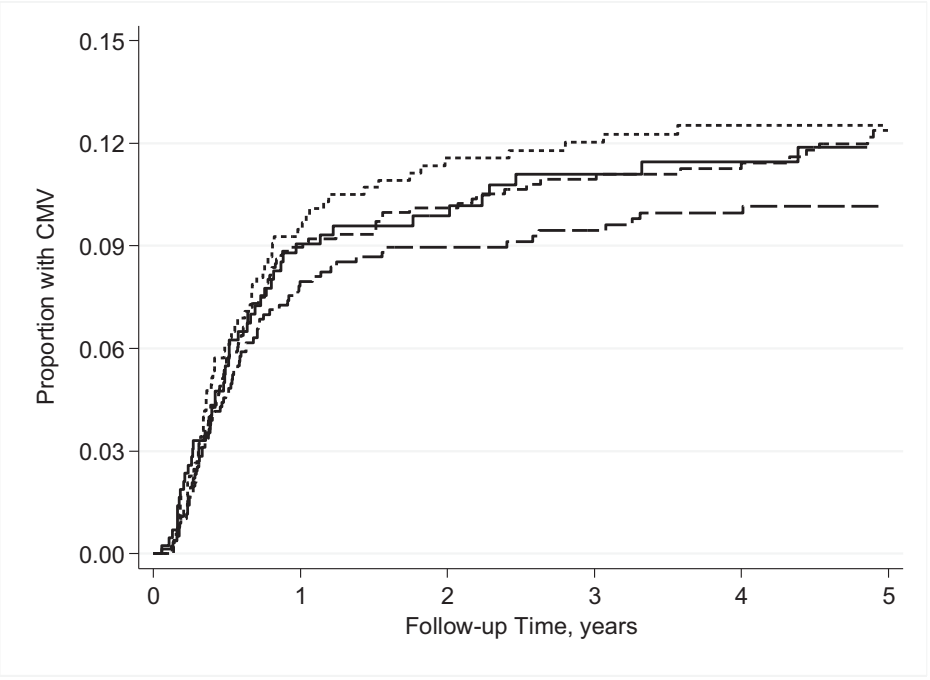

Fig 1. Kaplan-Meier curve of proportion of patients with CMV infection post-transplant by cause of ESRD. Patients with DM as cause of ESRD have the highest incidence of CMV infection ($P < .05$ but not significant after adjustment for age) (DM dotted black line, HTN solid black line, ADPKD small dashed black line, GN large dashed black line). CMV, cytomegalovirus.

developing CMV infection post-transplant in comparison to patients with GN as cause of ESRD ($P < .05$). However, after adjusting for age, the risk of developing CMV infection was similar in all 4 subgroups (Table 2).

Age Was a Risk Factor for CMV Infection Post-transplant

Increasing age of kidney transplant recipients was associated with a higher incidence of CMV infection after transplant. In both unadjusted as well as adjusted cox-regression analysis, recipient age was a significant risk factor for development of CMV infection post-transplant in all patients in our study (hazard ratio 1.40 95% C.I.1.26–1.55, $P < .001$). The risk of CMV infection increased significantly in the kidney transplant recipients over the age of 50 years (Fig 2).

CMV Infection in High-Risk Subgroup by Cause of ESRD

We stratified the entire group based on CMV serostatus of donor and recipient. The group with donor positive/recipient negative (D+/R-) for CMV serostatus has the highest incidence of CMV infection post-transplant (4.18 per 100 person years), and the donor negative/recipient negative group (D-/R-) had the lowest incidence of CMV infection at 0.4 per 100 person years. D+/R+ had an incidence rate of CMV infection of 2.52 per 100 person years, which was higher than D-/R+ group at 1.52 per 100 person years (Supplementary Table 1). D+/R- group had a 9.4 times higher risk of CMV infection in comparison to D-/R- group ($P < .001$) (Supplementary Table 1). We examined the high-risk group of D+/R- serostatus based on cause of ESRD. In the high-risk group, recipients with GN as cause of ESRD had the lowest incidence rate of CMV infection at 3.28 per 100 person years, and the HTN group had the highest rate of CMV infection at 5.78 per 100 person years. However, this difference was not statistically significantly different.

DISCUSSION

We found that kidney transplant patients with DM as the cause of ESRD have the highest incidence of CMV infection post-transplant. However, after adjusting for age, the risk of CMV infection was similar among all kidney transplant recipients irrespective of cause of ESRD. We found that the age of the recipient is an important risk factor for developing CMV infection after kidney transplant, particularly over the age of 50 years.

There is no study in literature examining the association between the cause of ESRD and risk of CMV infections. The 2 most important known risk factors associated with higher risk of CMV infection after transplant are the serostatus of recipient and donor and degree of immunosuppression. The mismatch in serostatus of CMV for donor and recipient is the most important risk factor for development of CMV infection post-transplant [10]. We confirmed this in our patient population in this study. We found that the serostatus group of D+/R- was associated with 9.4 times higher risk of CMV infection compared to the group of patients with D-/R-, which is the most significant risk factor for developing CMV infection. We also found that the subgroup D+/R+ had a higher incidence of CMV infection compared to D-/R+, which is thought to be due to an infection by a different CMV strain from the donor to

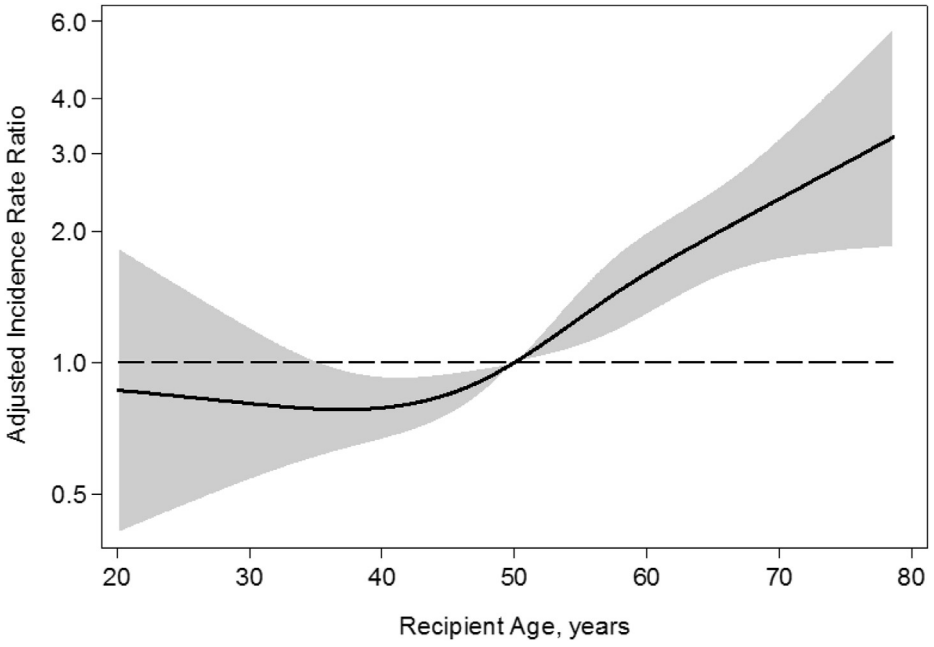

Fig 2. Recipient age is significantly associated with risk of CMV infection post-transplant Incidence of CMV infection with age ($P < .001$ adjusted for sex, race, dialysis pre-transplant, duration of dialysis, donor status, donor age, DGF, HLA mismatch >2, induction immunosuppression use, and CMV serostatus of donor and recipient).

the recipient in the D+/R- group [11]. We also found age to be a significant risk factor for development of CMV infection and that every 10 years of age increases the risk of developing CMV infection by 32%. The risk of CMV infection steadily increases with increasing age, but after the recipient's age of 50 years is when the risk of CMV infection increases significantly.

The 2 methods for prevention of CMV post-transplant currently used in clinical practice are universal prophylaxis or pre-emptive treatment. Universal prophylaxis is giving pharmacotherapy to all patients after transplant for a certain period after transplant to prevent CMV infection. In pre-emptive treatment, no pharmacotherapy is used, but patients are followed closely for CMV infection in the blood and started on therapy as soon as they develop CMV infection. Either of these therapies have their own benefits and disadvantages [12]. Prophylaxis therapy is associated with increased side effects as well as the cost of medication. Pre-emptive therapy is associated with a higher rate of CMV infection as well as the cost of testing for CMV. The best approach for decreasing cost as well as incidence of CMV infection is a combination of both approaches for different cohorts of patients. Patients with a high risk of CMV infection post-transplant will likely benefit from prophylaxis therapy, and those with low risk can be followed pre-emptively without prophylaxis. The important factor here is defining high-risk and low-risk patients for development of CMV infection. The goal of this study was to define the risk factors for CMV infection.

Our study is limited because it is a single-center observation of a condition in primarily white, male patients. However, the granularity of the information and data on CMV serology and polymerase chain reaction provide important clues in the association between the primary cause of ESRD and CMV infection.

In summary, we found that diabetics have the highest incidence of CMV infection after transplant but the major factor contributing to their higher risk was the higher age in these patients compared to other groups. The cause of ESRD per se was not associated with increased risk of CMV infection after transplant. We also found that the increasing age of recipients is associated with a higher risk of CMV infection and the recipient's age greater than 50 years is associated with significantly higher risk of infection. The findings from our study help in defining the risk factors for CMV infection after transplant. We propose to develop a risk factor calculator for development of CMV infection post-transplant, taking into account the different variables that contribute to the increased risk of CMV infection. Future studies are needed to examine other risk factors for CMV infection to define patient-centered monitoring and preventive strategies.

SUPPLEMENTAL DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.transproceed.2019.02.029.

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