Characterization of Cytomegalovirus Viremia in Renal Transplant Recipients

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ABSTRACT

Background: Kidney transplantation, while improving outcomes for patients with end-stage renal disease, comes with a risk of potentially life-threatening infections such as infection with cytomegalovirus (CMV), a virus associated with allograft rejection, organ dysfunction, and increased mortality.

Objectives: To characterize whether the choice and dose of immunosuppressant therapy and the duration of antiviral prophylaxis after transplant are associated with the incidence of CMV viremia.

Methods: This study was a retrospective review of all kidney-only transplant recipients at the authors' centre from 2012 to 2016, with a minimum 1 year of follow-up. Patients with CMV viremia (defined as serum CMV viral load greater than 1000 IU/mL) were compared with patients who did not have viremia to investigate potential demographic and treatment-related risk factors.

Results: A total of 653 patients were included in the study, of whom 161 (25%) met the criteria for CMV viremia. In univariate analysis, patients with CMV viremia had older age (55 versus 53 years, $p = 0.038$) and lower mean body weight (75 versus 79 kg, $p = 0.015$); in addition, the CMV viremia group included larger proportions of patients with Asian descent (40% [64/161] versus 21% [104/492]) and donor-positive/recipient-negative CMV serostatus (29% [47/161] versus 14% [70/492]). With respect to immunosuppressant therapy, patients with CMV viremia more frequently received antithymocyte globulin (ATG) induction (50% [80/161] versus 28% [138/492], $p < 0.001$) and received a higher weight-based cumulative ATG dose (mean 4.5 versus 4.1 mg/kg, $p = 0.038$). The multivariate analysis retained use of ATG, cumulative dose of ATG, Asian descent, and CMV serostatus as risk factors for CMV viremia. No statistically significant differences were found for the maintenance immunosuppressant dosing or duration of antiviral prophylaxis.

Conclusions: Use of ATG for induction and higher weight-based dose of ATG were associated with an increased risk of CMV viremia. In addition, a component of race may also be involved, with patients of Asian descent being at higher risk. No differences were found in the maintenance dose of immunosuppression or the duration of antiviral prophylaxis.

Keywords: cytomegalovirus, viremia, kidney transplant recipient, antithymocyte globulin, mycophenolate mofetil, valganciclovir

RÉSUMÉ

Contexte : La transplantation rénale, bien qu'elle améliore les résultats des patients atteints d'insuffisance rénale en phase terminale, s'accompagne d'un risque d'infections potentiellement mortelles telles que l'infection par le cytomégalovirus (CMV) : un virus associé au rejet d'allogreffe, à un dysfonctionnement d'organe et à une plus grande mortalité.

Objectifs : Caractériser si le choix et la dose du traitement immunosuppresseur et la durée de la prophylaxie antivirale après la transplantation sont associés à l'incidence de virémie à CMV.

Méthodes : Cette étude était un examen rétrospectif de tous les receveurs d'une transplantation rénale uniquement mené au centre des auteurs de 2012 à 2016, avec un suivi d'au moins 1 an. Les patients atteints de virémie à CMV (définie comme une charge virale sérique CMV supérieure à 1000 UI/mL) ont été comparés à des patients sans virémie; cette comparaison avait pour but d'étudier les facteurs de risque démographiques ou liés aux traitements.

Résultats : L'étude comprenait 653 patients, dont 161 (25 %) répondaient aux critères de virémie à CMV. En analyse univariée, l'âge des patients atteints de virémie à CMV était plus élevé (55 contre 53 ans, $p = 0{,}038$) et leur poids corporel moyen était moins élevé (75 contre 79 kg, $p = 0{,}015$); en outre, le groupe des patients atteints de virémie à CMV comprenait une plus grande proportion de patients d'origine asiatique (40 % [64/161] contre 21 % [104/492]) et de statut sérologique CMV donneur positif/receveur négatif (29 % [47/161] contre 14 % [70/492]). En ce qui concerne le traitement immunosuppresseur, les patients atteints de virémie à CMV ont reçu plus fréquemment une induction de sérum anti-lymphocytaire (SAL) (50 % [80/161] contre 28 % [138/492], $p < 0{,}001$) ainsi qu'une dose cumulative de SAL plus élevée en fonction du poids (moyenne de 4,5 contre 4,1 mg/kg, $p = 0{,}038$). L'analyse multivariée a retenu l'utilisation du SAL, la dose cumulative de SAL, l'origine asiatique et le statut sérologique du CMV comme facteurs de risque de virémie à CMV. Aucune différence statistiquement significative n'a été trouvée pour la posologie d'entretien des immunosuppresseurs ou la durée de la prophylaxie antivirale.

Conclusions : L'utilisation du SAL pour l'induction et une dose plus élevée de SAL en fonction du poids étaient associées à un risque accru de virémie à CMV. De plus, une composante raciale pourrait également être impliquée – les patients d'origine asiatique étant plus à risque. Aucune différence n'a été trouvée dans la posologie d'entretien des immunosuppresseurs ou la durée de la prophylaxie antivirale.

Mots-clés : cytomégalovirus, virémie, transplanté rénal, globuline antithymocyte, sérum anti-lymphocytaire, mycophénolate mofétil, valganciclovir

INTRODUCTION

To ensure transplant success, kidney transplant recipients require profound immunosuppression, which places them at risk of serious life-threatening infections. One pathogen of concern is cytomegalovirus (CMV), a member of the herpesvirus family that is found latently in large segments of the global population.[1] In the setting of immunosuppression, reactivation of the virus may cause significant disease, potentially resulting in allograft rejection, organ dysfunction, or death.[1,2] CMV disease can be further described as CMV syndrome (infection with fever, malaise, leukopenia, and/or thrombocytopenia) or tissue-invasive CMV disease (infection resulting in organ dysfunction, such as enteritis, colitis, hepatitis, pancreatitis, pneumonitis, meningoencephalitis, and retinitis).[2]

Multiple studies have placed the incidence of CMV viremia between 20% and 30% among kidney transplant recipients.[3-5] Although the most significant risk factor for CMV viremia is the CMV serostatus of the donor and recipient (D/R), with donor-positive and recipient-negative (D+/R–) status having the highest risk, several other demographic and clinical parameters have been identified as risk factors, such as older age, deceased donor, duration of hemodialysis before transplant, and estimated glomerular filtration rate (eGFR) after transplant.[5-8]

In addition to these pre- and post-transplant risk factors, certain other post-transplant factors, such as the choice of induction and maintenance immunosuppression, have also been implicated in the incidence of CMV infections. Agents of interest have included antithymocyte globulin (ATG), tacrolimus, and mycophenolate mofetil (MMF).[5,7,8] However, there is currently a paucity of information in the literature as to whether the dose intensity of these agents is associated with CMV viremia. An example is the therapeutic regimen for MMF, which at our site is initiated and maintained at a dose of 1 g twice daily, irrespective of body weight (except in cases of intolerable adverse effects, such as neutropenia or diarrhea). There is concern that this dosing strategy may place patients with lower body weight (and thus a higher per-kilogram dose of MMF) at greater risk of immunosuppressive complications. Pharmacokinetic studies have implicated lower body weight with a higher area under the curve for mycophenolic acid.[9,10] A study conducted by Tsang and others[11] comparing MMF and azathioprine therapy in Chinese kidney transplant recipients found that among the 41 patients who received MMF, a dose of 2 g/day resulted in a significantly higher incidence of CMV infection relative to MMF doses of 1.5 and 1 g/day. However, it is unclear whether these findings warrant adopting a weight-based dosing strategy to prevent immunosuppressive complications.

For select patients with higher-risk D/R serostatus or ATG induction, a key preventive strategy is the initiation of CMV prophylaxis after transplant. At our site, this is most commonly achieved with administration of the oral antiviral agent valganciclovir. The usual duration for CMV prophylaxis ranges from as long as 6 months for cases involving D+/R– CMV serostatus to just 1–3 months for cases involving CMV-positive recipients who received ATG induction. Recipients with basiliximab induction do not receive CMV prophylaxis unless the CMV serostatus is D+/R–. Anecdotal reports indicate that CMV infections appear to be more frequent among kidney transplant recipients with shorter duration of post-transplant prophylaxis. Hence, there is also great interest in the duration of antiviral prophylaxis and its relation with the subsequent incidence of CMV viremia. Although there is evidence supporting the use of longer-duration prophylaxis (up to 200 days) for cases with D+/R– CMV serostatus,[12] there are limited data on the optimal duration of prophylaxis for cases involving other serostatus combinations.

The objective of our study was to identify post-transplant risk factors for CMV viremia. In particular, we studied the choice and dosing regimen of induction and maintenance immunosuppressants and examined whether CMV viremia was associated with a shorter duration of valganciclovir prophylaxis.

METHODS

Study Design and Data Sources

We conducted a single-centre retrospective study of kidney-only transplant recipients who underwent their surgery between January 1, 2012, and December 31, 2016, with a minimum 1 year of follow-up. To identify potential risk factors for CMV viremia, we compared patients with and without CMV viremia. CMV viremia was defined as at least 1 serum CMV viral load greater than 1000 IU/mL. This cut-off was selected to mirror our institutional definition of CMV viremia in 2012.

The study was conducted at St Paul's Hospital, in Vancouver, Canada. Data for the incidence of viremia, patient demographic characteristics, and immunosuppressant exposure were extracted from the Patient Records and Outcome Management Information System (PROMIS) electronic renal database. PROMIS is the provincial clinical information system employed by renal and transplant centres in British Columbia to coordinate patient care, record clinical data, and support research. The data included within the database reflect pre- and post-transplant care throughout a patient's lifetime once registered with the transplant program.

This study was approved by Providence Health Care Research Ethics Board, and informed consent was not required.

Data Collection

Demographic characteristics collected were age, sex, weight at time of transplant, race, CMV D/R serostatus, donor type,

cause of end-stage renal disease, number of renal transplants, dialysis requirement before transplant, dialysis vintage, panel-reactive antibody, number of human leukocyte antigen (HLA) mismatches, and results of pretransplant virological testing, such as HIV, hepatitis, and Epstein–Barr virus. Clinical outcomes extracted were eGFR 1 year after transplant, BK virus co-infection, graft failure, graft rejection, and death. For patients with CMV viremia, additional data collected were peak viral load and time to viremia.

For the analysis of induction immunosuppression, we documented use of ATG, use of basiliximab, or no induction. Patients who received both basiliximab and at least 1 dose of ATG were categorized as having received ATG induction. The cumulative weight-based dose of ATG was calculated using total ATG doses administered divided by the patient's weight at the time of transplant. Cumulative ATG dose was then compared between patients with and without viremia who received at least 1 dose of ATG.

Maintenance immunosuppression was assessed by collecting the use of tacrolimus, MMF, mycophenolic acid, and/or cyclosporine. Drug exposure data were also collected for tacrolimus and MMF, the 2 most commonly used maintenance immunosuppressants at our site. For patients receiving tacrolimus, drug exposure was defined as the average trough concentrations for the following 4 periods after the transplant: day 0 to 30, month 1 to month 3, month 4 to month 6, and month 7 to month 12. These timeframes were selected to reflect the declining therapeutic trough targets for tacrolimus after transplant. For MMF, drug exposure was defined as the average daily MMF dose per kilogram body weight (mg/kg/day) for the same periods as outlined for tacrolimus. No drug exposure data are reported for mycophenolic acid and cyclosporine because of low utilization at our site.

With respect to antiviral prophylaxis, the use and duration of valganciclovir prophylaxis were collected. Patients were deemed to have received valganciclovir for CMV prophylaxis if this drug was initiated within 5 days after the transplant date and before the first episode of CMV viremia.

Statistical Analysis

Categorical variables are reported as frequencies and percentages, with analysis by the χ^2 test. Quantitative variables are reported as means with standard deviations (SDs), with analysis by *t* test. Statistical tests were conducted at the $\alpha = 0.05$ level of significance. Multivariate analysis was conducted with logistic regression, with adjustment for statistically significant confounders identified in the univariate analysis.

RESULTS

Baseline Characteristics

A total of 653 patients received a kidney transplant at our centre during the 5-year study period. Of these, 161 (25%) met our definition of CMV viremia. As demonstrated in Table 1, those with CMV viremia were older (55 versus 53 years, $p = 0.038$) and had lower body weight (75 versus 79 kg, $p = 0.015$), with greater proportions being of Asian descent (40% versus 21%) and having CMV serostatus D+/R– (29% versus 14%) or D+/R+ (44% versus 36%). Other statistically significant differences included more deceased donors, greater prevalence of dialysis, longer duration of dialysis before transplant, and higher percentage with panel-reactive antibody in the group with CMV viremia. Although there was a greater proportion of female patients among those with CMV viremia, the difference was not statistically significant. No significant differences were observed between the 2 groups in terms of diagnosis of end-stage renal disease, number of prior transplants, number of HLA mismatches, or other aspects of pretransplant virology status.

Kidney transplant recipients with CMV viremia had lower eGFR at 1 year after transplant compared with non-viremic patients (mean 47.1 versus 56.6 mL/min/m^2, $p < 0.001$). No statistically significant differences in BK virus co-infection, graft failure, graft rejection, or death were observed (data not shown).

Immunosuppression and Duration of Valganciclovir Prophylaxis

Table 2 and Figure 1 illustrate the differences in induction regimens used. Kidney transplant recipients with CMV viremia had significantly higher use of ATG for induction (50% versus 28%) and a higher mean cumulative weight-based ATG dose (4.5 [SD 1.7] versus 4.1 [SD 1.5] mg/kg, $p = 0.038$).

Table 3 illustrates differences in maintenance immunosuppression between the groups with and without viremia. We did not observe any higher tacrolimus or MMF exposure by weight in the group with CMV viremia. On the contrary, it was the group without CMV viremia, relative to the CMV viremia group, that had a significantly higher average tacrolimus exposure from months 1 to 3 (9.3 versus 8.8 µg/L, $p < 0.001$) and a significantly higher average MMF exposure from months 4 to 6 (21.8 versus 19.8 mg/kg/day, $p = 0.009$) and from months 7 to 12 (20.1 versus 17.3 mg/kg/day, $p < 0.001$). However, the CMV viremia group did have greater use of MMF (99% versus 96%, $p = 0.046$) and cyclosporine (9% versus 5%, $p = 0.029$) than the group without CMV viremia.

In our study, antiviral prophylaxis with valganciclovir was received by 71% (115/161) of patients with CMV viremia and 42% (205/492) of those without viremia. Among those who received prophylaxis, the mean duration of treatment was similar: 93.9 days in the group with CMV viremia versus 92.2 days in the group without CMV viremia ($p = 0.86$). When further categorized according to CMV D/R serostatus, the duration of prophylaxis was longest in the D+/R– group, but no statistically significant difference was found between the groups with and without viremia (168.2 versus 188.7 days, $p = 0.14$).

TABLE 1. Baseline Characteristics

Characteristic	CMV Status; No. (%) of Participants[a]		*p* Value
	No CMV (*n* = 492)	CMV (*n* = 161)	
Age (years) (mean ± SD)	52.9 ± 13.4	55.4 ± 13.4	0.038
Sex			0.053
Male	311 (63)	88 (55)	
Female	181 (37)	73 (45)	
Weight (kg) (mean ± SD)	78.9 ± 17.7	75.0 ± 17.4	0.015
Race			< 0.001
White	349 (71)	83 (52)	
Asian	104 (21)	64 (40)	
Indigenous	17 (3)	6 (4)	
Hispanic	6 (1)	3 (2)	
Black	4 (1)	4 (2)	
Other or multiracial	12 (2)	1 (1)	
D/R CMV serostatus			< 0.001
+/–	70 (14)	47 (29)	
+/+	177 (36)	71 (44)	
–/+	122 (25)	38 (24)	
–/–	110 (22)	1 (1)	
Missing	13 (3)	4 (2)	
ESRD diagnosis			0.74
Diabetes	80 (16)	26 (16)	
Hypertension	56 (11)	19 (12)	
IgA nephropathy or glomerulonephritis	105 (21)	28 (17)	
Unknown or other	251 (51)	88 (55)	
Donor type			< 0.001
Living donor	257 (52)	53 (33)	
Standard criteria donor	147 (30)	44 (27)	
Expanded criteria donor	47 (10)	33 (20)	
Donation after cardiac death	41 (8)	31 (19)	
No. of kidney transplants			0.43
1	435 (88)	146 (91)	
≥ 2	57 (12)	15 (9)	
Dialysis before transplant	379 (77)	141 (88)	0.004
Dialysis vintage[b]			0.003
< 1 year	58 (12)	14 (9)	
1–5 years	242 (49)	78 (48)	
> 5 years	79 (16)	49 (30)	
PRA percentage			0.005
Overall	258 (52)	96 (60)	
0–19	202 (41)	60 (37)	
20–80	35 (7)	18 (11)	
> 80	21 (4)	18 (11)	
HLA mismatch			0.51
0–3	185 (38)	57 (35)	
4–6	295 (60)	103 (64)	
Missing	12 (2)	1 (1)	
Virology			
HIV	1 (< 1)	1 (1)	0.42
Hepatitis B	5 (1)	4 (2)	0.16
Hepatitis C	7 (1)	1 (1)	0.41
Epstein–Barr virus	414 (84)	143 (89)	0.18

CMV = cytomegalovirus, D = donor, ESRD = end-stage renal disease, HLA = human leukocyte antigen, IgA = immunoglobulin A, PRA = panel-reactive antibody, R = recipient, SD = standard deviation.
[a]Except where indicated otherwise.
[b]Percentages based on those who received dialysis before transplant.

TABLE 2. Induction Agents

Agent	CMV Status; No. (%) of Patients[a]		*p* Value
	No CMV (*n* = 492)	CMV (*n* = 161)	
Induction agent			< 0.001
ATG	138 (28)	80 (50)	
Basiliximab	347 (71)	78 (48)	
No induction	7 (1)	3 (2)	
Cumulative ATG dose (mg/kg) (mean ± SD)	4.1 ± 1.5	4.5 ± 1.7	0.038

ATG = antithymocyte globulin, SD = standard deviation.
[a]Except where indicated otherwise.

Characterization of Patients with CMV Viremia

A breakdown of the patients with CMV viremia by serostatus is presented in Table 4. Induction agents were similar for cases with D+/R– and D+/R+ serostatus, with D–/R+ patients more likely to receive ATG and less likely to be treated with basiliximab. Kidney transplant recipients within the high-risk serostatus group (D+/R–) received prophylaxis with valganciclovir for a longer duration, in accordance with American Society of Transplantation guidelines[2] (mean 168.2, 40.9, and 45.5 days for cases with D+/R–, D+/R+, and D–/R+ serostatus, respectively; $p < 0.001$). On average, these patients also had a significantly higher peak viral load than the moderate-risk (D+/R+) and low-risk (D–/R+) groups (66 243, 14 476, and 9031 IU/mL; $p = 0.001$). Although longer prophylaxis appeared to delay the occurrence of viremia from the time of transplant, the time to viremia after discontinuation of prophylaxis was similar for the high- and low-risk groups but shorter for the moderate-risk group.

Multivariate Analysis

The proportion of patients with ATG use was significantly higher among kidney transplant recipients with CMV viremia than among those without CMV viremia (OR 2.53, 95% confidence interval [CI] 1.79–3.73, $p < 0.001$). As described in Table 5, this result remained significant after adjustment for other potential confounders, specifically age, race, weight at transplant, donor type, CMV D/R serostatus, and duration of valganciclovir prophylaxis (OR 2.41, 95% CI 1.52–3.83, $p < 0.001$).

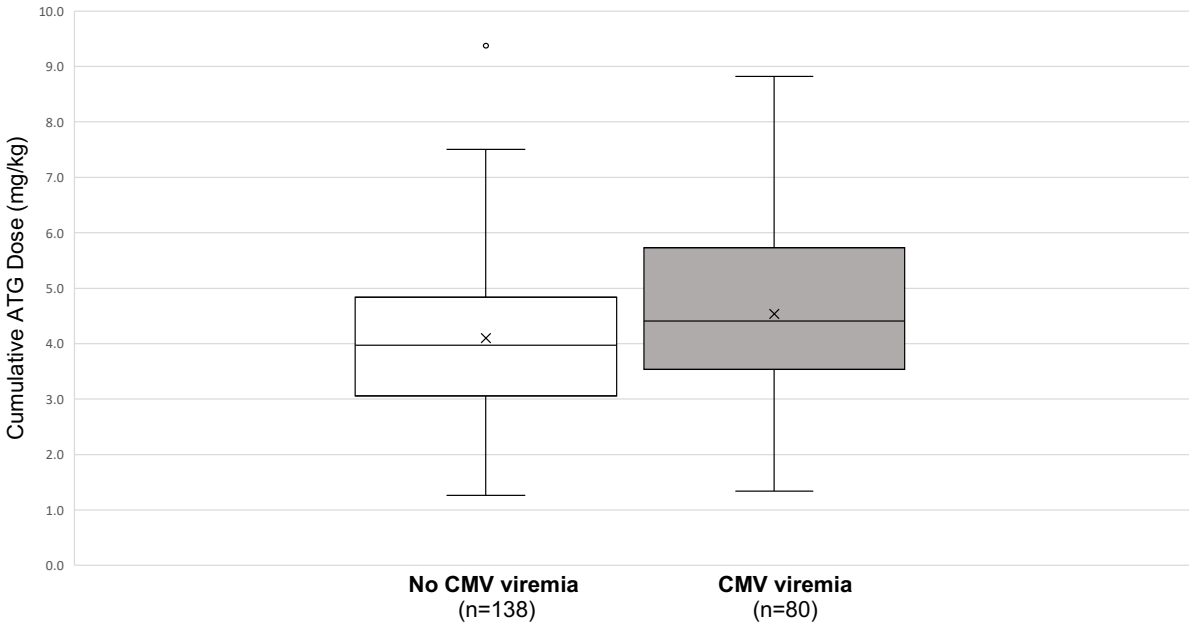

FIGURE 1. Box plot of cumulative dose of antithymocyte globulin (ATG). The horizontal line within each box denotes the median value, and the box extends vertically from the 25th percentile (bottom edge) to the 75th percentile (top edge) of values. The area of the box denotes the middle 50% of values. The whiskers denote lower and upper adjacent values (within 1.5 interquartile range of the first and third quartiles, respectively). The letter "x" denotes the mean value for each group, and the letter "o" denotes an outlier value for the group without cytomegalovirus (CMV) viremia, beyond the range of adjacent values.

TABLE 3. Maintenance Regimens

Medication[a]	CMV Status; Mean ± SD[b]		*p* Value
	No CMV (*n* = 492)	CMV (*n* = 161)	
Tacrolimus			
No. (%) of patients	479 (97)	153 (95)	0.15
Mean trough concentration (μg/L)			
Day 1–30	8.9 ± 2.3	8.6 ± 2.5	0.11
Month 1–3	9.3 ± 1.4	8.8 ± 1.4	< 0.001
Month 4–6	7.7 ± 1.4	7.6 ± 1.4	0.48
Month 7–12	6.6 ± 1.3	6.6 ± 1.2	0.69
Cyclosporine, no. (%) of patients	23 (5)	15 (9)	0.029
Mycophenolate mofetil			
No. (%) of patients	474 (96)	160 (99)	0.046
Mean dose (mg/kg/day)			
Day 1–30	25.4 ± 6.3	26.1 ± 6.6	0.20
Month 1–3	25.0 ± 6.4	24.6 ± 7.5	0.62
Month 4–6	21.8 ± 7.2	19.8 ± 8.2	0.009
Month 7–12	20.1 ± 7.1	17.3 ± 7.9	< 0.001
Mycophenolic acid, no. (%) of patients	37 (8)	11 (7)	0.77

[a]Periods for drug exposure refer to time after transplant. Drug exposure data were collected only for the maintenance immunosuppressants most commonly used at the study hospital (i.e., tacrolimus, mycophenolate mofetil).
[b]Except where indicated otherwise.

TABLE 4. Characterization of Patients with CMV Viremia

Parameter	D/R Serostatus; No. (%) of Patients[a]			*p* Value
	D+/R– (*n* = 47)	D+/R+ (*n* = 71)	D–/R+ (*n* = 38)	
Induction				0.10
ATG	19 (40)	33 (46)	26 (68)	
Basiliximab	27 (57)	37 (52)	11 (29)	
None	1 (2)	1 (1)	1 (3)	
Valganciclovir prophylaxis				< 0.001
Yes	47 (100)	38 (54)	28 (74)	
No	0 (0)	33 (46)	10 (26)	
Duration (days) (mean ± SD)	168.2 ± 77.11	40.9 ± 24.51	45.5 ± 38.20	< 0.001
Time to viremia (days) (mean ± SD)				
From transplant	278.5 ± 156.42	103.3 ± 92.34	156.3 ± 308.31	< 0.001
From end of prophylaxis	116.8 ± 47.00	60.8 ± 94.12	109.0 ± 308.78	0.36
Peak viral load (IU/mL) (mean ± SD)	66 243 ± 142 891	14 476 ± 33 501	9031 ± 15 328	0.001

ATG = antithymocyte globulin, D = donor, R = recipient, SD = standard deviation.
[a]Except where indicated otherwise.

Similarly, the cumulative ATG dose remained significantly higher in the group with CMV viremia relative to the group without CMV viremia after adjustment for the same confounders (OR 1.21, $p < 0.001$; data not shown).

DISCUSSION

We examined data for a cohort of 653 kidney transplant recipients to identify demographic and treatment-related risk factors for CMV viremia at our centre. Approximately 25% of our cohort was defined as having CMV viremia, consistent with the incidence reported in previous studies.[3-5] With respect to demographic characteristics, the univariate analysis showed that older age, Asian descent, and lower body weight were more prominent in the group with CMV viremia, although only Asian descent remained significant in the multivariate analysis (OR 2.04, 95% CI 1.25 to 3.34, $p = 0.04$). Female sex was also more represented

TABLE 5. Results of Multivariate Analysis[a]

Parameter	Adjusted OR[b] (95% CI)		*p* Value
ATG use	2.41	(1.52–3.83)	< 0.001
Age at transplant (years)	1.01	(1.00–1.03)	0.12
Weight at transplant (kg)	1.00	(0.98–1.01)	0.42
Race			0.02
Asian versus white	2.04	(1.25–3.34)	0.04
Other versus white	1.40	(0.66–2.95)	0.95
D/R serostatus			< 0.001
D+/R+ versus D−/R−	29.91	(4.02–222.47)	0.02
D+/R− versus D−/R−	87.46	(9.75–784.37)	< 0.001
D−/R+ versus D−/R−	18.57	(2.45–141.02)	0.48
Donor type (living donor versus other)	0.63	(0.41–0.99)	0.04
Valganciclovir duration		–	0.74

ATG = antithymocyte globulin, CI = confidence interval, CMV = cytomegalovirus, D = donor, OR = odds ratio, R = recipient.
[a]For kidney transplant recipients with CMV viremia, relative to those without CMV viremia.
[b]Adjusted for age, race, weight at transplant, donor type, CMV D/R serostatus, and duration of valganciclovir prophylaxis.

in the group with CMV viremia, but this variable did not reach statistical significance. It has been hypothesized that Asian patients, who on average have lower body weight, may be at increased risk of immunosuppressive complications,[10] with other studies having implicated race and sex as potential risk factors for reduced clearance of MMF.[13,14] Small studies involving Chinese patients have been able to use lower doses of MMF (1 and 1.5 g/day) while maintaining efficacy of treatment.[11,15] Tsang and others[11] found a higher incidence of CMV infection among patients receiving 2 g/day relative to those receiving 1.5 or 1 g/day of MMF, although this finding was limited by small sample size and an unclear definition of CMV. Even though our study did not show a relationship between weight-based dosing of MMF (in mg/kg) and incidence of CMV viremia, MMF dose reduction (particularly in Asian patients) may be a promising treatment modality warranting further investigation through prospective studies.

With respect to immunosuppression, the use of ATG for induction was higher among kidney transplant recipients with CMV viremia, even after adjustment for confounding factors. Our multivariate analysis also maintained the observed higher cumulative weight-based ATG dosing in the CMV group. This relationship between ATG use and CMV viremia has been documented previously.[5,16-19] Potential mechanisms include release of tumour necrosis factor-α, depletion of T-helper cells, and inversion of the CD4/CD8 ratio after administration of ATG.[16] While induction therapy is given for only a few days after transplant, one study found that ATG had a half-life of approximately 30 days.[20] Beyond this, immunosuppressive effects can persist even after ATG has cleared, with Servais and others[21] finding compromised recovery of T-cell counts up to 1 year after induction.

Nevertheless, the applicability of this finding is somewhat limited, as the study outcome (CMV viremia) is not the final clinical end point of interest. We did not collect data for the incidence of symptomatic CMV disease, such as CMV colitis or pneumonitis, because of inconsistent documentation of clinical complications in our database. Most cases of low-grade CMV viremia are asymptomatic and, if recognized early, resolve with appropriate antiviral therapy. Results from 2 small prospective studies that assessed both CMV viremia and symptomatic CMV disease demonstrated no increased risk of CMV when induction was coupled with appropriate antiviral prophylaxis.[22,23] Although our study suggested that ATG use appeared to increase the incidence of CMV viremia, it is difficult to advocate for alteration in ATG prescribing, despite our findings, given that the risk of transplant rejection far outweighs the potential benefit of mitigating a treatable viremia. However, close surveillance should be in place for patients who have received higher doses of ATG, and for patients who become unwell, there should be a low index of suspicion for CMV disease.

No differences in the dosing of maintenance immunosuppression (with tacrolimus or MMF) were identified in our study. Our initial design was intended to mimic the gradual decrease in maintenance dosing of immunosuppression seen in clinical practice. However, drug exposure was ultimately treated as a discrete variable encompassing an average over a period of time. A study design with drug exposure as a continuous variable over time might have yielded a clearer correlation. It is unclear why the group without viremia had higher average exposure to maintenance immunosuppression (with MMF and tacrolimus) in the later months. This could have been the result of confounding, as the patients with viremia were older and more

frail, and dose reductions might have been needed because of non–CMV-related adverse reactions. Alternatively, CMV infection itself or administration of valganciclovir can result in neutropenia, which would then necessitate a reduction in MMF dosage in patients with CMV. These reasons may explain why drug exposures were lower during later time intervals in the group with CMV viremia relative to those without CMV viremia.

This study also confirmed the well-documented increase in CMV risk in accordance with pretransplant D/R serostatus. Of the highest-risk group (D+/R–) in this cohort, approximately 40% developed viremia; similarly, 30% of those with CMV D+/R+ serostatus developed viremia.

We did not observe any difference in the duration of antiviral prophylaxis between the groups with and without CMV viremia. As referenced earlier, Humar and others[12] found that extended valganciclovir prophylaxis (to 200 days) in CMV D+/R– patients resulted in reduced CMV viremia and infection at 12 months relative to shorter duration of prophylaxis (for 100 days). In our study, D+/R– patients (with or without CMV viremia) received appropriate prolonged courses of valganciclovir. The other 2 risk groups (D–/R+ and D+/R+) received shorter durations of antiviral prophylaxis. However, while not statistically significant, there appeared to be a shorter duration of prophylaxis in the D+/R+ group with viremia compared to the D+/R+ group without viremia, and a reduced time to the first occurrence of viremia after finishing prophylaxis compared with the other 2 risk groups. While our overall sample size was quite large, there may have been insufficient patients for analysis once categorized by serostatus. Ultimately, a randomized prospective study would be needed to more adequately assess this issue.

This study had several other limitations. The retrospective nature of the study introduced significant potential for confounding. For instance, we observed higher panel-reactive antibody percentage and HLA mismatch in the CMV viremia group. It is unclear if these factors intrinsically increase the likelihood of CMV viremia or most likely are a product of the subsequent use of ATG. Given that all of our data were retrospectively collected from an electronic database, there is a significant risk that gaps in charting may have skewed our results. Fortunately, our data consisted largely of objective numeric data, so there is limited concern about detection bias due to lack of standardization.

CONCLUSION

This study demonstrated that patients with CMV viremia tended to be older, to have lower body weight, and to be of Asian descent. D+/R– and D+/R+ serostatus were also more strongly associated with CMV viremia. The use and higher dosing of ATG also increased the risk of CMV even when we accounted for confounding variables. There was no difference in tacrolimus trough concentrations or weight-based MMF dosing between patients with and without CMV viremia. Finally, no difference in duration of prophylactic valganciclovir was observed.

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ON THE FRONT COVER

Trees Blanketed in Snow, Sault Ste Marie, Ontario

This photograph was taken by Mary Michelina Davies using an Apple iPhone. Mary was enjoying a sunny day while cross-country skiing near her home in Sault Ste Marie when she stopped to capture this image. She works at the Sault Area Hospital on a casual basis, having retired from full-time work in September 2017. Mary has 34 years of service to the hospital and 45 years of pharmacy practice. In her spare time, she likes going for walks, exercising with her fitness club via Zoom, and reading history and fiction. She occasionally travels to London, Ontario with her husband to visit their daughter, son-in-law, and 4 young grandchildren. They keep in touch with their grandchildren using WhatsApp when not in London. This summer, Mary and her husband travelled to the east coast with their daughter and family. They visited New Brunswick, Prince Edward Island, and Nova Scotia. During the winter, Mary enjoys watching Soo Greyhounds hockey games with her husband.

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the Journal. Winter-themed photographs are especially needed, so get your cameras out! If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to publications@cshp.ca.