Research Square

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Antithymocyte globulin dose and cytomegalovirus DNAemia in kidney transplant recipients: a retrospective cohort study of the dose–response relationship

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Abstract

Background

Cytomegalovirus (CMV) is a leading cause of morbidity and graft loss after kidney transplantation. Although antithymocyte globulin (ATG) induction is known to increase CMV risk, whether this effect is dose-dependent remains unclear in populations with high seroprevalence receiving universal prophylaxis. We evaluated the effect of ATG dose and other factors on CMV DNAemia, and the association of CMV with graft and patient survival.

Methods

We retrospectively reviewed 494 adult recipients who underwent kidney transplantation at a single centre between 2019 and 2024. Nearly all patients received 100 days of valganciclovir prophylaxis. CMV DNAemia was defined as detection of CMV DNA ≥ 80 copies/mL at least once during follow-up. Independent risk factors were identified by multivariable logistic regression.

Results

CMV DNAemia developed in 259 patients (52.4%). The DNAemia rate increased stepwise with ATG dose: 41.3% in basiliximab recipients and 44.9%, 61.8% and 65.0% across ATG dose tertiles (p for trend = 0.002). In multivariable analysis, each additional 100 mg of ATG increased the odds of DNAemia by 10% (OR 1.10; 95% CI 1.04–1.16). ATG-containing induction (OR 1.86; 1.20–2.89), donor age (OR 1.39 per 10 years; 1.21–1.61), hyperlipidaemia (OR 1.77; 1.11–2.83) and hypertension (OR 4.32; 1.46–12.73) were other independent risk factors. CMV infection requiring antiviral treatment was twice as frequent in recipients of kidneys from donors older than 43 years (27.1% vs 12.7%). CMV-related hospitalization was an independent risk factor for graft loss (OR 3.88; 2.28–6.59) and mortality (OR 2.41; 1.17–4.96). Mortality was four times higher when DNAemia began within the first four weeks than with later onset (20.9% vs 5.5%). Patients with CMV DNAemia had higher serum creatinine at 1 year (1.30 vs 1.10 mg/dL; $p < 0.001$).

Conclusions

ATG increases the risk of CMV DNAemia in kidney transplant recipients in a dose-dependent manner, and older donor age is the most consistent predictor of clinically significant infection. CMV infection requiring hospitalization is a strong, independent risk factor for graft loss and mortality. Individualizing the ATG dose and intensifying post-prophylaxis CMV monitoring are recommended for patients receiving high-dose ATG and those receiving kidneys from older donors.

Background

Cytomegalovirus (CMV) is the most common opportunistic viral pathogen after solid organ transplantation [1, 2]. In kidney transplant recipients, CMV may follow a broad clinical spectrum ranging from asymptomatic DNAemia to CMV syndrome and tissue-invasive disease [2, 3]. In addition to its direct effects, indirect effects such as acute rejection, opportunistic infections, post-transplant diabetes and cardiovascular events have been described [4, 5]. CMV infection is therefore regarded as an important determinant of long-term graft and patient survival [6, 7].

The strongest determinant of CMV risk is the serological status of the donor and recipient; the highest risk is seen in the group with a seropositive donor and a seronegative recipient (D+/R−) [2, 3]. However, in countries such as Türkiye, where adult seroprevalence exceeds 90% [8], most transplant recipients are D+/R+. In this group, infection usually arises from reactivation of latent virus or donor-derived superinfection, and the main factor determining risk is the depth of immunosuppression [1, 9]. In the cohort study by Law et al., D+/R+ recipients were shown to carry the highest risk of rapid early loss of kidney function [10].

T-cell-depleting induction agents such as antithymocyte globulin (ATG) are known to increase CMV risk [3, 11, 12]. However, whether this relationship is dose-dependent has been examined in only a limited number of studies, and much of the available data come from high-risk (D+/R−) patients who did not receive prophylaxis [13]. The effect of ATG dose in cohorts receiving universal prophylaxis, in which nearly all recipients are seropositive, is unknown. This information is of direct clinical relevance for individualizing the induction dose and planning post-prophylaxis monitoring.

In this study, in kidney transplant recipients from a population with high CMV seroprevalence, we aimed to evaluate (i) the effect of cumulative ATG dose on the risk of CMV DNAemia, (ii) other independent risk factors associated with CMV DNAemia and clinically significant CMV infection, and (iii) the association of the course of CMV infection with graft loss, mortality and graft function.

Methods

Study design and patients

This retrospective cohort study included recipients aged 18 years or older who underwent kidney transplantation at Gaziantep University Faculty of Medicine Hospital between 1 January 2019 and 31 December 2024. Patients younger than 18 years, those followed up outside our centre, those with insufficient data and those with a post-transplant follow-up of less than one month were not included. After exclusion of patients who did not meet these criteria, 494 patients were included in the analysis. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [14].

Immunosuppression and CMV prevention protocol

Immunosuppression and CMV prevention protocol
Induction therapy consisted of basiliximab, ATG or basiliximab plus ATG, given together with prednisolone according to immunological risk assessment. ATG was dosed according to body weight (mg/kg) and recorded as the total (cumulative) dose administered during induction. For maintenance, all patients received a triple regimen of tacrolimus, mycophenolate mofetil and prednisolone. At our centre, all recipients receive valganciclovir prophylaxis, adjusted for kidney function, for 100 days after transplantation. Plasma CMV DNA was monitored monthly during prophylaxis (first 3 months) and approximately every two weeks after prophylaxis ended; in patients with levels above the threshold, immunosuppression was reduced and/or antiviral treatment (intravenous ganciclovir or oral valganciclovir) was started according to the clinical picture (hybrid approach).

Definitions

Plasma CMV DNA was measured by quantitative real-time PCR using the artus CMV PCR kit (QIAGEN, Hilden, Germany), and results were reported in copies/mL. CMV DNAemia was defined as detection of CMV DNA ≥ 80 copies/mL at least once during post-transplant follow-up [15]. Clinically significant CMV infection was defined as infection requiring ganciclovir and/or valganciclovir treatment for CMV DNAemia. The onset of CMV DNAemia was recorded as the week after transplantation; positivity within the first 12 weeks was classified as early onset and positivity after 12 weeks as late onset. CMV relapse was defined as detection of CMV DNA ≥ 80 copies/mL again after DNAemia had become negative. CMV-related hospitalization refers to admissions for the diagnosis or treatment of CMV infection. Graft loss was defined as permanent return to dialysis and/or retransplantation, accepted as loss of graft function by decision of the nephrology council.

Data collection

Recipient demographics, comorbidities (hypertension, diabetes mellitus, hyperlipidaemia, chronic obstructive pulmonary disease, history of malignancy), aetiology of end-stage kidney disease, type and duration of pre-transplant dialysis, history of plasmapheresis, donor characteristics (age, living/deceased, relatedness), pre-transplant CMV IgG status of donor and recipient, induction and maintenance therapy including ATG dose, CMV prophylaxis, CMV DNA results, CMV treatment and hospitalization data were obtained from the hospital information system and patient records. C-reactive protein (CRP), complete blood count and serum creatinine were recorded before transplantation and at 1, 3, 6 and 12 months after transplantation. The lymphocyte/CRP ratio was calculated from the lymphocyte count and CRP measured at peak CMV DNAemia.

Statistical analysis

Normality of continuous variables was assessed with the Shapiro–Wilk test. Non-normally distributed variables were presented as median (interquartile range, IQR) and compared with the Mann–Whitney U test. Categorical variables were presented as number (percentage) and compared with Pearson's chi-square test or, when a cell had an expected count below 5, Fisher's exact test.

Multivariable logistic regression was performed to identify factors independently associated with CMV DNAemia. Variables significant in univariable analysis and those considered clinically important (recipient age, sex, diabetes mellitus and deceased donor) were entered into the model. Because of the strong association between ATG-containing induction and ATG dose, two separate models were built: Model 1 evaluated induction type in all patients, and Model 2 evaluated cumulative ATG dose (per 100 mg increase) in ATG recipients only. To illustrate the dose–response relationship, ATG dose was also divided into tertiles, and the trend in DNAemia rates was assessed with the linear-by-linear association test. In the primary models, the number of events (patients with the outcome) per variable exceeded 20 [16]. Model calibration was assessed with the Hosmer–Lemeshow test and discrimination with the area under the curve (AUC). The same models were repeated for the outcome of clinically significant CMV infection.

The ability of continuous variables to discriminate CMV DNAemia was examined by receiver operating characteristic (ROC) analysis; 95% confidence intervals for the AUC were calculated with the DeLong method [17], and optimal cut-off values were determined with the Youden index. Factors associated with graft loss and mortality were evaluated with logistic regression models adjusted for recipient age, donor age, deceased donor and diabetes mellitus. To assess the possible effect of incomplete follow-up, the proportions of patients with a CMV DNA result at follow-up time points were compared between groups. Complete-case analysis was used for missing data. A p value < 0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA) and Python 3.11 (SciPy). Details on the use of a large language model in preparing the manuscript are given in the Declarations (Acknowledgements).

Results

Patient characteristics and course of CMV DNAemia

A total of 494 recipients were included. The median recipient age was 43 (32–54) years, and 65.8% were male. Of the donors, 93.1% were living donors, and the median donor age was 45 (34–56) years. Of the recipients, 487 (98.6%) were D+/R+, six (1.2%) were D+/R − and one (0.2%) was D−/R+. As induction therapy, 298 patients (60.3%) received ATG + prednisolone, 126 (25.5%) basiliximab + prednisolone, 63 (12.8%) basiliximab + ATG + prednisolone and two (0.4%) prednisolone only. In the 361 ATG recipients, the median cumulative ATG dose was 900 (550–1200) mg. Baseline characteristics are presented in Table 1.

Table 1
Recipient, donor and transplant characteristics according to CMV DNAemia status

Characteristic	All patients (n = 494)	No CMV DNAemia (n = 235)	CMV DNAemia (n = 259)	p
Recipient age, years	43 (32–54)	43 (33–54)	43 (30–54)	0.486
Male sex	325 (65.8)	154 (65.5)	171 (66.0)	0.908
Married	386 (78.1)	189 (80.4)	197 (76.1)	0.241
Foreign national	111 (22.5)	71 (30.2)	40 (15.4)	< 0.001
Current smoker	197 (40.0)	93 (39.7)	104 (40.2)	0.926
BMI, kg/m²	25.0 (22.0–28.0)	25.0 (22.0–28.0)	25.0 (22.0–29.0)	0.893
Diabetes mellitus	196 (39.7)	93 (39.6)	103 (39.8)	0.965
Hypertension	472 (95.5)	218 (92.8)	254 (98.1)	0.004
Hyperlipidaemia	126 (25.5)	49 (20.9)	77 (29.7)	0.024
COPD	37 (7.5)	13 (5.5)	24 (9.3)	0.115
History of malignancy	6 (1.2)	1 (0.4)	5 (1.9)	0.219
Cause of kidney failure †				**0.254**
Diabetes mellitus	103 (20.9)	59 (25.1)	44 (17.0)	
Hypertension	122 (24.7)	52 (22.1)	70 (27.0)	
Glomerulonephritis	43 (8.7)	17 (7.2)	26 (10.0)	
Polycystic kidney disease	17 (3.4)	9 (3.8)	8 (3.1)	
Nephrolithiasis	15 (3.0)	9 (3.8)	6 (2.3)	
Pregnancy-related	8 (1.6)	3 (1.3)	5 (1.9)	
Other/unknown	186 (37.7)	86 (36.6)	100 (38.6)	
Pre-transplant dialysis				**0.162**
Pre-emptive	176 (35.6)	80 (34.0)	96 (37.1)	
Haemodialysis	288 (58.3)	145 (61.7)	143 (55.2)	
Peritoneal dialysis	30 (6.1)	10 (4.3)	20 (7.7)	

Data are presented as median (IQR) or n (%). Mann–Whitney U, chi-square or Fisher's exact test. † Contains cells with an expected count below 5. Donor–recipient age difference: donor age − recipient age. BMI: body mass index; COPD: chronic obstructive pulmonary disease; ATG: antithymocyte globulin.

Characteristic	All patients (n = 494)	No CMV DNAemia (n = 235)	CMV DNAemia (n = 259)	p
Dialysis vintage, weeks	4 (0–50)	4 (0–50)	3 (0–52)	0.857
Pre-transplant plasmapheresis	94 (19.0)	40 (17.0)	54 (20.8)	0.279
Donor age, years	45 (34–56)	41 (31–52)	50 (38–59)	< 0.001
Donor–recipient age difference, years	2 (− 10–19)	−1 (− 14–8)	5 (− 6–22)	< 0.001
Deceased donor	34 (6.9)	13 (5.5)	21 (8.1)	0.259
Related donor	324 (65.6)	158 (67.2)	166 (64.1)	0.463
Induction therapy †				**0.010**
Basiliximab + prednisolone	126 (25.5)	74 (31.5)	52 (20.1)	
ATG + prednisolone	298 (60.3)	130 (55.3)	168 (64.9)	
Basiliximab + ATG + prednisolone	63 (12.8)	26 (11.1)	37 (14.3)	
Prednisolone only	2 (0.4)	2 (0.9)	0 (0.0)	
ATG dose, mg (ATG recipients)	900 (550–1200)	700 (492–1100)	950 (600–1300)	< 0.001
Recipient CMV IgG negative	6 (1.2)	4 (1.7)	2 (0.8)	0.431
Donor CMV IgG negative	1 (0.2)	0 (0.0)	1 (0.4)	1.000
No CMV prophylaxis	7 (1.4)	5 (2.1)	2 (0.8)	0.266
Graft loss	102 (20.6)	40 (17.0)	62 (23.9)	0.058
Mortality	47 (9.5)	21 (8.9)	26 (10.0)	0.677

Data are presented as median (IQR) or n (%). Mann–Whitney U, chi-square or Fisher's exact test. † Contains cells with an expected count below 5. Donor–recipient age difference: donor age − recipient age. BMI: body mass index; COPD: chronic obstructive pulmonary disease; ATG: antithymocyte globulin.

CMV DNAemia developed in 259 patients (52.4%), and 70.5% of cases occurred after the end of prophylaxis (median week 23; IQR 4–29). The median peak viral load was 645 (181–2918) copies/mL. Among patients with DNAemia, 101 (39.0%) developed clinically significant infection requiring antiviral treatment (median peak viral load 4085 [1456–11 565] copies/mL); 80 patients (30.9%) were hospitalized because of CMV (median length of stay 8 [6–15] days).

ATG dose and CMV DNAemia

The rate of CMV DNAemia increased in parallel with the intensity of T-cell depletion: 41.3% with basiliximab, 56.4% with ATG + prednisolone and 58.7% with basiliximab + ATG. Among ATG recipients, the cumulative dose was significantly higher in those who developed DNAemia (median 950 vs 700 mg; $p < 0.001$). The DNAemia rate increased stepwise across ATG dose tertiles: 44.9% with ≤ 650 mg, 61.8% with 651–1100 mg and 65.0% with > 1100 mg (p for trend = 0.002) (Fig. 1). The DNAemia rate was 65.2% in patients receiving more than 700 mg of ATG and 43.6% in those receiving 700 mg or less.

In multivariable analysis, ATG-containing induction approximately doubled the odds of CMV DNAemia independently of other risk factors (OR 1.86; 95% CI 1.20–2.89; Table 2, Model 1). Among ATG recipients, each additional 100 mg increased the odds of DNAemia by 10% (OR 1.10; 1.04–1.16; $p < 0.001$; Model 2). When the model was additionally adjusted for body mass index, the effect of ATG dose was unchanged (OR 1.10 per 100 mg; 95% CI 1.04–1.16; p = 0.001). Accordingly, the odds of DNAemia in a patient receiving 1200 mg of ATG are approximately 1.6 times higher than in a patient receiving 700 mg. Model fit was adequate (Hosmer–Lemeshow p = 0.272 and p = 0.635).

Table 2
Factors associated with CMV DNAemia: univariable and multivariable logistic regression analysis

Variable	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Model 1: all patients				
Recipient age (per 10 years)	0.95 (0.83–1.08)	0.398	0.85 (0.73–0.99)	0.034
Male sex	0.97 (0.66–1.41)	0.859	1.06 (0.71–1.59)	0.761
Foreign national	0.42 (0.27–0.65)	< 0.001	0.58 (0.36–0.94)	0.026
Diabetes mellitus	0.99 (0.69–1.42)	0.944	1.03 (0.67–1.58)	0.886
Hypertension	3.52 (1.26–9.83)	0.017	4.32 (1.46–12.73)	0.008
Hyperlipidaemia	1.58 (1.05–2.39)	0.030	1.77 (1.11–2.83)	0.017
Donor age (per 10 years)	1.39 (1.22–1.59)	< 0.001	1.39 (1.21–1.61)	< 0.001
Deceased donor	1.49 (0.73–3.04)	0.279	1.59 (0.71–3.54)	0.256
ATG-containing induction	1.87 (1.24–2.82)	0.003	1.86 (1.20–2.89)	0.006
Model 2: ATG recipients				
Recipient age (per 10 years)	0.90 (0.77–1.06)	0.210	0.82 (0.68–0.99)	0.035
Male sex	0.85 (0.55–1.33)	0.480	0.72 (0.44–1.17)	0.185
Foreign national	0.43 (0.25–0.71)	0.001	0.55 (0.31–0.96)	0.036
Diabetes mellitus	0.78 (0.51–1.19)	0.247	0.81 (0.49–1.33)	0.401
Hypertension	2.36 (0.68–8.21)	0.177	2.83 (0.75–10.66)	0.123
Hyperlipidaemia	1.74 (1.06–2.86)	0.030	2.04 (1.16–3.59)	0.014
Donor age (per 10 years)	1.39 (1.19–1.62)	< 0.001	1.36 (1.15–1.61)	< 0.001
Deceased donor	1.30 (0.61–2.74)	0.495	1.63 (0.68–3.91)	0.277
ATG dose (per 100 mg)	1.09 (1.04–1.14)	< 0.001	1.10 (1.04–1.16)	< 0.001

Model 1: n = 487, patients with CMV DNAemia = 257; 5 patients with missing induction data and 2 patients receiving prednisolone only were excluded. Model 2: n = 361, patients with CMV DNAemia = 205. Model 1: Nagelkerke R^2=0.152; Hosmer–Lemeshow p = 0.272; AUC 0.69 (0.64–0.74). Model 2: Nagelkerke R^2=0.178; Hosmer–Lemeshow p = 0.635; AUC 0.71 (0.66–0.77). OR: odds ratio; CI: confidence interval; ATG: antithymocyte globulin.

Other independent risk factors

Older donor age was the most consistent risk factor for both DNAemia and clinically significant infection. In multivariable analysis, each 10-year increase in donor age increased the odds of DNAemia by 39% (OR 1.39; 1.21–1.61; $p < 0.001$). The DNAemia rate was 64.3% in recipients of kidneys from donors older than 43 years and 38.6% in recipients of kidneys from younger donors, and infection requiring antiviral treatment was more than twice as frequent (27.1% vs 12.7%; $p < 0.001$). Donor age also remained an independent risk factor for clinically significant CMV infection (OR 1.35; 1.14–1.60; $p < 0.001$) (Additional file 1: Table S1).

Hyperlipidaemia (OR 1.77; 1.11–2.83) and hypertension (OR 4.32; 1.46–12.73) were also independently associated with DNAemia, whereas younger recipient age was associated with higher risk (OR 0.85 per 10 years; 0.73–0.99) (Table 2). A donor–recipient age difference greater than 15 years discriminated DNAemia with a specificity of 83.0% (Additional file 1: Table S2). Although DNAemia was less frequent in foreign nationals, follow-up measurements were significantly less complete in these patients, and the difference disappeared when the analysis was restricted to patients with complete follow-up ($p = 0.256$; Additional file 1: Table S3).

Impact of CMV infection on graft and patient survival

During follow-up, graft loss occurred in 102 patients (20.6%) and 47 patients (9.5%) died. CMV-related hospitalization was the strongest CMV-associated predictor of graft loss and mortality. In hospitalized patients, graft loss was three times (45.0% vs 14.5%) and mortality three times (18.8% vs 6.1%) as frequent, and CMV relapse was significantly more frequent (58.8% vs 35.2%) ($p \leq 0.004$ for all). After adjustment for age, donor age, donor type and diabetes, CMV-related hospitalization increased the odds of graft loss 3.9-fold (OR 3.88; 2.28–6.59) and the odds of death 2.4-fold (OR 2.41; 1.17–4.96) (Table 3). Graft loss was numerically more frequent in patients who developed CMV DNAemia (23.9% vs 17.0%; $p = 0.058$), but in the adjusted analysis the presence of DNAemia alone was not an independent risk factor (OR 1.29; 0.81–2.05). Transplantation from a deceased donor was also an independent risk factor for graft loss (OR 2.99; 1.39–6.45) and mortality (OR 9.21; 4.02–21.08). Outcomes according to treatment approach are presented in Additional file 1: Table S4.

Table 3
Factors associated with graft loss and mortality

Variable	Univariable OR (95% CI)	p	Adjusted OR (95% CI)	p
Graft loss				
CMV DNAemia (≥ 80 copies/mL)	1.53 (0.98–2.39)	0.059	1.29 (0.81–2.05)	0.286
CMV-related hospitalization	4.31 (2.58–7.21)	< 0.001	3.88 (2.28–6.59)	< 0.001
Recipient age (per 10 years)	0.86 (0.73–1.01)	0.064	0.87 (0.73–1.04)	0.131
Donor age (per 10 years)	1.21 (1.04–1.41)	0.016	1.24 (1.06–1.47)	0.009
Deceased donor	2.58 (1.24–5.35)	0.011	2.99 (1.39–6.45)	0.005
Diabetes mellitus	0.71 (0.45–1.12)	0.143	0.83 (0.51–1.37)	0.468
Mortality				
CMV DNAemia (≥ 80 copies/mL)	1.14 (0.62–2.08)	0.677	0.95 (0.49–1.83)	0.878
CMV-related hospitalization	2.75 (1.41–5.37)	0.003	2.41 (1.17–4.96)	0.017
Recipient age (per 10 years)	1.09 (0.88–1.36)	0.435	1.12 (0.88–1.44)	0.352
Donor age (per 10 years)	1.00 (0.81–1.24)	0.965	1.12 (0.89–1.40)	0.329
Deceased donor	7.76 (3.57–16.83)	< 0.001	9.21 (4.02–21.08)	< 0.001
Diabetes mellitus	1.14 (0.62–2.10)	0.672	1.13 (0.58–2.22)	0.720

n = 494; patients with graft loss = 102; deaths = 47. CMV DNAemia and CMV-related hospitalization were evaluated in separate models, both adjusted for recipient age, donor age, deceased donor and diabetes mellitus. ORs for the other variables are from the CMV DNAemia model.

Time of onset, lymphocyte/CRP ratio and graft function

Mortality was approximately four times higher in DNAemia starting within the first four weeks than in DNAemia starting after 12 weeks (20.9% vs 5.5%; p < 0.001), and relapse was also more frequent (53.7% vs 36.8%; p = 0.018) (Table 4). A low lymphocyte/CRP ratio at peak DNAemia was significantly associated with relapse (median 0.12 vs 0.20; p = 0.011) and graft loss (0.07 vs 0.20; p < 0.001).

Table 4
Outcomes in patients with CMV DNAemia according to time of onset and hospitalization

Time of onset (after transplantation)	CMV relapse	Graft loss	Mortality
0–4 weeks	36/67 (53.7%)	18/67 (26.9%)	14/67 (20.9%)
5–12 weeks	6/9 (66.7%)	4/9 (44.4%)	2/9 (22.2%)
> 12 weeks	67/182 (36.8%)	39/182 (21.4%)	10/182 (5.5%)
p	0.018	0.219	< 0.001
CMV-related hospitalization			
No hospitalization	63/179 (35.2%)	26/179 (14.5%)	11/179 (6.1%)
Hospitalized	47/80 (58.8%)	36/80 (45.0%)	15/80 (18.8%)
p	< 0.001	< 0.001	0.004

Data are presented as n/N (%). One patient with unknown time of onset was excluded. Chi-square test.

CMV DNAemia was associated with lower leukocyte counts throughout follow-up, lower lymphocyte counts from month 3 onwards and worse graft function (Additional file 1: Table S5). Serum creatinine was significantly higher in patients who developed DNAemia at all follow-up time points from month 1 onwards. At month 12, median creatinine was 1.30 (1.00–1.70) vs 1.10 (0.90–1.43) mg/dL ($p < 0.001$), and the proportion of patients with creatinine above 1.5 mg/dL was almost twice as high in those who developed DNAemia (34.2% vs 19.4%; $p = 0.002$).

Discussion

This study shows that, in a cohort receiving universal prophylaxis in which nearly all recipients were seropositive, ATG increases the risk of CMV DNAemia in a dose-dependent manner. The risk of DNAemia increased stepwise with ATG compared with basiliximab, and with cumulative dose within the ATG group, with each additional 100 mg raising the odds of DNAemia by 10%. Older donor age was the most consistent risk factor for both DNAemia and clinically significant infection. CMV-related hospitalization increased the odds of graft loss approximately fourfold and the odds of death 2.4-fold. In addition, CMV DNAemia was associated with worse graft function throughout the first year after transplantation.

The increase in CMV risk with ATG has been demonstrated in international guidelines and comparative studies [2, 3, 12]. However, the dose dependence of this effect has previously been examined mainly in high-risk recipients not receiving prophylaxis [13]. Our study shows that the dose–response relationship is also evident in recipients who receive prophylaxis and are predominantly D+/R+. The stepwise increase across tertiles and the effect observed with dose as a continuous variable in multivariable

analysis support the view that this relationship reflects a true biological gradient. The profound and prolonged suppression of T-cell counts by ATG means that CMV-specific cellular immunity may not yet have recovered when prophylaxis ends, predisposing to reactivation [1]. CMV infection requiring antiviral treatment was also more frequent in ATG recipients (16.7% with basiliximab vs 21.5–23.8% with ATG; multivariable OR 1.30), but this difference was not statistically significant. A likely reason is that the number of patients requiring antiviral treatment (n = 101) was considerably smaller than the number who developed DNAemia (n = 259), making the difference harder to demonstrate statistically. In light of these findings, it may be advisable to determine the ATG dose according to the patient's immunological risk and to monitor CMV DNA more frequently after prophylaxis, particularly in patients receiving more than 700 mg of ATG.

In our study, older donor age was an independent and consistent risk factor for both DNAemia and infection requiring antiviral treatment; clinically significant infection was more than twice as frequent in recipients of kidneys from donors older than 43 years. This finding is consistent with meta-analytic data identifying donor age as a risk factor [11]. A higher latent viral burden in grafts from older donors and inflammation due to ischaemia–reperfusion injury facilitating reactivation are possible mechanisms. Transplantation from deceased donors has been associated with higher CMV risk in the literature [18]; the low proportion of deceased donors in our cohort (6.9%) may have limited the power to demonstrate this association. In contrast to studies reporting older recipient age as a risk factor [19], DNAemia was more frequent in younger recipients in our cohort; this may reflect the more intensive induction and monitoring applied to younger recipients.

Hyperlipidaemia and hypertension were independently associated with CMV DNAemia. CMV infection is known to be associated with endothelial injury and accelerated atherosclerosis [4, 20]. Our findings suggest a possible bidirectional interaction between the metabolic and vascular risk profile and CMV; because 95.5% of the cohort had hypertension, the effect size for this variable should be interpreted in light of its wide confidence interval.

One of the most important clinical findings of our study is that the prognostic burden of CMV depends on the clinical severity of infection rather than on the presence of DNAemia. CMV-related hospitalization increased the odds of graft loss approximately fourfold and the odds of death 2.4-fold, independently of conventional risk factors. CMV infection has previously been associated with long-term graft loss and mortality [6, 7, 21, 22]. Reischig et al. also reported that the effect on graft survival depends on the level of viral load [23]. In our cohort, approximately half of DNAemia episodes had low viral loads and did not require treatment, which explains why the presence of DNAemia alone did not emerge as an independent risk factor. Universal prophylaxis followed by a hybrid monitoring approach may have enabled early management of low-level replication [2]. The findings of Law et al., showing an adverse effect of CMV serostatus on early graft function in D+/R+ recipients, also support close monitoring of this group [10]. These findings suggest that recipients hospitalized because of CMV should be regarded as a high-risk group requiring intensive nephrological follow-up after discharge.

CMV DNAemia was also associated with worse graft function throughout the first year: at month 12, the proportion of patients with creatinine above 1.5 mg/dL was almost twice as high in those who developed DNAemia. This suggests that an effect on graft loss may emerge with longer follow-up. The fourfold higher mortality in early-onset DNAemia suggests that replication developing despite prophylaxis may be a marker of deeper immunosuppression or early post-transplant complications. The occurrence of 70% of cases after prophylaxis is consistent with literature showing that this is the highest-risk period [2, 3]; data on the prognosis of late-onset infection are not yet consistent [24, 25].

A low lymphocyte/CRP ratio at peak DNAemia was strongly associated with relapse and graft loss. This simple and inexpensive ratio, which reflects both impaired cellular immunity and increased systemic inflammation, is known to be associated with poor prognosis in various clinical settings [26, 27]. Our findings suggest that this ratio may be a practical biomarker for identifying kidney transplant recipients with CMV infection who require close monitoring.

Strengths and limitations

The strengths of our study include a large cohort managed with a standardized prophylaxis protocol, demonstration of a dose–response relationship by examining ATG dose as both a continuous and a categorical variable, a separate analysis for clinically significant infection, and systematic assessment of possible detection bias. The retrospective, single-centre design limits causal inference. Because event dates were not available, time-to-event analysis could not be performed; and although ATG was dosed by body weight, patient weight was not available in the database, so cumulative dose (mg) was used in the analyses and could not be standardized as mg/kg. Incomplete follow-up measurements in foreign nationals who returned to their home countries after transplantation may have led to underestimation of the frequency of DNAemia in these patients; indeed, data from the United States show no difference in CMV frequency by nationality [28]. CMV DNA results were not converted to international units (IU/mL) [2]. Graft loss was defined by nephrology council decision rather than by biopsy. The small number of D+/R− patients limits the generalizability of the findings to this high-risk group.

Conclusions

ATG increases the risk of CMV DNAemia in kidney transplant recipients in a dose-dependent manner, and this effect is evident despite universal prophylaxis. Older donor age is the most consistent predictor of clinically significant CMV infection. CMV infection requiring hospitalization is a strong and independent risk factor for graft loss and mortality, and CMV DNAemia is associated with worse graft function throughout the first year. These findings support individualizing the ATG dose and intensifying post-prophylaxis CMV monitoring in patients receiving high-dose ATG or kidneys from older donors. Prospective multicentre studies incorporating mg/kg dosing and time-to-event outcomes are needed to confirm these recommendations.

Abbreviations

ATG
Antithymocyte globulin
AUC
Area under the curve
CI
Confidence interval
CMV
Cytomegalovirus
CRP
C-reactive protein
D+/R+
Donor seropositive/recipient seropositive
D+/R−
Donor seropositive/recipient seronegative
IQR
Interquartile range
OR
Odds ratio
PCR
Polymerase chain reaction
ROC
Receiver operating characteristic
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Gaziantep University Clinical Research Ethics Committee (decision date: 9 April 2025; decision no: 2025/95). Owing to the retrospective design of the study, the ethics committee waived the requirement for informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and analysed during the current study is not publicly available owing to patient confidentiality but is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DFU: data collection, analysis, first draft. ÖU: interpretation of nephrological data, critical revision. AÖM: study design, supervision, critical revision. KK and EG: supervision, critical revision. AB: data collection, supervision. All authors read and approved the final manuscript.

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Figures

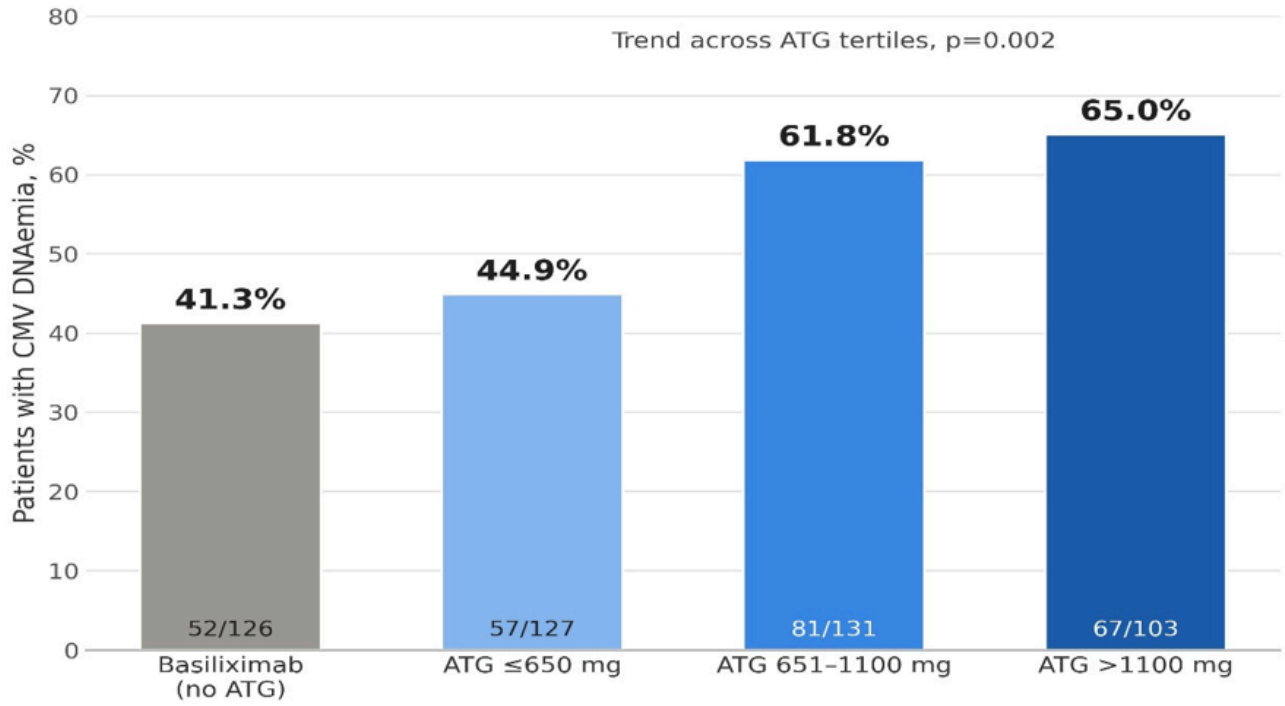


Figure 1

Proportion of patients with CMV DNAemia according to induction therapy and cumulative ATG dose. ATG recipients were divided into dose tertiles (≤650 mg, 651–1100 mg, >1100 mg). Values within the bars are n/N. The trend across tertiles was assessed with the linear-by-linear association test. ATG: antithymocyte globulin.

Supplementary Files

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