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Age matters. Older age as a risk factor for CMV reactivation in the CMV serostatus positive kidney transplant recipient.

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Abstract

Purpose: Evaluate risk factors for cytomegalovirus (CMV) reactivation during the first year after kidney transplantation in the CMV seropositive older recipient.

Methods: Retrospective single-center study.

Results: Between 2011-2015, 91 patients ≥65 years received a kidney transplant; these were matched with 91 controls, aged 40-60. Risk of CMV reactivation in the CMV seropositive recipients was analyzed. Sixty-three older and 54 younger recipients were included; 50% had received CMV-directed prophylaxis. CMV reactivation was significantly more frequent in the older group (71.4% vs 44.4%, p=0.003) and occurred earlier (p=0.003). A multivariate model showed that only age was associated with CMV reactivation (OR 2.48, p=0.03). After excluding patients that received thymoglobulin, older age group remained the only risk factor of CMV reactivation (OR 3.81, p=0.014). Recurrent event analysis showed that the older cohort had an HR of 1.94 (p=0.01) of CMV viremia; there was significant episode-cohort interaction (p<0.01). While the older group had a higher risk of infection (HR=2.43), after the initial episode the relative hazards were approximately equal (HR=1.08, at period 2).

Conclusion: This suggests that it is key to specifically avoid the first episode of reactivation. Universal prophylaxis or a hybrid prophylaxis model should be considered in the CMV seropositive kidney transplant recipient aged ≥65 years.

Keywords

Older Adults; Cytomegalovirus; Kidney Transplantation; Infection

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Introduction

Older adults are at higher risk of infectious complications[1,2] due to immunosenescence, frailty, functional impairment and comorbidities. In older kidney transplant (KT) patients, immunosuppressive therapies further increase the risk of infections and chances of a poor outcome[3-6]. Cytomegalovirus (CMV) infection is one of the most frequent and severe infectious complications after kidney transplantation[7]. Older KT recipients have a high prevalence of CMV seropositivity and accordingly are a growing population at risk for this infectious complication [8-10].

CMV seronegative KT recipients that receive an organ from a seropositive donor are at highest risk for CMV viremia and disease and typically receive universal prophylaxis with an anti-CMV active antiviral, usually ganciclovir or valganciclovir[7]. KT recipients at intermediate risk for CMV infection (CMV seropositive recipients of a seronegative or seropositive organ) can receive either universal prophylaxis or undergo pre-emptive therapy consisting of weekly CMV polymerase chain reaction (PCR) monitoring for 3 months and receipt of antiviral therapy only if viremia is documented[7].

Several studies compared pre-emptive therapy versus universal prophylaxis in KT recipients at intermediate risk for CMV[11-22], but there is a gap in knowledge regarding which is the best approach in the growing population of older seropositive solid organ transplant recipients. We previously described an increased risk of CMV infection in older adults compared to younger adults after KT[23]. In fact, older adults were twice as likely to reactivate CMV compared to the younger group (p=0.012). We therefore performed a study to determine whether age is a risk for CMV reactivation in the CMV seropositive (CMV R+) KT population, as this would potentially influence the type of preventive approach employed for older seropositive KT recipients.

Material and methods

Study design and Study Center

This was a single-center retrospective cohort study of kidney-only transplants performed between 2011-2015 at Duke University Medical Center in Durham, NC; 551 KT were performed during the study period. Older KT recipients were defined as adults aged ≥65 years; younger KT recipients or “controls” were 40-60 years of age. The study was approved by the Duke University Health System Institutional Review Board for Clinical Investigation (Pro00076804).

Patient cohorts

An institutional tool, the Duke Enterprise Data Unified Content Explorer (DEDUCE)[24], was used to identify all KT recipients during the 5-year study period and their age. All 91 patients aged ≥65 that received a kidney-only transplant were included. Of the 257 potential controls aged 40-60 years, 91 patients were randomly matched 1:1 to the older KT recipients by year of transplantation, sex and, if possible, race. For this analysis only the CMV R+ subpopulation was included.

Antiviral prophylaxis for CMV recipient positive recipients

Antiviral prophylaxis for CMV R+ patients consisted of pre-emptive monitoring with weekly CMV PCR tests for 3 months and initiation of antiviral therapy (ganciclovir or valganciclovir) in patients with a CMV viral load of 450 IU/ml or above. CMV R+ recipients that received anti-thymocyte globulin induction received universal prophylaxis with ganciclovir/valganciclovir for 180 days followed by CMV PCR monitoring every 2 weeks for a minimum of 3 months.

Data Extraction and CMV definitions

Demographic, clinical, microbiological and outcome data were extracted manually from the medical charts. Data collected were managed using REDCap™ electronic data capture tool hosted at Duke[25]. Infection data collection included information about infectious syndromes and PCR. Standard CMV definitions and definitions per CDC/NSHN as described elsewhere were used[26,27]. At our institution, the threshold of detection of CMV is 137 IU/ml and this was used to define a positive CMV PCR, the primary endpoint of the study. Our secondary endpoint was clinically significant CMV disease defined as CMV syndrome, tissue-invasive disease or a CMV PCR of 450 IU/ml, all of which resulted in initiation of antiviral therapy. A comprehensive list of previously identified risk factors for CMV reactivation[28,29]or factors thought to be of clinical importance in the authors' views was used for the risk analysis.

Statistical Analysis

Descriptive results are shown as total numbers/percentages, mean/standard deviations (SD) and medians/interquartile range (IQR). Differences between groups were analyzed using the chi-square goodness-of-fit or t-test. The analysis of CMV infection (including any CMV viremia over the above mentioned threshold) was parameterized in several ways, each assessing different aspects of the disease process; presence-absence over specific time periods, time to first CMV infection, number of episodes of CMV viremia; each estimated by different models: Chi-square (for tests of proportions), time to event (for assessment of time to CMV infection post-transplant), Poisson regression (to assess group differences in number of infections). Several analyses were performed. First, the difference by age group of any versus no CMV infection; second, the difference in the total number of episodes within a period. Third, a multivariable prediction model for CMV was developed, combining the two age cohorts to assess which set of variables best predict CMV during the first year. A sub-analysis was performed excluding patients that received thymoglobulin as they were considered at high risk for CMV reactivation and had received universal CMV prophylaxis followed by preemptive monitoring as outlined above. Time to first CMV viremia post-transplant was tested by Kaplan-Meier techniques and the log-rank test. Patients were censored at death, or at the one-year mark after transplant, whichever occurred first. Marginal modeling for recurrent events was used to analyze recurrent episodes of CMV reactivation. Statistical analysis was performed using R studio (Version 1.1.463) for R.

Results

Baseline characteristics

The total cohort included 117 CMV R+ kidney transplant recipients, including 63 (53.85%) older and 54 (46.15%) younger adults. Baseline characteristics are shown in Table 1.

CMV viremia – Primary endpoint

Forty-five older adults (71.43%) had at least one positive CMV PCR test compared to 24 (44.44%) of the younger adults (p=0.003). The odds of an older adult having a positive CMV test was 3.13 times higher (95% CI 1.45, 6.72) than the odds of someone of the younger cohort. The total number of episodes of any CMV viremia was higher in the older compared to the younger cohort, although not statistically significant; 69 versus 49 episodes (p=0.07). See Figure 1. Cox regression analysis showed a hazard ratio (HR) of 2.30 (95% CI 1.40, 3.80) of an episode of CMV in the older CMV R+ age group (p=0.001). Time to first viremia by age group is shown in Figure 2 (p=0.003), median time to first positivity was 68 days in the older group (IQR 7, 109) and 96 days in the younger group (IQR 25, 215.5).

A univariate analysis of variables suspected to be risk factors for CMV reactivation for the whole cohort is shown in Table 2. All variables with a $p \leq 0.1$ were carried forward into the multivariate model. Results of the multivariate model are shown in Table 3. *Age group was the only variable significantly associated with CMV reactivation*, with the older cohort having an odds of 2.48 (95% CI 1.10, 5.72) of CMV reactivation (p=0.03).

Clinically significant CMV disease – Secondary Endpoints

There was only one episode of CMV syndrome in the older group, no tissue-invasive disease was documented. Additionally, no significant difference between groups was observed in number of patients with a CMV PCR above the pre-established threshold of 450 IU/ml: 30 older (47.6%) and 22 younger adults (40.7), p=0.459.

Non-anti-thymoglobulin cohorts

A total of 77 patients (65.8%) remained after removing KT recipients that had received thymoglobulin during the first year. Table 4 shows the result of the univariate analysis of risk factors for CMV reactivation. The multivariate analysis was only done for the group with any positive CMV PCR (i.e. ≥137 IU/ml), that is 77 patients. Older age was associated with having a positive CMV PCR with an OR of 3.81 (95% CI 1.33, 11.43), p=0.0140, ß coefficient 1.34.

Recurrent-event analysis

Marginal models showed that older adults had a HR of CMV viremia of 1.94 (95% CI 1.15, 2.78) when compared to the younger cohort (p=0.0131). There was significant episode-cohort interaction (p<0.001), see Figure 3. The two groups differed in the risk of the 1st episode (HR=2.45). However, for subsequent episodes, the HR was near unity (HR=1.14 for the second episode), indicating no difference in risk. When removing the patients that received thymoglobulin the significant episode-cohort interaction persisted (p<0.001).

Discussion

Our results confirm that age is an important risk factor for CMV reactivation in the older (age 65 years or older) KT population. In fact, the odds of the older KT population having a positive CMV PCR in the first year after transplantation was 3.13 times (95% CI 1.45, 6.72) more likely than their younger peers (aged 40-60). Further, one episode of CMV reactivation led to a higher risk of subsequent episodes of CMV reactivation and treatment.

Others studies have also found age to be associated with CMV reactivation risk in CMV seropositive patients albeit with a HR of 1.02 (95% CI 1.01, 1.04) and in a younger (mean age 53.4 years) cohort [20]. D+/R+ KT recipients aged 55 years and older undergoing pre-emptive monitoring and with CMV reactivation had poorer 5-year survival than those without CMV reactivation[16]. Additionally, and mirroring our experience, most infections took place in the first 6 months after transplantation[16,23].

CMV is thought to be one of the drivers of the pro-inflammatory process that goes along with aging, also known as “inflammaging” [30]. CMV has been associated with frailty and mortality[31,32] by a series of mechanisms that involve T-cell expansion, increase in the production of cytokines and the state of chronic inflammation. These factors are associated with other comorbidities e.g. cardiovascular disease, diabetes mellitus, autoimmune diseases and other infectious processes. While it is not possible to prevent CMV seropositivity in the older KT candidate, it is possible to change CMV prevention protocols to reduce the risk of CMV reactivation after KT.

We also found that the older cohort had a significantly shorter time to CMV viremia and, while not reaching statistical significance (p=0.07), more episodes of CMV reactivation occurred in this group. While the presence of diabetes mellitus, a history of prior transplant and basiliximab induction therapy were associated with CMV viremia in the univariate model, only older age group remained significant in the multivariate analysis.

When applying the 450 IU/ml cut-off, only a history of prior transplantation was significantly associated with the development of CMV viremia in the non-anti-thymoglobulin group. A clinical threshold of CMV viremia has not yet been defined. This is mainly due to a lack of a reference range and viral load values not being comparable between different assays[29,28,33]. We set the threshold for this study at 450 IU/ml because that is the cut-off where treatment for CMV viremia at our institution is initiated. The above-mentioned meta-analysis set their cut-off at 400 IU/ml[22]. One could argue that the results from the different studies are not directly comparable and that the absence of a defined threshold make these results difficult to interpret. Additionally, low-level viremia is often seen in immunocompromised transplant recipients that present with severe infections[34]. For this reason, we included several non-CMV infections syndromes (bacteremia and pneumonia) in our analysis. We did not find a significant association between these infections and CMV viremia in our models. Other authors showed that CMV prophylaxis in solid organ transplant recipients decreases the risk of other infections[35] and that CMV infection increases the risk of subsequent bacterial infection[36], hence preventing CMV reactivation could also diminish the risk of bacterial infections. Although this analysis was

outside the scope of our study, these literature findings reinforce the importance of preventing CMV reactivation.

A unique finding of our study is that the first CMV reactivation portends an increased risk for subsequent reactivations, emphasizing the need to avoid that initial episode of CMV reactivation. Taken together, our findings raise several questions. Most importantly, should we use universal prophylaxis in older CMV seropositive kidney transplant recipients given their “high risk” of reactivating CMV and given that avoiding that first CMV reactivation in older adults may be critical. Although very effective in the CMV R+ population[12,17], universal prophylaxis does come with financial as well as non-monetary cost which may be accentuated in the adult patient[37]. For example, a decline in renal function[15,38] and leukopenia which is a relatively common side effect of valganciclovir[39-41], is also a common problem in older KT recipients[41]. Further, the routine addition of valganciclovir to the medical regimen would further contribute to polypharmacy, another source of morbidity.

While our study is limited owing to its single-center, retrospective nature, 12 months follow up and sample size, it does raise important new questions regarding optimal CMV prophylaxis strategies in older KT recipients, a growing subpopulation of KT recipients underrepresented in prior studies.

Future directions should include multicenter trials comparing universal prophylaxis versus pre-emptive therapy or a hybrid model in the older CMV R+ transplant recipient population, as well as immunologic studies to better understand the specific mechanisms that predispose older patients to reactivate CMV [42,43,7]. Finally, frailty[31] and resilience should be included as endpoints of special interest in this patient population, with the aim of avoiding CMV reactivation and improving functional status and outcomes for older adults after KT.

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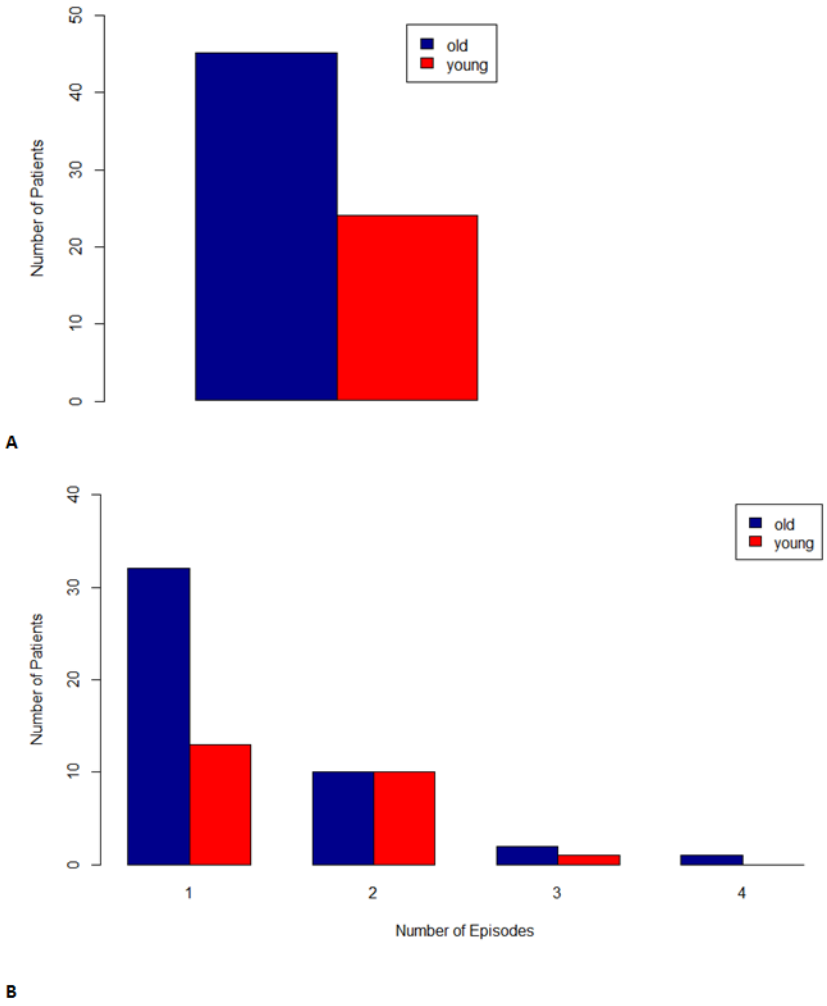


Fig. 1.

A. Number of patients with any CMV viremia in the older versus younger cohort. **B.** Number of episodes of CMV viremia in the first year after kidney transplantation in the older versus younger cohort.

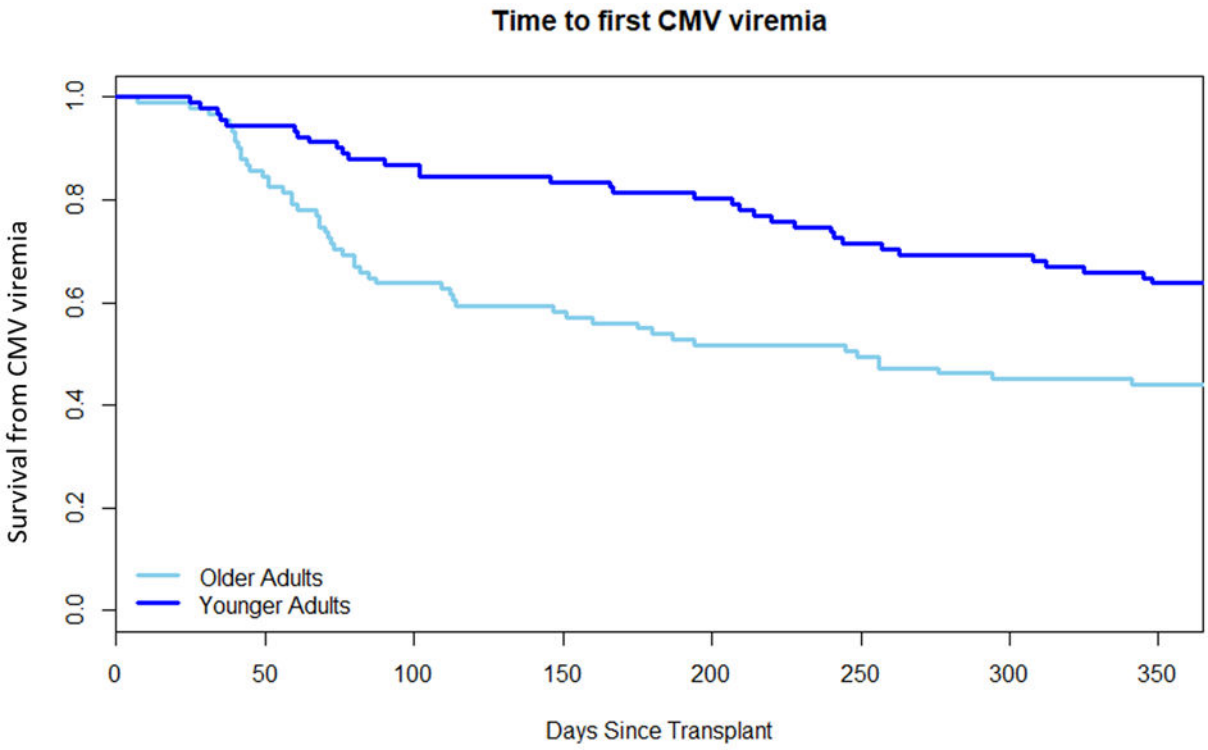
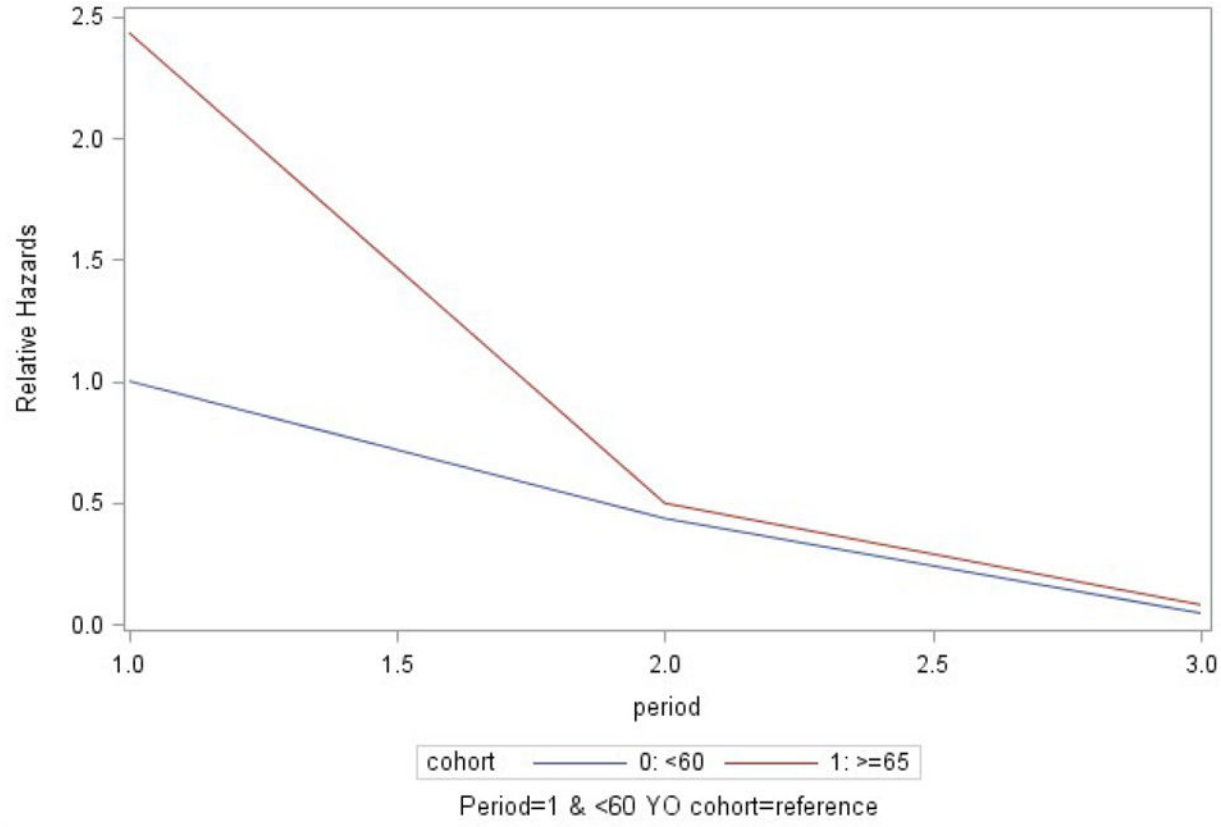
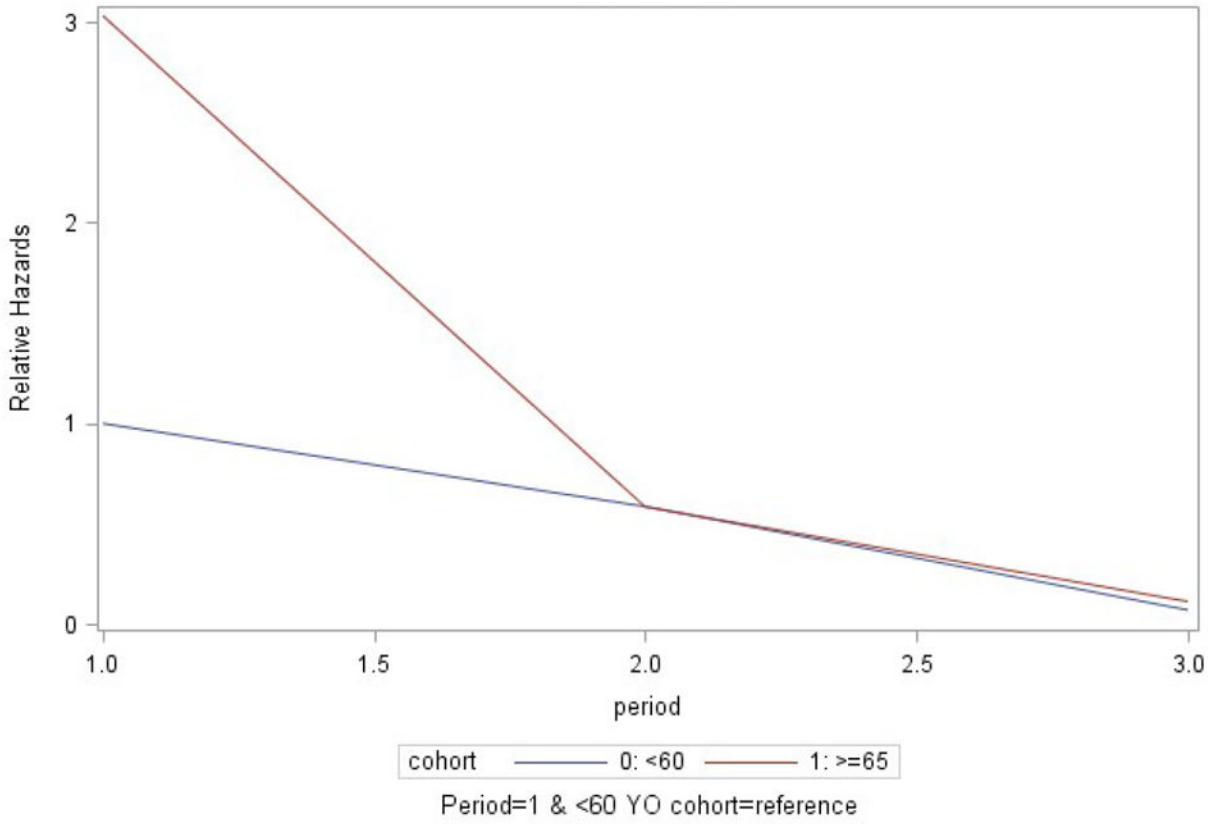


Fig. 2. Time to first episode of CMV viremia. p=0.003.



A.



B.

Fig. 3. Marginal models. Episode-cohort interaction. First three episodes.

A. All patients. **B.** Excludes patients that received thymoglobulin in the first year after kidney transplantation. Cohort 0 (blue): 40-60 years of age. Cohort 1 (red): aged ≥ 65 years. Hz: hazard ratio. While the older group had a higher risk of CMV reactivation, after the initial episode the relative hazards of were approximately equal between the age groups (at period 2).

Table 1.
Baseline characteristics of CMV recipient positive transplant recipients.

ATG: anti-thymocyte globulin; CMV: cytomegalovirus; CVD: cardiovascular disease; IQR: interquartile range; KT: kidney transplant; MMF: mycophenolate mofetil; PRA: panel reactive antibody.

Variable	Total n (%) n=117
Age in years, median [IQR]	65 (50,68)
Older cohort	63 (53.85)
Sex female	50 (42.74)
Race	
African-American	43 (36.75)
Caucasian	67 (57.26)
Asian	7 (5.98)
Comorbidities	
Diabetes mellitus	42 (35.90)
Hypertension	105 (89.74)
CVD	42 (35.90)
Prior transplant	21 (17.95)
Prior KT	16 (76.19)
PRA in percentage, median [IQR]	0 [0,52]
Induction regimen	
Basiliximab	61 (52.14)
ATG	40 (34.19)
Steroids only	18 (15.38)
Ureteral stent used	91 (77.78)
Maintenance immunosuppression	
Prednisone	115 (98.29)
MMF	114 (97.44)
Tacrolimus	116 (99.15)
Length of hospital stay in days, median [IQR]	6 [5,10]
Delayed graft function	28 (23.93)
Discharged home	117 (100%)
CMV seropositive donor	86 (73.50)
CMV directed therapy (at least 30 days)	59 (50.43)
Death	5 (4.27)
Graft loss	3 (2.56)
Functional status before transplant (available in n=115)	
Independent for ambulation	99 (86.09)
Dependent for ambulation (cane, walker or need help)	16 (13.91)
Functional status after transplant (available in n=98)	
Independent for ambulation	76 (77.55)
Dependent for ambulation (cane, walker or need help)	22 (22.45)

Table 2.

Univariate logistic regression analysis of potential risk factor in predicting CMV reactivation in CMV seropositive kidney transplant recipients.

Univariate Logistic Regression (n = 117)			
Variable	**n (%)**	**p**	**Odds ratio (95% CI)**
Older age cohort	63 (53.85)	**0.003**	1.31 (1.10,1.56)
Sex female	50 (42.74)	0.855	0.98 (0.82,1.18)
DM	42 (35.90)	**0.0144**	1.26 (1.05, 1.51)
Prior transplant	21 (17.95)	**0.0319**	0.78 (0.82,0.98)
CMV seropositive donor	86 (73.50)	0.589	1.06 (0.86,1.30)
No induction (=steroids only)	18 (15.38)	0.404	0.90 (0.70,1.15)
Basiliximab induction	61 (52.14)	**0.023**	1.23 (1.03,1.47)
Rejection	15 (12.8)	0.638	0.94 (0.72, 1.23)
Augmented I/S	14 (11.97)	0.471	0.90 (0.69, 1.20)
BKV	31 (27.19)	0.724	0.96 (0.79, 1.18)
Use of CMV directed ppx for at least 30 days (GCV/VGCV)	59 (50.43)	0.411	1.08(0.90,1.29)
Bacteremia	17 (14.30)	0.99	1.00 (0.77,1.29)
Pneumonia	13 (11.11)	0.43	1.12 (0.84,1.49)
Urinary tract infection	51 (43.59)	0.729	1.03 (0.86, 1.24)
Admission for infection [patient level] ¥	52 (44.44)	0.382	1.08 (0.91, 1.30)
Surgery [patient level] ¥¥	30 (25.64)	0.577	1.06 (0.86, 1.30)
Ambulation before transplant (independent/needs assistance/dependent) ¥¥¥	99 (84.62)	0.365	0.92 (0.78, 1.10)

¥52 patients with at least one admission for infection.

¥¥30 patients with at least 1 re-operation/surgery (39 total episodes).

¥¥¥Missing in 2 cases. DM: diabetes mellitus; I/S: immunosuppression; BKV: BK polyomavirus; ppx: prophylaxis; GCV: ganciclovir; VGCV: valganciclovir.

Table 3.

Multivariate logistic regression analysis in predicting the risk of CMV reactivation in CMV serospositive kidney transplant recipients.

Multivariate Logistic Regression			
Variable	**ß coefficient**	**p**	**Odds ratio (95% CI)**
Older cohort	0.91	**0.03**	2.48 (1.10, 5.72)
Diabetes mellitus	0.54	0.24	1.71 (0.70, 4.3)
Prior transplant	−0.69	0.19	0.50 (0.17, 1.40)
Basiliximab induction	0.74	0.07	2.11 (0.95, 4.75)

Table 4.

Univariate logistic regression analysis of potential risk factor in predicting CMV reactivation in CMV seropositive kidney transplant recipients that did not receive thymoglobulin.

DM: diabetes mellitus; I/S: immunosuppression; BKV: BK polyomavirus; ppx: prophylaxis; GCV: ganciclovir; VGCV: valganciclovir.

Univariate Logistic Regression (n=77)					
Variable	**n (%)**	**Any CMV PCR**		**CMV PCR 450+ IU/ml[¥]**	
		p	**Odds ratio (95% CI)**	**p**	**Odds ratio (95% CI)**
Older age cohort	45 (58.44)	**0.0008**	1.44 (1.17,1.76)	0.174	1.17 (0.93, 1.47)
Sex female	26 (33.77)	0.954	1.01 (0.80, 1.27)	0.688	1.05 (0.83, 1.33)
DM	32 (42.86)	**0.0413**	1.25 (1.01, 1.55)	0.163	1.18 (0.94,1.48)
Prior transplant	8 (10.39)	**0.012**	0.64 (0.46,0.90)	**0.0407**	0.68 (0.48, 0.98)
CMV seropositive donor	49 (66.64)	0.117	1.20 (0.96, 1.49)	0.327	1.12 (0.89, 1.42)
No induction (=steroids only)	18 (23.38)	0.133	0.822 (0.64, 1.06)	0.452	0.90 (0.69, 1.18)
Basiliximab induction	59 (76.62)	0.133	1.22 (0.95, 1.56)	0.452	1.11 (0.85, 1.45)
Rejection [$$]	9 (11.69)	0.537	0.90 (0.64, 1.26)	0.884	0.97 (0.69, 1.38)
Augmented I/S	9 (11.69)	0.356	0.85 (0.60, 1.20)	0.585	0.90 (0.62, 1.30)
BKV	20 (25.97)	0.279	1.15 (0.90, 1.46)	0.172	1.20 (0.93, 1.54)
Use of CMV directed ppx for at least 30 days (GCV/ VGCV)	13 (15.58)	0.782	0.96 (0.72, 1.28)	0.963	0.99 (0.73, 1.34)
Bacteremia	15 (19.48)	0.66	0.94 (0.72, 1.23)	0.565	0.92 (0.69, 1.22)
Pneumonia	12 (15.58)	0.893	1.02 (0.76, 1.37)	0.388	1.15 (0.84, 1.56)
Admission for infection [patient level]	36 (46.75)	0.769	1.03 (0.83, 1.28)	0.327	1.12 (0.89, 1.40)
Surgery [patient level]	20 (25.97)	0.597	0.94 (0.73, 1.20)	0.739	1.04 (0.81, 1.35)

[¥] n=52

[$$] Nine patients with rejection, 2 of them had 2 episodes.