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Impact of Antiviral Preventive Strategies on the Incidence and Outcomes of Cytomegalovirus Disease in Solid Organ Transplant Recipients

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We assessed the impact of antiviral prophylaxis and preemptive therapy on the incidence and outcomes of cytomegalovirus (CMV) disease in a nationwide prospective cohort of solid organ transplant recipients. Risk factors associated with CMV disease and graft failure-free survival were analyzed using Cox regression models. One thousand two hundred thirty-nine patients transplanted from May 2008 until March 2011 were included; 466 (38%) patients received CMV prophylaxis and 522 (42%) patients were managed preemptively. Overall incidence of CMV disease was 6.05% and was linked to CMV serostatus (D+/R− vs. R+, hazard ratio [HR] 5.36 [95% CI 3.14–9.14], $p < 0.001$). No difference in the incidence of CMV disease was observed in patients receiving antiviral prophylaxis as compared to the preemptive approach (HR 1.16 [95% CI 0.63–2.17], $p = 0.63$). CMV disease was not associated with a lower graft failure-free survival (HR 1.27 [95% CI 0.64–2.53], $p = 0.50$). Nevertheless, patients followed by the preemptive approach had an inferior graft failure-free survival after a median of 1.05 years of follow-up (HR 1.63 [95% CI 1.01–2.64], $p = 0.044$). The incidence of CMV disease in this cohort was low and not influenced by the preventive strategy used. However, patients on CMV prophylaxis were more likely to be free from graft failure.

Key words: Antiviral prophylaxis, graft loss, indirect effects, preemptive therapy, valganciclovir

Abbreviations: CMV, cytomegalovirus; D/R, donor/recipient; HR, hazard ratio; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; SOT, solid organ transplant; STCS, Swiss Transplant Cohort Study.

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Background

Cytomegalovirus (CMV) disease has been considered as the most important viral infection developing after solid organ transplantation (SOT) (1,2). Major risk factors associated with CMV disease are the CMV serostatus (donor positive, recipient negative [D+/R−] being at the highest risk), the type of organ transplanted and the immunosuppressive regimen used (3). CMV disease in this population presents with viral syndrome or tissue-invasive disease, which can be life-threatening if untreated. In

addition, CMV disease in SOT recipients has been associated with a number of conditions, the so-called ''indirect effects,'' such as acute rejection and chronic allograft dysfunction (4). Indirect effects of CMV are thought to result from immunological dysregulation, although local damage due to residual CMV replication has been suggested as an alternative mechanism (5).

Current preventive strategies against CMV disease include universal prophylaxis and preemptive therapy (2). Universal prophylaxis consist in the administration of an antiviral drug for a given period of time, generally 3–6 months posttransplant (6). The preemptive approach consists in monitoring the CMV viral load and administering an antiviral drug in case of CMV detection in the blood, before the development of symptoms. Both strategies have greatly reduced CMV-associated morbidity and mortality (7,8), although the efficacy of the preemptive approach has been less well-established (9). Current guidelines recommend both approaches, although antiviral prophylaxis is generally preferred for high-risk patients (1,2). However, direct comparison of both strategies has been assessed only in a few small randomized controlled trials (10–14).

Key questions are unresolved regarding the prevention of CMV disease. First, a significant number of patients (approximately 20–30% of D+/R− patients) may still develop CMV disease after discontinuation of prophylaxis (15,16). This is termed ''late-onset CMV disease'' and some studies suggest that it remains associated with poor outcomes in SOT recipients (17,18). Second, the preemptive approach, by allowing low-grade viral replication during the early posttransplant period, may not appropriately prevent the occurrence of CMV-associated indirect effects, and therefore long-term transplant outcomes might be inferior as compared to patients receiving antiviral prophylaxis (11).

The clinical significance of CMV disease in the current era has not been extensively evaluated in prospective, multicenter studies. The aim of our study was to assess the incidence, risk factors and transplant outcomes associated with CMV disease in a large nationwide cohort of SOT recipients (Swiss Transplant Cohort Study [STCS]) (19). We specifically evaluated the impact of antiviral prophylaxis and preemptive therapy on the incidence of CMV disease and transplant outcomes, taking advantage of the variable strategies used in local transplant programs.

Methods

Study design and data collection

The STCS is a multicenter cohort study including SOT performed in Switzerland from May 2008 onward (19). The acceptance rate of participating in the STCS is approximately 95% among all SOT recipients. The STCS comprises six transplant centers in Switzerland. Kidney transplantation is performed in all centers, liver and heart transplantation in three centers and lung and pancreas transplantation in two centers, but clinical follow-up is performed in all the centers. For the present study, we included patients transplanted from May 2008 to March 2011 with at least one postbaseline follow-up assessment and current written informed consent for participation in the STCS. The STCS has been approved by the ethic committees of all participating centers.

Data is collected on demographic parameters, transplant type, comorbidities, immunosuppressive treatment, antimicrobial drugs, rejection, infectious and noninfectious events at enrollment, at 6 months and every 12 months on standardized data forms. Specific data on CMV infection available in the STCS database include the use of antiviral drugs and the type classified as asymptomatic replication, viral syndrome and probable and proven end-organ disease. Additional clinical information for all cases of CMV disease was gathered through a data collection form filled by an investigator (transplant infectious disease specialist) in each center, including symptoms and laboratory data of CMV disease, CMV viral load at the time of diagnosis, presence of CMV in a biopsy, therapy for CMV disease, recurrence of CMV replication and/or disease and reported presence of CMV genome mutations defining antiviral resistance (20).

Antiviral strategies

The antiviral preventive strategy per protocol varied among centers and type of transplant. As a rule, D+/R− patients received valganciclovir prophylaxis for three to 6 months, either upfront or after switch from IV ganciclovir. D+/R− liver and kidney transplant recipients not treated with antilymphocyte globulins were followed preemptively in two transplant programs. Seropositive (R+) patients were managed either by preemptive therapy or antiviral prophylaxis according to the transplant program, except for lung transplant recipients who all received antiviral prophylaxis. D−/R− patients generally did not receive anti-CMV prophylaxis. Immunosuppressive regimens also varied among centers and type of organ transplant.

The protocol of the preemptive approach consisted in screening for CMV DNAemia by PCR every 1–2 weeks during the first month posttransplant and then every 2 weeks until 3–6 months posttransplant thereafter according to routine visits and clinical symptoms. Only results of positive CMV DNAemia (and whether DNAemia was treated or not) were recorded in the STCS database. We also calculated the percentage of patients who actually received a preemptive therapy following asymptomatic CMV DNAemia. D−/R− patients were classified as being at low risk for CMV disease, independently whether they have received anti-CMV prophylaxis or not.

Clinical definitions

Antiviral prophylaxis was defined as the use of ganciclovir or valganciclovir started during the first 2 weeks posttransplantation. Patients without such a prophylactic treatment who were at risk for CMV disease (D+/R− and R+ patients) were considered as being managed by the preemptive approach. Definition of CMV disease followed international guidelines (21). Active CMV infection was defined as the evidence of laboratory confirmation of CMV replication irrespectively of symptoms. CMV disease was defined as CMV replication with corresponding signs and symptoms. CMV disease was further classified as viral syndrome if one or more of the following symptoms or signs were present: fever $>38^{\circ}$C for at least 2 days, new or increased malaise, leukopenia, atypical lymphocytes, thrombocytopenia and elevation of hepatic transaminases. In case of symptoms compatible with organ dysfunction, CMV disease was classified as end-organ disease. Only cases with a positive detection of CMV in biopsy (either by PCR or immunohistochemistry) were defined as proven, all other cases were categorized as probable disease. Transplant outcome was defined as graft failure-free survival (i.e. graft loss or death, whichever occurred first). Acute rejection was defined for each organ according to standard international criteria.

Statistical analysis

Risk factors for time to first CMV disease were analyzed with a Cox proportional hazards regression, taking into account death as competing risk by using nonparametric multiple imputation techniques to recover the missing potential censoring information for individuals with occurred deaths (22–24). Exposure to ganciclovir or valganciclovir was added in the model as a time-dependent covariate to adjust for the protective effect of the exposure to antiviral drug on the occurrence of CMV disease. To directly compare antiviral prophylaxis and preemptive therapy, D−/R− patients were excluded from the analysis of risk factors for CMV disease. Cumulative incidence functions were calculated to estimate the probability over time of CMV disease. The effect of antiviral prophylaxis and preemptive therapy by serostatus group (D+/R−: high risk; R+: intermediate risk) were compared using a sensitivity analysis. The impact of antiviral preventive strategy and CMV disease on graft failure-free survival was investigated using a Cox proportional hazards model with additional covariates age, sex and transplanted organ. As the type of antiviral strategy (prophylaxis vs. preemptive therapy) was defined according to whether the patient was on antiviral drug during the first 2 weeks after transplantation, patients who died during this early period posttransplant might not have been properly assigned to a defined preventive group. Therefore, we excluded those patients with early death and/or graft failure. D−/R− patients served as control group for the analysis of graft and patient survival. Patients with missing information on baseline CMV serology were excluded from the analysis. All covariates with missing information were imputed by the most frequent class (categorical covariates) or by the median of the available values (continuous covariates). All analyses were performed with R version 2.15.1 (25).

Results

Study population

Overall, 1239 patients received a SOT from May 2008 until March 2011 and had signed an informed consent to enroll in the STCS. The last date of follow-up was September 2011, and median follow-up was 1.02 years (interquartile range [IQR] 0.93–1.99). The baseline characteristics of these patients are described in Table 1. Thirty-eight percent of all patients received antiviral prophylaxis with either valganciclovir or IV ganciclovir. Median duration of antiviral prophylaxis was 117 days (IQR 87–174). Forty-two percent of all patients were managed according to the preemptive approach, 30% of whom actually received antiviral therapy for asymptomatic CMV DNAemia. Regarding D+/R− patients (n = 236), 168 (71%) received antiviral prophylaxis and 68 (29%) were managed preemptively (28% of those were treated for asymptomatic CMV DNAemia). The majority of D−/R− patients did not receive any anti-CMV drug.

Incidence and risk factors for the development of CMV disease

Seventy-five patients developed 83 episodes of CMV disease (Table 2). The majority of cases were classified as being either viral syndrome or probable CMV disease (i.e. presenting with specific symptoms of organ involvement, but not biopsy proven). Thirteen cases (16%) were proven tissue-invasive disease, mostly colitis. Recurrent CMV replication was frequent after discontinuation of antiviral therapy, although only eight cases of clinical disease were observed. Two patients developed ganciclovir-resistant CMV disease; one had received antiviral prophylaxis and the other had been managed with the preemptive approach. Figure 1 shows the cumulative incidence of CMV disease according to the organ transplant.

Risk factors for developing CMV disease are shown in Table 3. D−/R− patients were excluded from this analysis. D+/R− serostatus was associated with a higher risk of CMV disease as compared to R+ serostatus (HR 5.36 [95% CI 3.14–9.14], $p < 0.001$). No difference in the incidence of CMV disease was observed in patients receiving antiviral prophylaxis as compared to patients managed by the preemptive approach (HR 1.16 [95% CI 0.63–2.17], $p = 0.63$), even though CMV disease was obviously delayed in prophylaxed patients. Figure 2 shows the cumulative incidence of CMV disease according to the serogroup risk and the preventive strategy used. In D+/R− patients, there was a trend toward a higher incidence of CMV disease in patients receiving antiviral prophylaxis (HR 1.87 [95% CI 0.81–4.36], $p = 0.15$). In R+ patients, there was a trend toward a lower incidence of CMV disease in patients receiving antiviral prophylaxis (HR 0.33 [95% CI 0.10–1.14], $p = 0.08$). Concurrent exposure to antiviral drug (due to either antiviral prophylaxis or preemptive therapy of asymptomatic CMV DNAemia) was associated with a lower incidence of CMV disease (HR 0.27 [95% CI 0.13–0.55], $p < 0.001$).

Outcomes associated with CMV disease

Overall, 85 patients (7%) experienced a graft loss and 104 patients died (8%) during follow-up. We excluded from this analysis 37 patients who had early graft loss and/or death (<14 days). Causes of graft loss were infection (22%), vascular (20%), immunological (14%), primary graft dysfunction (12%), other (24%) and unknown (8%). We did not find any significant association between the development of CMV disease and graft loss or death (Table 4). Patients followed by the preemptive approach had a lower graft failure-free survival (HR 1.63 [95% CI 1.01–2.64], $p = 0.044$) as compared to patients receiving antiviral prophylaxis (Figure 3). Because only D+/R− liver and kidney transplant recipients were managed with both approaches (preemptive vs. prophylaxis), we performed a sensitivity analysis by excluding lung, heart and pancreas transplant recipients. Patients on preemptive approach had lower graft failure-free survival (HR 2.11 [95% CI 1.21–3.64], $p = 0.007$).

We hypothesized that the lower graft failure-free survival observed in patients managed by the preemptive approach was due to the development of asymptomatic CMV viremia, especially during the first weeks posttransplant. We therefore included early onset (<90 days) asymptomatic CMV viremia in a new multivariate Cox regression model. In this model, CMV viremia was associated with a higher incidence of graft loss or death (HR 1.79 [95% CI 1.13–2.85], $p = 0.013$), but the preemptive approach was no longer significantly associated (HR 1.36 [95% CI

Table 1: Baseline characteristics and outcomes of the patients included in the analysis, according to whether they developed CMV disease or not

Characteristics	All patients (n = 1239)	CMV disease (n = 75)	No CMV disease (n = 1164)
Follow-up, years; median (IQR)	1.02 (0.93–1.99)	1.06 (0.98–1.97)	1.02 (0.91–1.99)
Male sex, n (%)	800 (65%)	44 (59%)	756 (65%)
Age, years; mean (sd)	49.6 (15.6)	52.2 (15)	49.5 (15.6)
Organ transplant, n (%)			
Kidney	742 (60%)	48 (64%)	694 (60%)
Liver	234 (19%)	17 (23%)	217 (19%)
Lung	110 (9%)	4 (5%)	106 (9%)
Heart	85 (7%)	3 (4%)	82 (7%)
Pancreas/kidney-pancreas	35 (3%)	3 (4%)	32 (3%)
Other	33 (3%)	0	33 (3%)
Induction, n (%)			
Basiliximab	737 (60%)	51 (68%)	686 (59%)
Antilymphocyte globulins	271 (22%)	13 (17%)	258 (22%)
None	231 (19%)	11 (15%)	220 (19%)
Maintenance immunosuppression[1]			
Tacrolimus	833 (67%)	49 (65%)	784 (67%)
Cyclosporine	441 (36%)	29 (39%)	412 (35%)
MMF/MPA	1145 (92%)	71 (95%)	1074 (92%)
mTOR inhibitors	102 (8%)	10 (13%)	92 (8%)
Steroids	1172 (95%)	73 (97%)	1099 (94%)
Azathioprine	57 (5%)	2 (3%)	55 (5%)
CMV serostatus			
D−/R−	259 (21%)	2 (3%)	257 (22%)
D−/R+	307 (25%)	7 (9%)	300 (26%)
D+/R+	412 (33%)	23 (31%)	389 (33%)
D+/R−	236 (19%)	40 (53%)	196 (17%)
Missing	25 (2%)	3 (4%)	22 (2%)
HLA full mismatch, n (%)	412 (33%)	23 (31%)	389 (33%)
CMV prevention All patients (n = 1239)			
Antiviral prophylaxis	466 (38%)	36 (48%)	430 (37%)
Duration of prophylaxis, d; median (IQR)	117 (87–174)	120 (84–169)	116 (88–174)
Preemptive approach	522 (42%)	34 (45%)	488 (42%)
Patients with treated CMV DNAemia, n (%)	159 (30%)	10 (29%)	149 (31%)
No prevention	232 (18%)	2 (3%)	230 (20%)
D+/R− patients (n = 236)	n = 236	n = 40	n = 196
Antiviral prophylaxis	168 (71%)	30 (75%)	138 (70%)
Duration of prophylaxis, d; median (IQR)	137.5 (95–176)	123 (85–171)	144 (98–176)
Preemptive approach	68 (29%)	10 (25%)	58 (30%)
Patients with treated CMV DNAemia, n (%)	19 (28%)	3 (30%)	16 (28%)
Number of episodes of acute rejection, mean (sd)	1.00 (2.17)	1.03 (1.55)	1.00 (2.2)
Death, n (%)	104 (8%)	5 (7%)	99 (9%)
Graft loss, n (%)	85 (7%)	7 (9%)	78 (7%)

CMV, cytomegalovirus; D, donor; R, recipient; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin.
[1]Some patients took sequentially more than one drug, so the addition of numbers may result in >100%.

0.82–2.25], p = 0.227). This suggests a masking effect of CMV viremia in the association between the preemptive approach and graft failure-free survival, as most of the early asymptomatic replications occurred in the preemptive treatment group.

Discussion

In this transplant cohort study enrolling 1239 SOT patients, we found an incidence of CMV disease of 6% after a median follow-up of 1 year. By including more than 95% of all SOT recipients in Switzerland during the years 2008–2011, our study provides an accurate picture of the epidemiology of CMV disease in today clinical practice. CMV disease incidence was 16.9% in high-risk patients (CMV D+/R−) and 4.4% in the intermediate-risk patients (CMV R+). These numbers are similar to or lower than those observed in the most recent published prospective cohort studies (9,26) or randomized controlled trials (15,16,27), reflecting the improved management on the prevention of CMV disease over the last years.

Table 2: Clinical characteristics of patients with CMV disease

Number of patients	n = 75
Number of episodes	n = 83
Median time from transplantation to first episode of CMV disease (IQR), days	136 (56–227)
Patients on prophylaxis	194 (137–240)
Patients on preemptive	58 (35–134)
Type of disease	
Viral syndrome	42 (51%)
End-organ disease	38 (46%)
Probable	25 (30%)
Proven	13 (16%)
Unknown	3 (4%)
Type of proven tissue-invasive disease	
Colitis	8 (61%)
Esophagitis	2 (15%)
Pneumonitis	1 (8%)
Unknown	2 (13%)
Antiviral therapy	
IV ganciclovir	11 (13%)
Valganciclovir	40 (48%)
IV ganciclovir + valganciclovir	22 (26%)
Foscarnet	1 (1.2%)
Unknown	9 (11%)
Recurrent CMV replication	37 (44%)
Recurrent CMV disease	8 (10%)
Proven antiviral resistance	2 (2.4%)

Importantly, our study provides the first comparative data on the efficacy of the two main strategies used for prevention of CMV, namely antiviral prophylaxis and preemptive therapy, in routine clinical practice outside of specific studies. The data indicate that antiviral prophylaxis or preemptive therapy were associated with a similar incidence of CMV disease. However, the prophylactic approach delayed the CMV event beyond the time of prophylaxis. Of note, antiviral prophylaxis tended to perform better in intermediate-risk patients and the preemptive therapy tended to perform better in high-risk liver and kidney transplant recipients with respect with the prevention of CMV disease. This is somewhat unexpected, as antiviral prophylaxis is generally preferred in D+/R− patients and the preemptive approach is used basically only in R+ patients (2). A few randomized controlled trials have recently compared prophylaxis and preemptive therapy. However, D+/R− patients were not included (14) or represented only a minority of all patients included in these trials (10,11). Some studies showed a marked benefit of the preemptive approach in D+/R− patients (28,29), although recent studies have shown a similar or even higher incidence of CMV diseases compared to the use of antiviral prophylaxis (9,30). In a French study, 80 D+/R− kidney transplant recipients followed preemptively were compared to a historical cohort of 32 D+/R− patients who received antiviral prophylaxis (30). Patients on preemptive therapy a had higher incidence of CMV disease, treatment failure and antiviral resistance, highlighting the difficulties of implementing an appropriate preemptive approach in high-risk patients, where the viral doubling time is rapid (31). While our study shows that preemptive therapy may appropriately prevent CMV disease even in high-risk patients, there remain some concerns with respect to the impact of preemptive therapy on preventing other relevant transplant outcomes, such as graft loss.

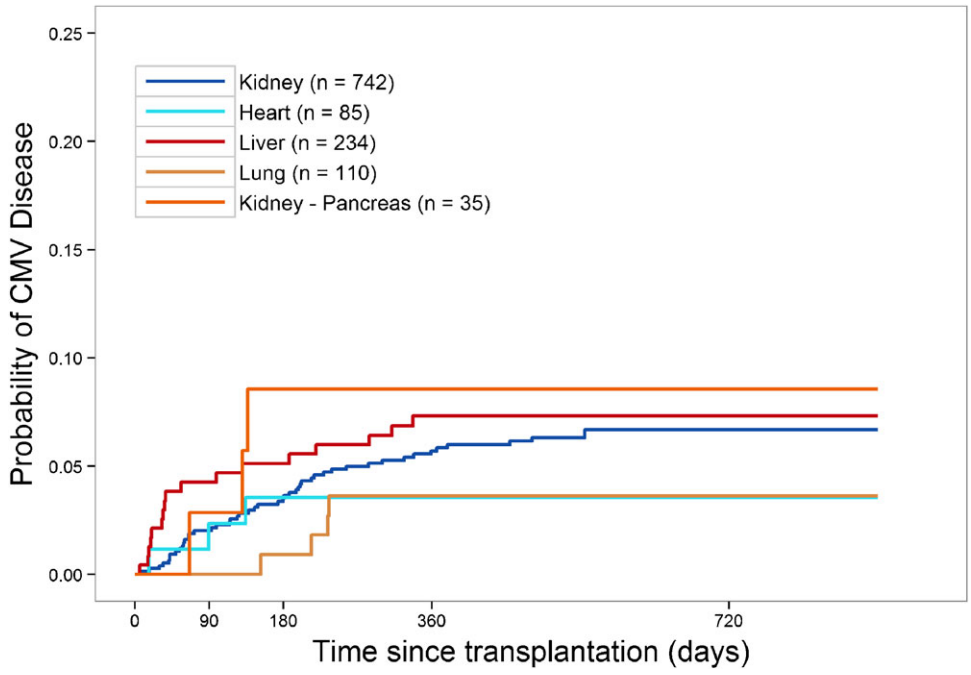

Figure 1: Cumulative incidence of cytomegalovirus disease by organ transplant.

Table 3: Risk factor for the development of CMV disease in all patients, and according to CMV serostatus risk group

	All patients			High-risk patients (D+/R−)			Intermediate-risk patients (R+)		
	Hazard ratio	95% Confidence interval	p-Value	Hazard ratio	95% Confidence interval	p-Value	Hazard ratio	95% Confidence interval	p-Value
Age	1.01	0.99–1.03	0.24	1.01	0.99–1.04	0.30	1.01	0.98–1.03	0.58
Sex (male)	0.71	0.43–1.17	0.18	0.55	0.28–1.07	0.08	1.19	0.54–2.60	0.67
Organ transplant									
Kidney (reference)	1			1			1		
Heart	0.67	0.19–2.45	0.55	0.93	0.18–4.87	0.93	0.33	0.04–2.93	0.32
Liver	1.28	0.69–2.38	0.43	1.96	0.88–4.35	0.10	0.67	0.25–1.83	0.44
Lung	0.60	0.2–1.77	0.35	0.67	0.18–2.45	0.54	0.69	0.08–5.95	0.74
Kidney-pancreas	1.46	0.43–4.94	0.54	4.25	1.05–17.24	0.04	—	—	—
Induction therapy									
None (reference)	1			1			1		
Basiliximab	1.60	0.81–3.14	0.17	1.05	0.42–2.62	0.91	1.90	0.72–5.02	0.20
ALG	1.59	0.64–3.94	0.32	1.11	0.32–3.87	0.87	2.93	0.77–11.21	0.12
Use of MMF	1.28	0.45–3.62	0.64	4.53	0.58–35.40	0.15	0.47	0.13–1.64	0.24
Antiviral preventive strategy									
Preemptive therapy	1			1			1		
Antiviral prophylaxis	1.16	0.63–2.17	0.63	1.87	0.81–4.36	0.15	0.33	0.10–1.14	0.08
Exposure to antiviral drug	0.27	0.13–0.55	**<0.001**	0.20	0.08–0.52	0.001	0.83	0.24–2.82	0.76
HLA full mismatch	0.59	0.33–1.08	0.09	0.56	0.25–1.23	0.15	0.65	0.23–1.61	0.35
CMV serostatus									
R+ (reference)	1	3.14–9.14	**<0.001**						
D+/R−	5.36								

ALG: antilymphocyte globulins; CMV: cytomegalovirus ; D: donor; R: recipient; MMF: mycophenolate mofetil; mTOR: mammalian target of rapamycin. p-values in bold are statistically significant (<0.05).

A significant finding in our study is the association of preemptive therapy with a higher incidence of graft loss or death, as compared to antiviral prophylaxis and to low risk D−/R− constellation without prophylaxis/treatment. Despite a similar incidence of CMV disease in both preventive groups, our analysis suggests that it was actually asymptomatic CMV viremia early after transplantation (which was almost exclusively observed in patients on the preemptive approach), which was associated with inferior transplant outcomes (32). CMV viremia has been associated with the production of inflammatory cytokines (such as IL-8, TNF-α), adhesion molecules (ICAM), growth factors (PDGF, TGF-β) and complement activation, which may be responsible for such indirect effects (4). Of note, our results on the worse transplant outcomes observed with the preemptive approach are in keeping with the study by Kliem et al. (11), showing that patients randomized to a preemptive approach had a lower graft survival than patients receiving antiviral prophylaxis with oral ganciclovir (78% vs. 92%, respectively), a difference accounted mostly by CMV

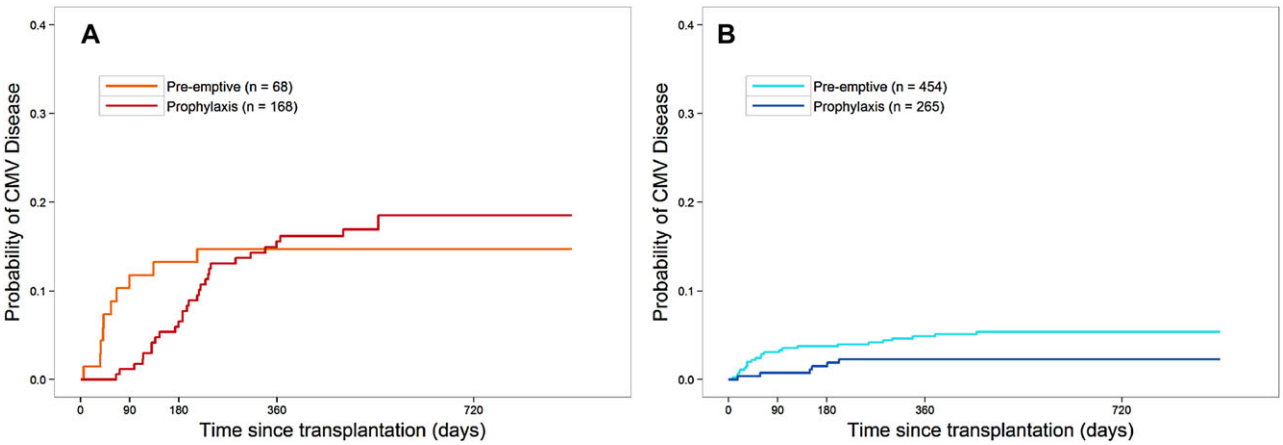

Figure 2: Cumulative incidence of cytomegalovirus (CMV) disease according to serological CMV risk group and antiviral preventive strategy. (A) High-risk patients (donor positive/recipient negative, [D+/R−]). (B) Intermediate-risk patients (recipient positive [R+]).

Table 4: Risk factors for graft failure-free survival in all SOT recipients and in kidney or liver transplant recipients

	All patients			Kidney or liver transplant recipients		
	Hazard ratio	95% Confidence interval	p-Value	Hazard ratio	95% Confidence interval	p-Value
Age	1.03	1.01–1.04	**0.001**	1.04	1.02–1.06	<**0.001**
Sex (male)	1.04	0.70–1.55	0.86	1.06	0.66–1.73	0.80
Organ transplant						
Kidney (reference)	1	0.12–1.74	0.25	—		
Heart	0.45	1.10–2.78	**0.019**			
Liver	1.75	1.73–5.55	<**0.001**			
Lung	3.10	0.54–5.74	0.34			
Kidney-pancreas	1.76					
CMV disease	1.27	0.64–2.53	0.50	1.59	0.78–3.23	0.20
Number of acute rejections	1.15	1.04–1.27	**0.007**	1.76	1.52–2.04	<**0.001**
Antiviral preventive strategy						
Antiviral prophylaxis (reference)	1			1		
No prevention (D−/R− patients)	1.12	0.62–2.00	0.71	1.70	0.83–3.48	0.15
Preemptive therapy	1.63	1.01–2.64	**0.044**	2.11	1.21–3.64	**0.007**

CMV, cytomegalovirus; D, donor; R, recipient. p-values in bold are statistically significant (<0.05).

intermediate-risk patients. In the Collaborative Transplant Study, D+/R− patients receiving antiviral prophylaxis had a significantly better graft survival at 3 years (79% vs. 73% in patients without prophylaxis) (33).

Our study has several limitations. First, the median follow-up of patients was approximately 1 year, so we were not be able to analyze the influence of the antiviral preventive strategies on long-term outcomes. Second, the management of CMV disease was specific for each transplant program and this may result in some center biases. For example, data on the use of the preemptive approach in D+/R− patients were based on the experience of only two centers involving basically kidney and liver transplant recipients; results may vary according to the intensity of the implementation of surveillance protocol of CMV viremia in these centers and threshold to treat a positive CMV viremia (34). In addition, our cohort represents a heterogeneous population of different organ transplant recipients; however, by excluding those patients that mostly received prophylaxis (i.e. lung, hearts and pancreas transplant recipients) the results of the survival analysis remained unchanged. Finally, the STCS database does not register whether a patient scheduled to receive a preemptive approach was actually monitored by CMV PCR; however, the absence of such a monitoring in a patient at risk for CMV disease not receiving antiviral prophylaxis can be actually considered as a failure of the preemptive therapy, related to the inherent complexity of the preemptive approach (35). All these limitations are counterbalanced by the main strength of study, which is the large number of patients included in a prospective manner, representing an accurate

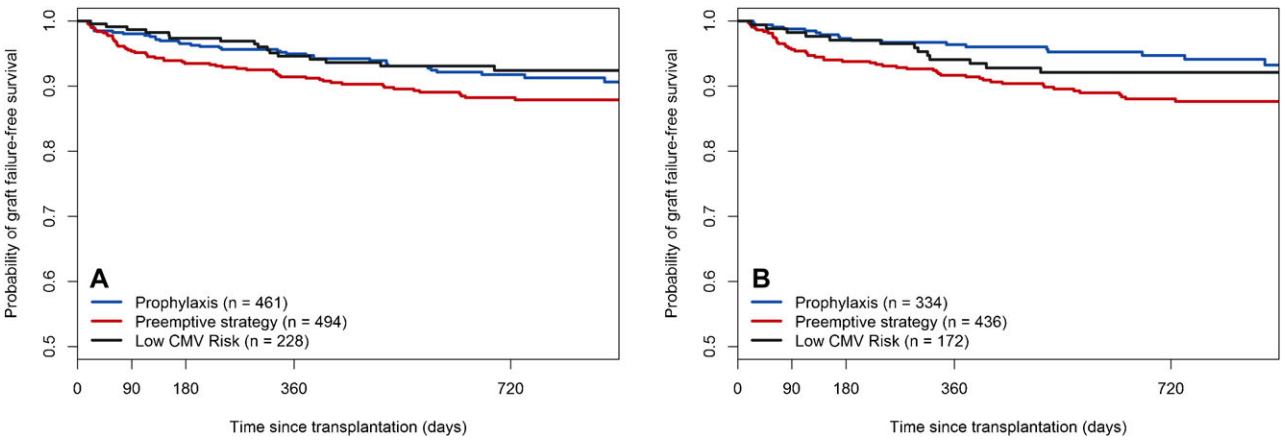

Figure 3: Incidence of graft failure-free survival in patients receiving either antiviral prophylaxis or preemptive therapy, compared to low-risk patients (donor negative/recipient negative, [D−/R−]), after exclusion of early death or graft failure. (A) All solid organ transplant recipients. Preemptive versus prophylaxis, HR 1.63, p = 0.04. (B) Kidney or liver transplant recipients. Preemptive versus prophylaxis, HR 2.11, p = 0.007.

description of the ''real-world'' epidemiology of CMV infection in the current era of transplantation using new protocols of immunosuppression.

In conclusion, in this nationwide multicenter cohort study of SOT recipients, we found a low incidence of CMV disease, which was not significantly associated with graft loss and death. Although the incidence of CMV disease was similar irrespectively of the antiviral preventive strategy used, we found a higher graft failure-free survival in patients receiving antiviral prophylaxis, most likely due to a better control of early onset CMV viremia. These results may help in the decision process to choose a strategy for the prevention of CMV disease.

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