DONOR CMV SEROPOSITIVITY IS ASSOCIATED WITH REDUCED KIDNEY GRAFT SURVIVAL IRRESPECTIVE OF RECEPTOR CMV STATUS

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INTRODUCTION & AIMS

Recently published data showed that donor (D) CMV seropositivity impacts adversely kidney graft survival and that HLA class I mismatches (MM) modulated that effect, as receptor (R) CD8+ T cells, syngenically restricted for class I, are probably unable to control effectively intragraft CMV replication after transplantation from a HLA-I MM CMV+ D. Therefore, we sought to explore D CMV serostatus role in kidney graft survival in our unit cohort.

METHODS

In a cohort of 646 adult kidney graft recipients from cadaveric donors, transplanted between 1983-2008, we analyzed long-term graft survival (as death-censored) considering D and R CMV serostatus through the Kaplan-Meier method (comparisons by log-rank test). To explore CMV D+ status as predictor of graft survival a multivariable Cox regression model was constructed [co-variables included (if univariable Cox *p*-value<0.1): R gender and age, D age, transplant year, ATG use, delayed graft function, acute rejection]. Furthermore, a subanalysis was undertaken to study the impact of HLA class I and II MM in the previous results.

Since 1995, CMV D+/R- received prophylaxis with immunoglobulin therapy and ganciclovir (1995-2001) or valganciclovir (2002-2008) for 6 months. Intermediate risk patients (CMV D-/R+ or D+/R+) received prophylaxis with ganciclovir (1995-2001) or valganciclovir (2002-2008) for 3 to 6 months if induced with ATG.

RESULTS

Study cohort had a median follow-up time of 118 months (interquartile range: 53-167).

	D+/R+ (n=441)	D+/R- (n=73)	D-/R+ (n=110)	D-/R- (n=31)	*p*
R age, *mean*	44	39	41	35	<0.01
R male, %	61	66	58	81	0.12
D age, *mean*	38	34	29	25	<0.01
D male, %	67	73	79	74	0.10
ATG use, %	33	30	29	42	0.22
1-year AR, %	18	23	20	26	0.61
DGF, %	33	19	22	7	<0.01
C-GF, %	21	23	13	23	0.26
R death, %	15	10	13	13	0.65

Legend: R, receptor; D, donor; ATG, anti-thymocyte globulin; AR, acute rejection; DGF, delayed graft function; C-GF, censored graft failure.

Table 1: Comparison between D/R CMV serostatus pairs

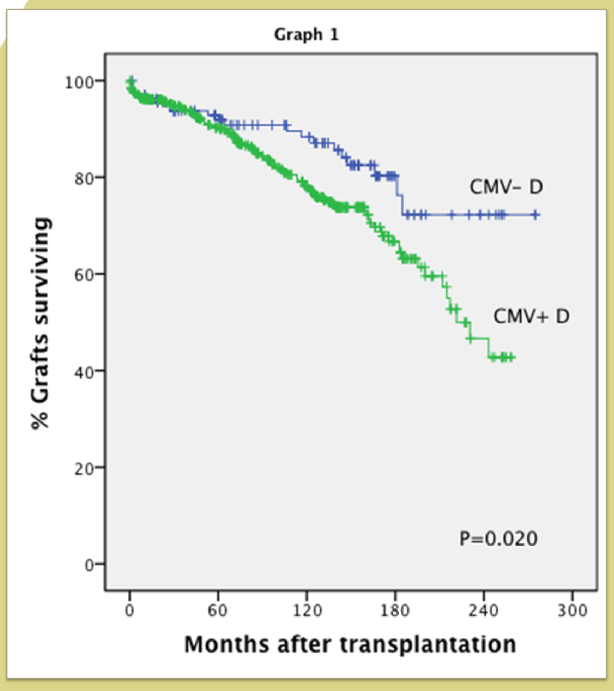
Considering all patients, graft survival was significantly reduced in R of CMV+ D (CMV D- vs. D+: 93%, 88%, 80% vs 90%, 78%, 67%; respectively at 5, 10 and 15 years; *p*=0.020) **(Graph 1)**.

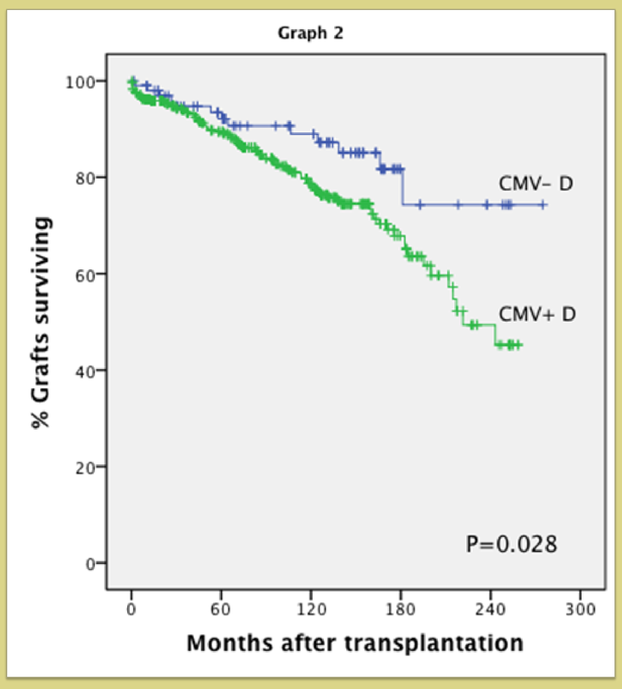
Analyzing only CMV+ R CMV+ D status was again associated with reduced graft survival (CMV D- vs D+: 94%, 89%, 82% vs 89%, 79%, 68%; respectively at 5, 10 and 15 years; *p*=0.03) **(Graph 2)**. Finally, no significant effect of D CMV serostatus on graft survival was detected when only CMV- R (n=104) were considered (CMV D- vs D+: 90%, 86%, 70% vs 95%, 75%, 62%; respectively at 5, 10 and 15 years; *p*=0.36).

We then stratified recipients according to the number of HLA class I MM (0-1 vs 2-4): only in the group with 2-4 MM (n=362) a significant deleterious effect of CMV+ D status on graft survival was noticeable (CMV D- vs D+: 91%, 88%, 82% vs 90%, 76%, 67%; at 5, 10 and 15 years respectively; *p*=0.03) **(Graph 3 & 4)**. Similar results were found when we stratified only CMV+ recipients (n=541). No significant effect of HLA class II MM was detected.

In the multivariable Cox model, **CMV+ D status was a significant predictor of censored graft failure in** any of the populations considered:

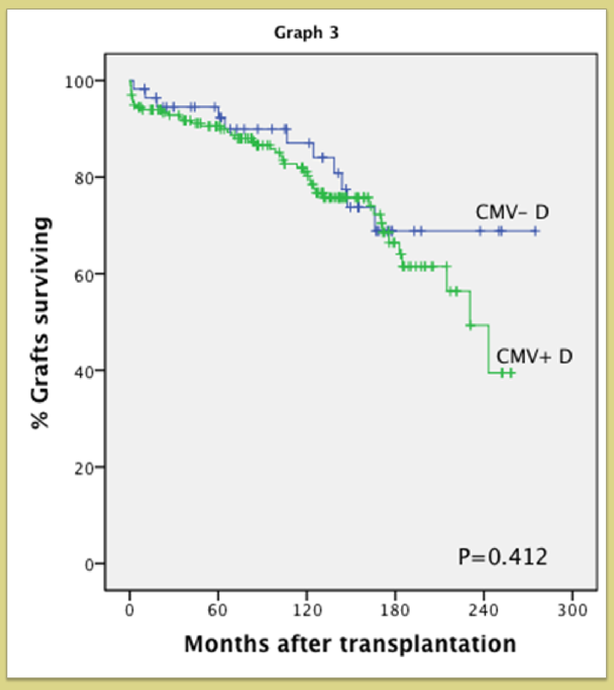
- **full cohort (HR=1.67; *p*=0.043);**
- **only CMV exposed pairs (HR=1.95; *p*=0.027);**
- **only CMV+ R (HR=1.88; *p*=0.040)**.

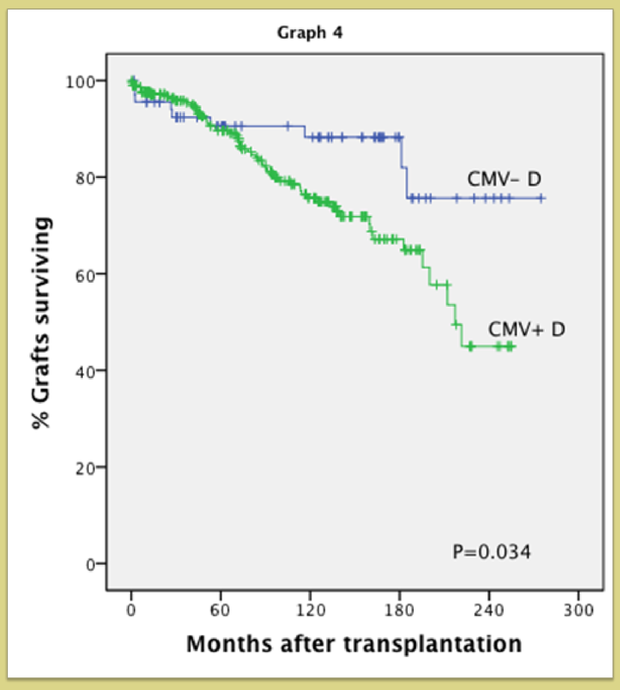




Graph 1: Kaplan-Meier curves of censored graft survival according to donor CMV status in the **full cohort (n=646)**.

Graph 2: Kaplan-Meier curves of censored graft survival according to donor CMV status in **CMV + receptors (n=541)**.





Graph 3: Kaplan-Meier curves of censored graft survival according to donor CMV status in **recipients with 0-1 HLA-I MM (n=257)**.

Graph 4: Kaplan-Meier curves of censored graft survival according to donor CMV status in **recipients with 2-4 HLA-I MM (n=362)**.

CONCLUSIONS

D CMV status was a potent predictor of graft survival independently from the recipient CMV serostatus, particularly in class I HLA mismatched transplants. Observed poorer kidney graft outcomes from CMV+ D in CMV+ R may be also related with CMV risk underestimation and subsequent inadequate prophylaxis strategies. Risk of CMV D+/R+ pair as intermediate should be reassessed.

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