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Donor cytomegalovirus serology impacts overall survival in children receiving first unrelated hematopoietic stem cell transplant for acute leukemia: European Society of Bone Marrow Transplantation Pediatric Diseases Working Party Study

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Running Heads: Impact of Donor CMV Status in Pediatric HSCT

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Despite the universal implementation of DNA-based screening and pre-emptive antiviral treatment, cytomegalovirus (CMV) infection remains a significant risk factor for morbidity and mortality in allogeneic hematopoietic stem cell transplantation (HSCT).[1-5] Patient CMV seropositivity prior to HSCT has consistently been associated with increased risk of CMV reactivation and CMV disease.[2, 6] Of note, overall survival (OS) remains inferior in CMV seropositive recipients irrespective of CMV disease[7, 8], suggesting that CMV mediates its detrimental impact not only via direct cytopathic effects but also through indirect effects related to viral replication and use of antiviral therapy on number and functionality of hematopoietic and immune cells. Previously published adult-focused registry analyses have shown that impact of patient's CMV serostatus on outcome may be mitigated by selecting donors displaying "compatible" CMV serostatus with selecting negative donors for negative patients providing more pronounced benefit.[1, 5] Based on paucity of such data in the setting of pediatric HSCT for acute leukemia (AL), the most frequent transplantation indication for children, we investigated the impact of CMV serostatus of donors and recipients in a large pediatric HSCT cohort homogeneously treated in the contemporary era and reported to the EBMT.

This is a retrospective study of pseudonymized clinical data reported to the European Society for Blood and Marrow Transplantation (EBMT) registry. The study was approved by the Pediatric Diseases Working Party (PDWP) of the EBMT institutional review board and conducted in accordance with the Declaration of Helsinki. Children (age <18y) with acute myeloid (AML) or lymphoblastic leukemia (ALL) receiving the first allogeneic HSCT between 2005 and 2021 were included. All patients received a bone marrow or peripheral blood transplant from an HLA-matched unrelated donor (10/10 at loci A, B, C, DRB1 and DQB1 in high resolution) uniformly. Transplant procedures using *in vivo* T-cell depletion (ATG or alemtuzumab) were included. Cord-blood transplantation, transplant procedures involving *ex vivo* T-cell depletion or PTCy were excluded. The primary objective was to assess the impact of donor CMV serology on overall survival (OS) in pediatric HSCT recipients with AML or ALL. The secondary objectives were the comparison of leukemia-free survival (LFS), non-relapse mortality (NRM), relapse incidence (RI), incidence of both acute graft versus host disease (aGvHD) and chronic GvHD (cGvHD), and GvHD-free/relapse-free survival (GRFS) between the seropositive (D+) and seronegative (D-) donor groups. Based on prior identification of substantial interaction between donor and recipient CMV serology in adult studies[1], all analyses were performed in two separate cohorts: CMV seropositive (R+) and CMV seronegative (R-) pediatric HSCT recipients. The analyses were performed separately in the 2 following groups: CMV positive patients and CMV negative children receiving an UD10/10 (MUD) HSCT. Quantitative variables were described as median, quartiles 1 and 3, minimum, and maximum. Differences between quantitative variables and donor CMV seropositivity were tested using Wilcoxon tests. Qualitative variables are described as numbers and percentages. Differences between qualitative variables and donor CMV seropositivity were tested using Chi-square tests or exact Fisher tests. OS, LFS, and GRFS were estimated using the Kaplan-Meier estimator. Variables with competing events were estimated using the cumulative incidence function. Median follow-up was estimated using the reverse Kaplan-Meier estimator. The impact of donor CMV serology was estimated and

tested using Cox models. Adjusting factors, which were selected according to their potential impact on survival, were source of cells (BM or PB), indicator of female donor to male recipient, Disease Risk Index (DRI) as two categories (Low/Intermediate vs High/Very High), use of TBI, patient age at transplant, donor age at transplant, and year of transplant. The Disease Risk Index was calculated as defined by Armand et al.[9] and using for the AML the cytogenetic classification of the ELN2017[10]. The center effect was considered frailty. Punctual estimation of the outcomes and hazard ratio were given with their 95% confidence interval. Two-sided P values <0.05 were considered statistically significant. Analyses were performed using the statistical R software version 4.0.2.

In total, 1640 AL patients (R+: 909; R-: 731) with a median age of 8.9 years (0.3–18 years) were analyzed. Patient, disease and transplant characteristics and transplant outcomes are summarized in *Online Supplementary Tables S1 and S2*, respectively.

In R+ patients, those receiving HSCT from a seropositive donor (R+/D+) had a significantly better OS (2y: 79% vs 69%, HR, 0.66; p=0.002) (Figure 1a), better LFS (2y: 70% vs 63%, HR 0.75; p=0.01) and lower NRM (2y: 7% vs 13%, HR, 0.52; p=0.004) compared to children transplanted from a seronegative donor (R+/D-) in Cox multivariable analyses. Donor CMV serology showed no significant association with RI, aGVHD, cGVHD or GRFS. Use of TBI (HR, 0.70; p=0.01) and HSCT in more recent years (HR, 0.79; p=0.01) correlated significantly with improved OS, whereas high/very high disease risk index (DRI) was associated with worse OS (HR, 1.57; p<0.001) (Table 1).

In contrast, in R- patients, donor CMV serology had no significant association with OS (Figure 1b) (2y: 79% vs 76%, HR, 1.13; p=0.47), LFS (2y: 70% vs 65%, HR, 1.15; p=0.35), RI (2y: 24% vs 24%, HR, 1.04; p=0.82) or NRM (2y: 7% vs 11%, HR, 1.53; p=0.14) in seronegative and seropositive donors, respectively in Cox multivariable analysis. The only factor independently associated with OS was increasing patient age (HR, 1.17; p<0.001) (Table 1).

In total, 237/909 patients in R+ group and 181/731 patients in R- group died (*Online Supplementary Table S3*). Relapse was the main cause of death in all serology categories followed by infections.

Multivariable Cox analysis revealed that several other patient, disease and transplant characteristics besides CMV serology proved significantly associated with LFS, NRM and RI: For R+ patients LFS was lower for patients with High/Vhigh DRI (HR, 1.60; p<0.001) and higher with TBI use (HR, 0.71; p=0.007). NRM was higher in older patients (HR, 1.18; p=0.01). RI was lower for patients with female to male donor (HR, 0.60; p=0.008), conditioning with TBI (HR, 0.73; p=0.04), increasing patient (HR, 0.89; p=0.01) and donor age (HR, 0.95; p=0.048), but higher for patients with high/Vhigh DRI (HR, 1.84; p<0.001). For R- patients, LFS was lower for patients with High/Vhigh DRI (HR, 1.39; p=0.01) and older patients (HR, 1.10; p=0.01). Increasing age of the patient and donor was associated with higher NRM (HR, 1.35; p<0.001 and HR, 1.10; p=0.04). RI was lower for patients with TBI conditioning (HR, 0.73; p=0.040) but higher for patients with high/Vhigh DRI (HR, 1.53,

p=0.006). The effect of TBI on transplant outcomes were thought to be related to the ALL patients as only 30 AML received TBI. Thus, multivariable Cox analysis validates well known risk factors for LFS, NRM, and RI in this cohort.

In this largest pediatric-only registry study performed to date, a CMV seropositive donor for a CMV seropositive patient was independently associated with significantly better OS (HR, 0.66; p=0.002), better LFS (HR, 0.75; p=0.01) and lower NRM (HR,0.52; p=0.004) compared with a CMV seronegative donor in 10/10 matched unrelated donor HSCT. However, no such effect was found in CMV seronegative patients. To date, some studies including predominantly adults have revealed that CMV serostatus of the donor had no influence on outcome[8] while others reported an advantage of D+ donor for a R+ patient with better OS and lower TRM[5] and decreased OS in D+/R- transplants[1]**.** In contrast, our analysis from a large contemporary and purely pediatric cohort comprising more than 1600 children undergoing allogeneic HSCT for AL shows that even in the current era of DNA-based CMV screening and pre-emptive antiviral therapy selecting a CMV-seropositive vs. CMV-seronegative donor for a CMV-seropositive patient is associated with 34% reduced risk for overall death and 48% lower risk for NRM in adjusted analyses.

While our registry-based analysis represents the largest pediatric study to date on the impact of donor CMV serology on HSCT outcome, it is important to acknowledge inherent limitations. These possibly include occasional discrepancies in the reported CMV serostatus data, the lack of detailed data on CMV reactivation, disease, and treatment, including prophylactic use of letermovir in recent years, as well as other infectious complications. This renders any mechanistic explanation of the effect of CMV donor serostatus on outcome speculative.[11] In addition, cautious interpretation of patient CMV serology results, considering both potential false positives (e.g. adoptive transfer) and negatives (e.g. loss of antibodies during pre-transplant treatment), is mandatory.[12, 13]

Our findings may significantly influence clinical practice regarding donor selection strategies, particularly when multiple 10/10 HLA-matched unrelated donors are available. As donor CMV serology had no obvious association with outcome in CMV seronegative children, our study implicates that choosing a seropositive donor might be a wise approach in cases of ambiguous recipient CMV serostatus. Within the well-appreciated limits of cross-study comparisons it is notable that the relative overall mortality risks of CMV mismatching in seropositive patients in our study ranges in the same order of magnitude as the negative impact of 7/8 vs. 8/8 HLA matching and exceeds that of donor age (in 10-year increments) in the recent CIBMTR analysis.[8]

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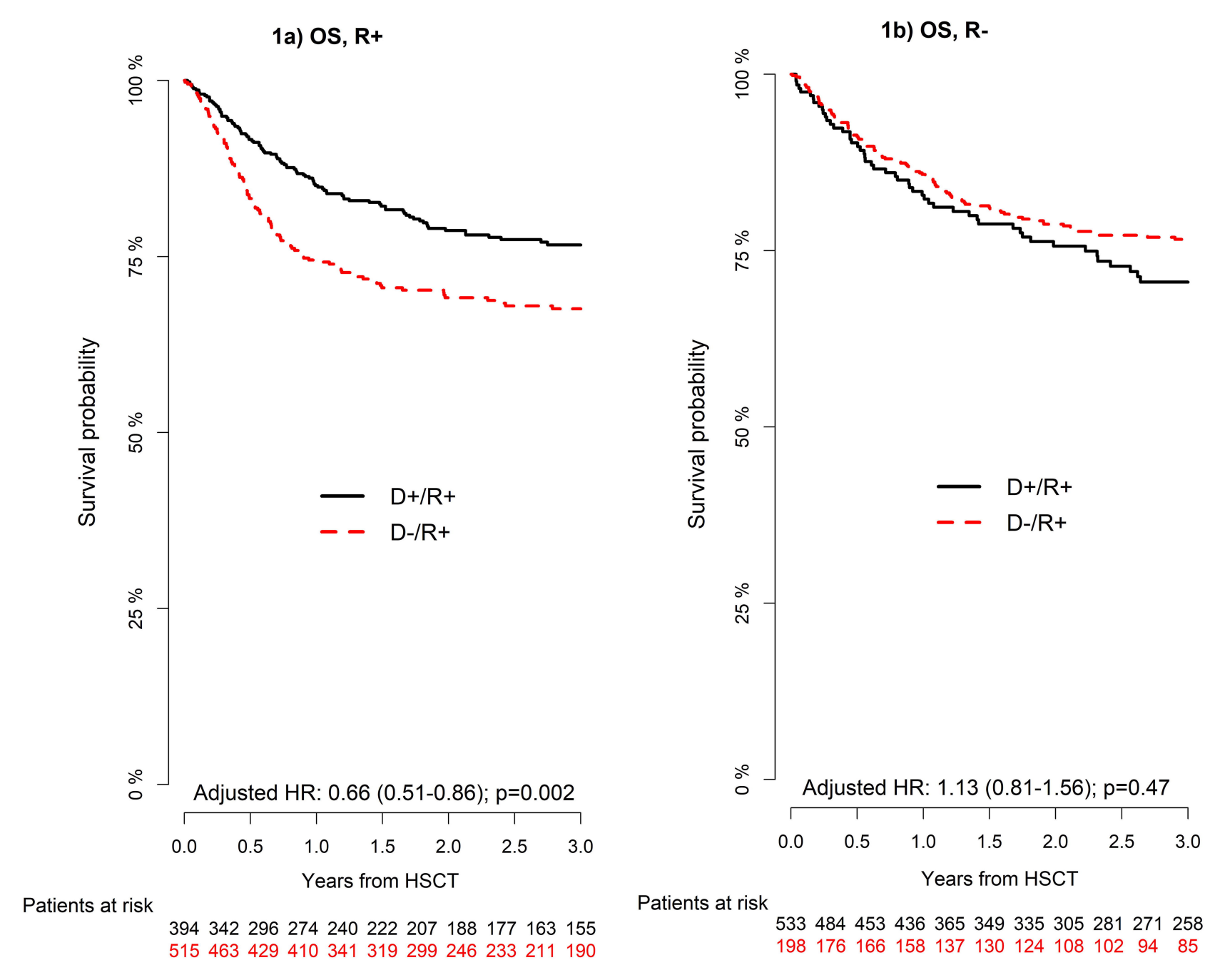
Table 1. Association of Donor CMV Serology with Transplant Outcomes in Multivariable Cox Regression Analysis

Parameter	OS	LFS	NRM	RI	Acute GVHD II-IV	Chronic GVHD	GRFS
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
CMV Seropositive Patients							
Donor CMV (-) vs (+)	**0.66 (0.51-0.86) p=0.002**	**0.75 (0.59-0.94) p=0.01**	**0.52 (0.34-0.81) p=0.004**	0.86 (0.66-1.13) p=0.28	0.97 (0.61-1.56) p=0.68	1.06 (0.72-1.56) p=0.76	0.83 (0.68-1.03) p=0.09
Source of cells (BM vs PB)	1.20 (0.90-1.58) p=0.21	1.27 (0.99-1.61) p=0.051	1.40 (0.88-2.23) p=0.15	1.22 (0.92-1.60) p=0.16	**1.43 (1.07-1.91) p=0.02**	1.18 (0.75-1.84) p=0.48	**1.39 (1.10-1.76) p=0.006**
Female to Male (No vs Yes)	0.73 (0.52-1.03) p=0.07	0.75 (0.56-1.01) p=0.06	1.21 (0.73-2.00) p=0.46	**0.60 (0.41-1.87) p=0.008**	1.32 (0.99-1.75) p=0.06	1.22 (0.78-1.90) p=0.38	1.16 (0.90-1.50) p=0.24
DRI (Low/Int vs High/Vhigh)	**1.57 (1.20-2.06) p<0.001**	**1.60 (1.26-2.02) p<0.001**	1.12 (0.72-1.73) p=0.63	**1.84 (1.39-2.44) p<0.001**	1.09 (0.85-1.40) p=0.5	0.97 (0.66-1.44) p=0.9	**1.39 (1.13-1.72) p=0.002**
TBI (No vs Yes)	**0.70 (0.52-0.92) p=0.01**	**0.71 (0.55-0.91) p=0.007**	0.67 (0.42-1.06) p=0.09	**0.73 (0.55-0.99) p=0.04**	1.30 (0.99-1.69) p=0.06	0.76 (0.51-1.15) p=0.19	**0.69 (0.55-0.86) p<0.001**
Age at HSCT (inc. 3y)	1.05 (0.97-1.14) p=0.20	0.97 (0.91-1.04) p=0.41	**1.18 (1.03-1.34) p=0.01**	**0.89 (0.82-0.97) p=0.01**	0.93 (0.86-1.01) p=0.08	**1.17 (1.04-1.32) p=0.01**	1.00 (0.94-1.06) p=0.97
Donor Age at HSCT (inc. 3y)	0.96 (0.92-1.01) p=0.13	0.96 (0.92-1.01) p=0.09	1.00 (0.92-1.08) p=0.91	**0.95 (0.90-0.99) p=0.048**	1.03 (0.99-1.08) p=0.15	1.00 (0.93-1.08) p=0.92	0.98 (0.95-1.02) p=0.42
Year of HSCT (inc. 5y)	**0.79 (0.65-0.95) p=0.01**	0.89 (0.75-1.05) p=0.16	0.88 (0.64-1.21) p=0.44	0.88 (0.72-1.07) p=0.19	0.99 (0.82-1.20) p=0.95	0.98 (0.74-1.31) p=0.9	0.86 (0.74-1.01) p=0.06
CMV Seronegative Patients							
Donor CMV (-) vs (+)	1.13 (0.81-1.56) p=0.47	1.15 (0.86-1.52) p=0.35	1.53 (0.87-2.69) p=0.14	1.04 (0.75-1.45) p=0.82	1.20 (0.88-1.65) p=0.25	0.82 (0.48-1.42) p=0.48	1.27 (0.99-1.63) p=0.06
Source of cells (BM vs PB)	1.05 (0.76-1.44) p=0.78	0.99 (0.74-1.31) p=0.93	0.71 (0.38-1.31) p=0.27	1.09 (0.79-1.50) p=0.62	**1.43 (1.02-1.99) p=0.04**	1.53 (0.91-2.58) p=0.11	1.04 (0.81-1.34) p=0.75
Female to Male (No vs Yes)	0.74 (0.49-1.13) p=0.16	0.75 (0.52-1.07) p=0.11	0.76 (0.35-1.63) p=0.48	0.75 (0.50-1.13) p=0.17	1.02 (0.68-1.51) p=0.94	1.23 (0.70-2.19) p=0.47	0.78 (0.57-1.08) p=0.14
DRI (Low/Int vs High/Vhigh)	1.11 (0.83-1.50) p=0.48	**1.39 (1.07-1.81) p=0.01**	1.04 (0.61-1.78) p=0.88	**1.53 (1.13-2.06) p=0.006**	0.88 (0.66-1.18) p=0.39	0.71 (0.45-1.14) p=0.16	**1.32 (1.04-1.66) p=0.02**
TBI (No vs Yes)	0.74 (0.55-1.01) p=0.05	0.80 (0.62-1.04) p=0.09	1.06 (0.61-1.85) p=0.82	**0.73 (0.54-0.98) p=0.04**	**1.68 (1.24-2.28) <0.001**	0.85 (0.52-1.38) p=0.5	0.92 (0.73-1.16) p=0.46
Age at HSCT (inc. 3y)	**1.17 (1.07-1.28) p<0.001**	**1.10 (1.02-1.19) p=0.01**	**1.35 (1.14-1.61) p<0.001**	1.04 (0.95-1.13) p=0.39	0.95 (0.86-1.03) p=0.21	**1.21 (1.05-1.41) p=0.01**	**1.08 (1.01-1.16) p=0.02**
Donor Age at HSCT (inc. 3y)	1.04 (0.98-1.09) p=0.19	1.02 (0.97-1.07) **p=**0.38	**1.10 (1.01-1.20) p=0.04**	1.00 (0.94-1.05) p=0.89	**1.07 (1.01-1.12) p=0.01**	1.07 (0.99-1.16) p=0.07	1.03 (0.99-1.07) p=0.14
Year of HSCT (inc. 5y)	0.94 (0.77-1.15) p=0.55	1.01 (0.85-1.20) p=0.94	0.91 (0.67-1.40) p=0.87	1.01 (0.83-1.24) p=0.9	0.88 (0.73-1.06) p=0.19	0.92 (0.68-1.25) p=0.6	0.81 (0.70-0.94) 0.006

OS: Overall survival; LFS: Leukemia free survival; RI: Relapse Incidence; NRM: Non relapse mortality; aGVHD: acute graft versus host disease; GRFS: Graft versus host disease free relapse free survival; cGVHD: chronic graft versus host disease; ext: extensive; DRI: Disease risk index; TBI: Total body irradiation; inc: increments; HSCT: Hematopoietic stem cell transplantation; BM: Bone marrow; PB: Peripheral blood; Low/Int: Low/Intermediate; High/Vhigh: High/Very High

Figure 1. Overall survival (OS) in relation to patient and donor CMV serology. 1a Kaplan-Meier estimates of OS in R+ patients undergoing matched unrelated HSCT from a seronegative (*in red*) versus seropositive (*in black*) donors. 1b. Kaplan-Meier estimates of OS in R- patients undergoing matched unrelated HSCT from a seronegative (*in red*) versus seropositive (*in black*) donors.


1a) OS, R+
100 %
75 %
50 %
25 %
0 %
Survival probability
D+/R+
D-/R+
Adjusted HR: 0.66 (0.51-0.86); p=0.002
0.0 0.5 1.0 1.5 2.0 2.5 3.0
Years from HSCT
Patients at risk
394 342 296 274 240 222 207 188 177 163 155
515 463 429 410 341 319 299 246 233 211 190
1b) OS, R-
100 %
75 %
50 %
25 %
0 %
Survival probability
D+/R+
D-/R+
Adjusted HR: 1.13 (0.81-1.56); p=0.47
0.0 0.5 1.0 1.5 2.0 2.5 3.0
Years from HSCT
Patients at risk
533 484 453 436 365 349 335 305 281 271 258
198 176 166 158 137 130 124 108 102 94 85

Supplement Table 1. Patient, disease and transplant characteristics

	All patients	CMV Seropositive Patients			CMV Seronegative Patients		
Variables	**n=1640**	**R+/D- (n=394)**	**R+/D+ (n=515)**	**p-value**	**R-/D- (n=533)**	**R-/D+ (n=198)**	**p-value**
Year of transplant Median (range)	2017 (2005-2021)	2017 (2006-2021)	2018 (2005-2021)	0.004	2016 (2005-2021)	2016 (2005-2021)	0.61
Patient age Median (range)	8.9 (0.3-18)	8.7 (0.5-18)	8.3 (0.3-18)	0.35	9.3 (0.4-18)	9.8 (0.5-17.9)	0.79
Donor age Median (range)	28 (18-57.4)	28 (18-57.4)	28.8 (18.6-54.9)	0.49	27 (18-53.3)	31.6 (18.2-54.4)	< 0.001
Source of cells							
BM	1022 (62.3)	241 (61.2)	274 (53.2)	0.02	388 (72.8)	119 (60.1)	< 0.001
PB	618 (37.7)	153 (38.8)	241 (46.8)		145 (27.2)	79 (39.9)	
Patient sex							
Female	640 (39)	143 (36.3)	211 (41)	0.15	204 (38.3)	82 (41.4)	0.44
Male	1000 (61)	251 (63.7)	304 (59)		329 (61.7)	116 (58.6)	
Donor sex							
Female	558 (34.1)	134 (34)	188 (36.6)	0.41	172 (32.3)	64 (32.3)	0.99
Male	1080 (65.9)	260 (66)	325 (63.4)		361 (67.7)	134 (67.7)	
Missing	2	0	2		0	0	
Female to Male							
No	1335 (81.4)	308 (78.2)	419 (81.4)	0.23	444 (83.3)	164 (82.8)	0.88
Yes	305 (18.6)	86 (21.8)	96 (18.6)		89 (16.7)	34 (17.2)	
Underlying Disease							
ALL	1071 (65.3)	247 (62.7)	348 (67.6)	0.13	348 (65.3)	128 (64.6)	0.87
AML	569 (34.7)	147 (37.3)	167 (32.4)		185 (34.7)	70 (35.4)	
DRI							
Low/Int	798 (48.7)	190 (48.2)	253 (49.1)	0.79	265 (49.7)	90 (45.5)	0.31
High/Very High	842 (51.3)	204 (51.8)	262 (50.9)		268 (50.3)	108 (54.5)	
MAC							
No	60 (3.7)	12 (3)	29 (5.6)	0.06	14 (2.6)	5 (2.5)	0.94
Yes	1580 (96.3)	382 (97)	486 (94.4)		519 (97.4)	193 (97.5)	
TBI							
No	909 (55.4)	229 (58.1)	303 (58.8)	0.83	271 (50.8)	106 (53.5)	0.52
Yes	731 (44.6)	165 (41.9)	212 (41.2)		262 (49.2)	92 (46.5)	
GVHD prevention							
CSA+MTX	1165 (71)	294 (74.6)	410 (79.6)	0.21	320 (60)	141 (71.2)	0.01 f
CSA	271 (16.5)	51 (12.9)	44 (8.5)		144 (27)	32 (16.2)	
CSA + Other	74 (4.5)	12 (3)	19 (3.7)		33 (6.2)	10 (5.1)	
CSA+MTX+other	31 (1.9)	7 (1.8)	6 (1.2)		15 (2.8)	3 (1.5)	
Other nonCSA	9 (6)	30 (7.6)	36 (7)		21 (3.9)	12 (6.1)	

Shown are numbers of patients (%) except ones indicated as median (Range) R+: CMV seropositive patient; R-: CMV-seronegative patient; D+: CMV-seropositive donor; D+: CMV-seronegative donor; BM: Bone Marrow; PB: Peripheral Blood; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; DRI: Disease Risk Index; Int: Intermediate; MAC: Myeloablative conditioning; TBI: Total Body Irradiation; GVHD: Graft versus Host Disease; CSA: Cyclosporine; MTX: Methotrexate; f: Exact Fisher test

Supplement Table 2. Association of CMV serostatus with OS, LFS, RI, NRM, Myeloid Recovery, aGVHD, cGVHD and GRFS in different HLA and patient CMV serology group

	All Patients	CMV Seropositive Patients		CMV Seronegative Patients	
Outcomes	N=1640	R+/D- (N=394)	R+/D+ (N=515)	R-/D- (N=533)	R-/D+ (N=198)
F/U (yrs) Median (95%CI)	3.6 (3.4 - 3.9)	3.5 (3.1 - 4)	2.9 (2.6 - 3.1)	4.4 (4 - 4.8)	4 (3.2 - 4.7)
OS (2 yrs)	74.8 (72.9 - 76.6)	69.1 (64.1 - 73.6)	78.7 (74.6 - 82.2)	78.7 (74.8 - 82.1)	75.6 (68.7 - 81.2)
LFS (2 yrs)	66.8 (64.7 - 68.8)	63.3 (58.1 - 68)	69.5 (65.1 - 73.5)	69.9 (65.7 - 73.8)	65.2 (57.8 - 71.6)
RI (2 yrs)	23.3 (21.5 - 25.1)	23.9 (19.6 - 28.3)	23.3 (19.5 - 27.3)	23.6 (19.9 - 27.4)	24.3 (18.3 - 30.7)
NRM (2 yrs)	9.9 (8.7 - 11.3)	12.9 (9.7 - 16.4)	7.2 (5.1 - 9.7)	6.5 (4.6 - 8.9)	10.5 (6.7 - 15.4)
Myeloid recovery (30 d)	89.8 (88.5 - 91)	89.2 (85.7 - 92)	92.1 (89.3 - 94.2)	90.5 (87.6 - 92.7)	90.1 (84.8 - 93.6)
Myeloid recovery (60 d)	97.6 (96.8 - 98.2)	97.9 (95.8 - 99)	98.1 (96.4 - 99)	99 (97.6 - 99.6)	96.9 (93 - 98.6)
aGVHD-II/IV (100 d)	33.8 (31.8 - 35.8)	33.3 (28.7 - 38.1)	32 (27.9 - 36.2)	27.8 (24 - 31.7)	36.1 (29.4 - 42.8)
aGVHD-III/IV (100 d)	11 (9.8 - 12.4)	9.9 (7.2 - 13.1)	9 (6.6 - 11.7)	7.6 (5.5 - 10.1)	12.4 (8.2 - 17.4)
GRFS (2 yrs)	54.2 (52 - 56.4)	52.5 (47.1 - 57.5)	57 (52.1 - 61.5)	58.7 (54.1 - 63.1)	49.8 (42 - 57.1)
CGVHD (2 yrs)	14.6 (13 - 16.2)	14.2 (10.7 - 18.1)	15.7 (12.3 - 19.3)	12.7 (9.7 - 16)	12.8 (8.1 - 18.6)
CGVHD Ext. (2 yrs)	5.8 (4.8 - 7)	5.3 (3.3 - 8.1)	6.5 (4.4 - 9.2)	4.4 (2.7 - 6.6)	5.6 (2.8 - 10)

F/U: follow-up; OS: Overall survival; LFS: Leukemia free survival; RI: Relapse Incidence; NRM: Non relapse mortality; aGVHD: acute graft versus host disease; GRFS: Graft versus host disease free relapse free survival; cGVHD: chronic graft versus host disease; Ext: Extensive; d: days; yrs: years

Supplement Table 3. Causes of Death

	Seropositive Patients		Seronegative Patients	
Cause of death	**R+/D- (N=125)**	**R+/D+ (N=112)**	**R-/D- (N=127)**	**R-/D+ (N=54)**
Relapse [n (%)]	75 (60)	76 (68.5)	91 (71.7)	33 (61.1)
Infections [n (%)]	25 (20)	18 (16.2)	17 (13.4)	8 (14.8)
GVHD + Infection [n (%)]	5 (4)	6 (5.4)	3 (2.4)	1 (1.9)
GVHD [n (%)]	6 (4.8)	2 (1.8)	5 (3.9)	2 (3.7)
Other transplant related [n (%)]	14 (11.2)	9 (8.1)	11 (8.7)	10 (18.5)
Missing	0	1	0	0

R+: CMV seropositive patient; R-: CMV-seronegative patient; D+: CMV-seropositive donor; D+: CMV-seronegative donor; GVHD: Graft versus Host Disease