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ORIGINAL ARTICLE

Cytomegalovirus infection is associated with AML relapse after allo-HSCT: a meta-analysis of observational studies

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Abstract

Cytomegalovirus (CMV) infection and primary disease relapse remain challenging problems after allogeneic hematopoietic stem cell transplantation (allo-HSCT). We sought to assess the association between CMV infection and disease relapse after transplantation. PubMed, EMBASE, the Cochrane Library, SCI, and Chinese Biomedicine Databases were searched up to July 1, 2018, for all studies that investigate pre-transplant CMV serostatus, CMV replication, and primary disease relapse in allo-HSCT patients with hematologic malignancies. Meta-analysis of 24 eligible cohort studies showed a significantly lower relapse risk after allo-HSCT in patients with CMV replication in acute myeloid leukemia (AML) (HR = 0.64, 95% CI, 0.50–0.83; $P < 0.001$) subgroup. However, CMV replication was associated with increased non-relapse mortality (NRM) in AML patients (HR = 1.64, 95% CI, 1.46–1.85; $P < 0.001$), but not associated with overall survival (OS) or graft-versus-host disease for AML patients ($P > 0.05$). There was no association between pre-transplant CMV serostatus and disease relapse, although D−/R− was associated with better OS in acute leukemia patients (HR = 0.89, 95% CI, 0.83–0.96; $P = 0.003$). In AML patients, CMV replication may be a protective predictor against disease relapse, although the potential benefit of CMV replication is offset by increased NRM.

Keywords Cytomegalovirus infection · Relapse · Acute myeloid leukemia · Allogeneic hematopoietic stem cell transplantation · Meta-analysis

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially lifesaving treatment for hematologic malignancies. Cytomegalovirus (CMV) infection remains a challenging problem in the allo-HSCT procedure from the early days of stem cell transplantation, causing significant morbidity and mortality [1]. Even in the era of prophylactic and preemptive therapy, viral replication is still regarded as bad, leading to CMV disease if not controlled by antivirals, which in turn cause cytopenia and renal damage [2, 3]. When selecting donors, CMV-negative bone marrow donors (D−) were considered preferable for CMV-negative patients (R−) because of the reduced risk of post-transplant CMV infection and disease in the recipients [4]; for CMV-seropositive patients (R+), CMV-seropositive donors (D+) were recommended, aided by increased levels of multifunctional CMV-specific T cells.

Consistent with previous results [5], we have demonstrated that a CMV-specific cytotoxic T lymphocyte (CTL) immune response must be reconstituted to confer long-term protection against CMV relapse and disease [6–8]. CMV replication after transplantation implies immunodeficiency and possible impaired immunosurveillance against residual leukemia. However, different groups have reported that CMV replication was associated with a reduced risk of disease relapse, while patients with pre-transplant CMV seronegativity serostatus from CMV-seronegative donors (D−/R−) had higher rate of disease relapse. This association was more prominent in patients with acute myeloid leukemia (AML) [9–11]. Additional studies [12, 13] have come to the inconsistent conclusion.

Yu-Lin Zhang and Yan Zhu contributed equally to this work.

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These observations derived from limited patient cohorts have not been reconfirmed so far. Given these data, we aimed to conduct a meta-analysis from all eligible studies published to date to evaluate whether CMV infection could affect the incidence of disease relapse after allo-HSCT with consideration of potential confounding factors. To address these issues, we have undertaken a systematic review of the literature and performed meta-analyses to investigate whether CMV infection was associated with disease relapse after allo-HSCT.

Materials and methods

Search strategy

We conducted a comprehensive literature search in Medline, EMBASE, the Cochrane Library, CINAHL, Web of Science, and Chinese Biomedicine Databases through July 2018. The search key words were as follows: "STEM CELL TRANSPLANTATION" or "HEMATOPOIETIC STEM CELL TRANSPLANTATION" or "BONE MARROW TRANSPLANTATION" or "PERIPHERAL BLOOD STEM CELL TRANSPLANTATION" or "CORD BLOOD STEM CELL TRANSPLANTATION" or "MESENCHYMAL STEM CELL TRANSPLANTATION" or "(PBPC or PBSCT or PSCT or BMT or SCT or HSCT)" or "allograft" or "allo-graft" or "allotransplant" or "allo-transplant" and "cytomegalovirus" or "cytomegalovirus infections" or "cmv" and "relapse" or "recurrence" or "relaps" or "recur." We excluded the studies published before 1980, as the development of transplantation dates back to the 1970s, and studies published between this period were considered less relevant [14]. The titles and abstracts were reviewed and full-text articles were selected based on our inclusion criteria. The reference list of each selected study was reviewed to search for additional studies.

Eligibility

An article was considered relevant if it contained original data from any type of study reporting the associations between CMV and disease relapse after allo-HSCT in all patients, regardless of the language in which it was published, with a minimum follow-up of 1 year. Furthermore, the relevant articles reported a hazard ratio (HR) or provided sufficient information to allow the calculation of relative risk (RR). Cross-sectional studies were excluded. The population of interest was patients with hematologic malignancies undertaking allo-HSCT, without any age restriction.

The included studies assessed at least one of the following outcomes: (1) The incidence of disease relapse in patients with CMV replication and in patients without replication; (2) the incidence of disease relapse in D−/R− patients and in other donor/recipient combination pairs. All included studies had clear definitions about pre-transplant CMV serology, CMV replication, and disease relapse after allo-HSCT. In the present study, CMV replication refers to CMV reactivation occurring in R+ and CMV primary infection in R−. CMV replication was monitored by quantitative real-time PCR, CMV PP65 antigenemia, or CMV culture assay. Studies were excluded when disease relapse and CMV replication were present at the start of the study. Any discrepancies on inclusion or exclusion of a study were resolved through consensus in all cases. If there were multiple publications from the same study, only the most recent was selected, and the older publications were used only to clarify methodology or characteristics of the population.

Data extraction

Two review authors (Y-L.Z, Y.Z) independently identified the articles by inclusion and exclusion criteria, assessed the quality of the articles, and completed a standardized data extraction form. Any discrepancies were addressed by a joint reevaluation of the original article with another author. For missing information, attempts were made to contact the authors of the original studies. If a direct report of the HR and a 95% confidence interval (95% CI) was not available, an estimated value was derived indirectly from other presented data using the methods described by Tierney et al [15]. The characteristics and quality of the studies included in this meta-analysis and their outcomes will be presented in accordance with the checklist proposed by the Meta-analysis Of Observational Studies group [16].

Statistical approach

The primary outcomes measured were the HR or RR with a 95% CI of developing disease relapse in patients with CMV replication, and that in D−/R− patients. We assessed for heterogeneity using the I^2 index [17] and Cochrane Q test [18]; I^2 values of 25, 50, and 75% were considered a reflection of mild, moderate, and severe heterogeneity, respectively. For analyses with unexplained statistical heterogeneity (I^2 statistics value of 75% or more), a random-effects model was used. The HR describes the RR of the complication based on comparison of event rates [19]. For the access of both the HR and RR, the HR was the first choice.

Publication bias was assessed with the trim-and-fill method, which estimated the missing studies that might exist in a meta-analysis and the effect that these studies might have had on its outcome [20]. The factors that may lead to heterogeneity were subjected to subgroup analysis. Subgroup analyses were performed by year of publication, region, disease diagnosis, graft manipulation, methods of detecting CMV infection, and antiviral therapy. If the heterogeneity between studies was too

large or when data sources could not be found, descriptive analysis was adopted. Subgroups were explored as covariates in the model, taking $P < 0.05$ as significant. All calculations and graphs were obtained with STATA11.0 (Stata Corp, College Station, TX). All studies were also evaluated independently by the same two reviewers for methodological quality by using the Newcastle-Ottawa Scale (NOS) [21]. We assigned NOS scores of 1–3, 4–6, and 7–9 for low, intermediate, and high-quality studies, respectively.

Results

Selection results

A total of 4221 articles were initially identified from the retrieved reports. The titles and abstracts were screened, and 4110 articles were excluded. From these remaining 111 studies, 82 were rejected after review of full-text. Finally, 24 studies [9–13, 22–40] were included in our analysis after excluding 5 letters because of low score (Fig. 1). For missing information, in fact, we have contacted the authors of the original studies to obtain missing information [10, 11]. The main characteristics of the 24 studies eligible for the systematic review are shown in Table 1. All included articles were cohort studies and were published between 1990 and 2018, accounting for 37,021 cases. According to the NOS, 23 studies (95.8%) were of high quality and 1 (4.2%) of intermediate quality. The mean quality score was 9 for the studies (maximum score 9).

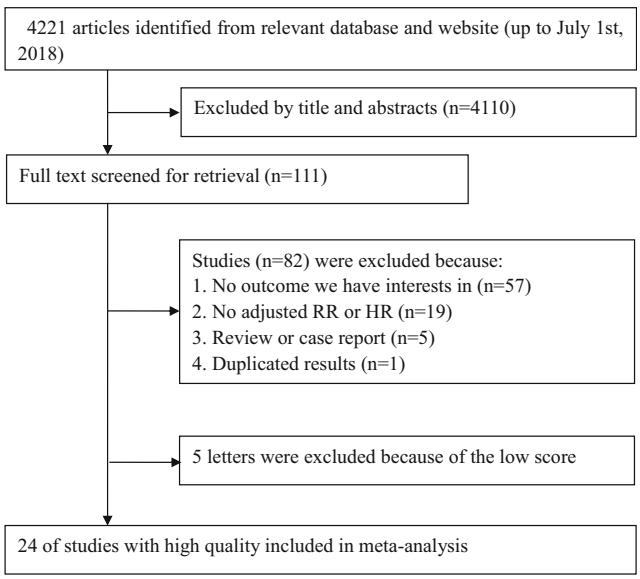

Fig. 1 Flow chart of the studies search and selection process

Incidence of relapse in D−/R− patients (D−/R− for relapse)

Ten studies [9–11, 22, 23, 27, 29, 33, 36, 39] reported the association between pre-transplant CMV serostatus and disease relapse. There was no evidence of publication bias (Begg's test $P = 1.000$; Egger's test $P = 0.189$) (Supplementary Fig. 1A). Unexpectedly, pre-transplant CMV seronegativity serostatus was not shown as an independent risk factor for relapse in the present analysis. In combined cohort, the HR of relapse in D−/R− patients with hematologic malignancies was 1.19 (95% CI, 0.93–1.52; $P = 0.169$), while HR of relapse in D−/R− patients with AML was 1.10 (95% CI, 0.82–1.48; $P = 0.51$) (Supplementary Fig. 2A-B). A study by Behrendt et al. [11] had the HR and RR at the same time, and a similar result was obtained when using the RR instead of the HR (HR = 1.17, 95% CI, 0.93–1.48; $P = 0.180$). Except studies using less ATG (> 10 and < 50%) (HR = 0.93, 95% CI, 0.87–0.99; $P = 0.026$), none of subgroup analyses proved a significant association between pre-transplant CMV serostatus and disease relapse (Table 2).

Incidence of relapse in patients with CMV replication (CMV replication for relapse)

The individual study values and complete subset analyses are shown in Table 2. Twenty-one studies [9, 10, 12, 13, 22, 24–38, 40] provided data on the association between CMV replication and disease relapse. Random-effects models were applied, for considerable heterogeneity was observed. Begg test indicated no publication bias even after trimming performed (Begg's test $P = 0.566$; Egger's test $P = 0.006$) (Supplementary Fig. 1B). In the combined studies, the HR of relapse in patients with CMV replication was 0.74 (95% CI, 0.63–0.87; $P < 0.001$) (Fig. 2a). There was a significant association observed in the acute leukemia (AL) (HR = 0.76, 95% CI, 0.64–0.89; $P = 0.001$), AML (HR = 0.64, 95% CI, 0.50–0.83; $P < 0.001$) (Fig. 2b), but not in acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), lymphoma, or myelodysplastic syndrome (MDS) groups. Moreover, the risk of disease relapse was decreased in patients with CMV replication in studies published after 2010 (HR = 0.73, 95% CI, 0.61–0.86; $P < 0.001$). Among them, AML accounts for 68.0% of patients with AL and 58.5% of patients in studies published after 2010. Interestingly, this association was observed in studies using methods of Q-PCR (HR = 0.65, 95% CI, 0.43–0.98; $P = 0.039$), with T cell replete (HR = 0.64, 95% CI, 0.51–0.81; $P < 0.001$), without ATG (HR = 0.61, 95% CI, 0.40–0.94; $P = 0.024$), with myeloablative conditioning (MAC) (HR = 0.71, 95% CI, 0.60–0.85; $P < 0.001$), with preemptive antiviral therapy (HR = 0.59, 95% CI, 0.43–0.81; $P = 0.001$), and stem cell source using peripheral blood stem cell (PB) (HR = 0.67, 95% CI, 0.54–0.84; $P = 0.001$). Moreover, studies performed in Asia (HR = 0.60, 95% CI, 0.42–0.86; $P = 0.005$), older patients (> = 40) (HR = 0.60, 95% CI, 0.43–0.84;

Table 1 Main characteristics of the eligible studies

Author (reference)	Publication	Country	Sample size	NOS score	Median patient age, years (range)	Methods of detecting CMV infection	Diagnosis	Graft type	Antiviral therapy	ATG/ alemtuzum	Graft manipulation	Conditioning intensity
Elmaagacli et al. [9]	2011	Germany (Europe)	266	9	47 (18–73)	CMV PP65 antigenemia	AML	Bone marrow (17%) and peripheral blood (83%)	Preemptive	NO	TCR	MAC
Nakamura et al. [13]	2004	USA (North America)	82	8	38 (10–56)	CMV PP65 antigenemia	Mixed (CML 50%)	Bone marrow (21%) and peripheral blood (79%)	Prophylaxis and preemptive	NO	TCD	MAC
Behrendt et al. [11]	2009	USA (North America)	140	9	11 (0–18)	CMV culture or Q-PCR	Mixed (ALL 57.9%, AML 38.6%, and MDS 3.6%)	Bone marrow (55%) and peripheral blood (45%)	Preemptive	NO	TCR	MAC
Beck et al. [22]	2010	USA (North America)	332	7	NR (0–35+)	CMV PP65 antigenemia, Q-PCR, or CMV culture	Mixed	Cord blood	Prophylaxis and preemptive	ATG (22.6%)	TCR	MAC (68%) and RIC (32%)
Jacobsen et al. [27]	1990	Sweden (Europe)	163	6	NR (1–49)	ELISA or CMV culture	AL (AML 44%, ALL 56%)	Bone marrow	NR	NO	TCR	MAC
Broers et al. [23]	2000	Netherland (Europe)	115	9	NR	CMV PP65 antigenemia or CMV culture	Mixed	Bone marrow (91%) and peripheral blood (9%)	Preemptive	NO	TCD (95%) and TCR (5%)	MAC
Tomonari et al. [39]	2008	Japan (Asia)	101	9	NR	CMV PP65 antigenemia	Mixed (AML 53%, ALL 17%)	Cord blood	Preemptive	NO	TCR	MAC
Green et al. [10]*	2013	USA (North America)	2566	9	42.4 (0.6–74.5)	CMV PP65 antigenemia	Mixed (AML, ALL, CML, MM, and lymphoma)	Peripheral blood (52%)	Preemptive	NO	TCR (96%) and TCD (4%)	MAC (83%)
Ito et al. [26]	2013	USA (North America)	110	9	36 (13–69)	CMV PP65 antigenemia or Q-PCR	CML	Bone marrow (24.5%) and peripheral blood (75.5%)	Prophylaxis and preemptive	NO	TCD (88%) and TCR (12%)	MAC (88%) and RIC (12%)
Schmidt-Hieber et al. [36]	2013	EBMT (Europe)	16,628	9	NR	NR	AL	Peripheral blood (73%)	NR	ATG (36.5%)	TCR (91.3%)	MAC (> 72%)
Manjappa et al. [12]	2014	USA (North America)	264	9	56	Q-PCR	AML	Bone marrow (9%) and peripheral blood (91%)	Preemptive	ATG (17%)	TCR	MA (78%) and RIC (22%)
Mariotti et al. [33]	2014	Italy (Europe)	265	8	45 (18–68)	CMV PP65 antigenemia	Lymphoma	Bone marrow (18%) and peripheral blood (92%)	Preemptive	ATG (45%)	TCD or TCR	MAC (26%) and RIC (74%)
Takenaka et al. [37]	2015	Japan (Asia)	3539	9	43 (16–74)	CMV PP65 antigenemia	Mixed	Bone marrow (72%) and peripheral blood (28%)	Preemptive	NO	TCR	MAC (78%) and RIC (23%)
Inagaki et al. [25]	2016	Japan (Asia)	143	9	7 (0–24)	CMV PP65 antigenemia	AL (AML and ALL)	Bone marrow (78%), peripheral blood	Preemptive	NR	NR	MAC

Table 1 (continued)

Author (reference)	Publication	Country	Sample size	NOS score	Median patient age, years (range)	Methods of detecting CMV infection	Diagnosis	Graft type	Antiviral therapy	ATG/ alemtuzum	Graft manipulation	Conditioning intensity
								(3%), and cord blood (18%)				
Jang et al. [28]	2015	Korea (Asia)	74	8	35 (15–59)	Q-PCR	AML	Bone marrow (7%) and peripheral blood (93%)	Preemptive	NO	TCR (85%)	MAC (92%) and RIC (8%)
Niu et al. [34]	2015	China (Asia)	62	8	30	Q-PCR	AML	NR	Preemptive	ATG (47%)	TCR	MAC
Teira et al. [38]	2016	CIBMTR (North America)	9469	9	NR	Q-PCR	Mixed (AML, ALL, MDS, and CML)	Bone marrow (26%) and peripheral blood (74%)	NR	ATG (28.5%)	TCR (5%)	MAC (75.7%), RIC (24.2%), and missing (0.1%)
Ramanathan et al. [35]	2016	CIBMTR (North America)	1684	9	NR	NR	AL	Cord blood	NR	NR	NR	MAC (74%) and RIC (26%)
Yoon et al. [40]	2016	Korea (Asia)	389	9	37.9 (18–65)	Q-PCR	AL	Bone marrow (48%), cord blood (1%), and peripheral blood (51%)	Preemptive and prophylaxis	ATG (28%)	NR	MAC (67%) and RIC (33%)
Kim et al. [30]	2006	Korea (Asia)	76	9	34.5 (17–54)	CMV PP65 antigenemia	Mixed	Peripheral blood	Preemptive and prophylaxis	ATG (13%)	TCR	MAC (75%) and RIC (25%)
Jeljeli et al. [29]	2014	France (Europe)	108	9	8 (0–18)	Q-PCR	AL	Bone marrow (74%), cord blood (16%) and peripheral blood (10%)	Preemptive	ATG (38%)	NR	MAC
Chen et al. [24]	2015	China (Asia)	248	9	31 (14–56)	Q-PCR	Mixed	Peripheral blood or bone marrow	Preemptive and prophylaxis	ATG	TCR	MAC
Koldehoff et al. [31]	2017	Germany (Europe)	136	9	47 (18–72)	CMV PP65 antigenemia or Q-PCR	NHL	Bone marrow (8%), peripheral blood (92%)	Preemptive	ATG (42%)	NR	MAC (79%) and RIC (21%)
Lin et al. [32]	2016	China (Asia)	61	8	25 (6–54)	Q-PCR	Mixed	Peripheral blood	Preemptive and prophylaxis	ATG	TCR	MAC

Abbreviations: *AML*, acute myeloid leukemia; *ALL*, acute lymphoblastic leukemia; *AL*, acute leukemia; *CML*, chronic myeloid leukemia; *MM*, multiple myeloma; *NHL*, non-Hodgkin lymphoma; *Mixed*, hematologic malignancies without a definite subtype; *TCR*, T cell replete; *TCD*, T cell deplete; *Preemptive*, preemptive therapy of CMV infection; *Prophylaxis*, prophylaxis therapy of CMV infection; *Q-PCR*, quantitative real-time PCR of CMV; *MAC*, myeloablative conditioning; *RIC*, reduced-intensity conditioning or non-myeloablative conditioning; *NR*, not reported

Table 2 Subset analyses of CMV serostatus/replication and risk of disease relapse

	D−/R− for relapse				CMV replication for relapse			
	No. of studies	HR (95% CI)	*P*	I^2 (%)	No. of studies	HR (95% CI)	*P*	I^2 (%)
Overall outcome	10	1.19 (0.93–1.52)	0.169	77.7	21	0.74 (0.63–0.87)	< 0.001	75.1
Publication year								
> 2010	5	1.04 (0.81–1.33)	0.761	76.4	17	0.73 (0.61–0.86)	< 0.001	75.0
≤ 2010	5	1.45 (0.74–2.85)	0.285	77.2	4	0.90 (0.41–2.00)	0.803	80.0
Diagnosis								
AML	3	1.10 (0.82–1.48)	0.514	87.3	9	0.64 (0.50–0.83)	< 0.001	80.8
ALL	2	0.82 (0.60–1.12)	0.213	55.4	5	1.07 (0.92–1.25)	0.383	3.90
AL	5	1.20 (0.86-1.68)	0.272	84.6	14	0.76 (0.64–0.89)	0.001	74.0
CML	1	0.78 (0.45–1.35)	0.372	.	5	0.84 (0.60–1.17)	0.303	35.0
Lymphoma	2	0.81 (0.54–1.22)	0.315	0.0	3	0.60 (0.31–1.16)	0.128	65.2
MDS	1	1.22 (0.75–1.99)	0.424	.	3	0.88 (0.62–1.25)	0.475	37.8
Region								
Europe	6	1.26 (0.77–2.05)	0.364	83.0	6	0.59 (0.33–1.03)	0.063	86.0
North America	3	1.20 (0.74–1.94)	0.460	81.0	7	0.86 (0.68–1.09)	0.207	74.0
Asia	1	0.66 (0.17–2.59)	0.551	.	8	0.60 (0.42–0.86)	0.005	47.1
Methods of detecting CMV infection								
CMV PP65 antigenemia	4	1.10 (0.60–2.00)	0.763	82.3	7	0.74 (0.52–1.07)	0.110	75.4
Q-CMV PCR	1	0.86 (0.38–1.95)	0.719	.	8	0.65 (0.43–0.98)	0.039	73.2
Graft manipulation								
T cell replete (> 50%)[a]	8	1.27 (0.97–1.66)	0.087	.	13	0.64 (0.51–0.81)	< 0.001	77.1
T cell deplete (> 50%)[a]	1	0.67 (0.27–1.67)	0.390	.	2	1.22 (0.22–6.87)	0.821	88.1
ATG/alemtuzum								
ATG (100%)[a]	0	–	–	.	2	0.68 (0.30–1.56)	0.363	52.2
ATG (> 10 & < 50%)[a]	4	0.93 (0.87–0.99)	0.026	0.0	10	0.89 (0.75–1.05)	0.174	56.4
No ATG	5	1.31 (0.69–2.47)	0.411	84.7	7	0.61 (0.40–0.94)	0.024	80.4
Conditioning intensity								
MAC (> 50%)[a]	9	1.23 (0.95–1.60)	0.117	80.1	20	0.71 (0.60–0.85)	< 0.001	76.3
RIC (> 50%)[a]	1	0.8 (0.40–1.60)	0.528	.	1	1.00 (0.61–1.63)	1.000	.
Antiviral therapy								
Preemptive	7	1.16 (0.73–1.85)	0.536	77.5	10	0.59 (0.43–0.81)	0.001	71.6
Prophylaxis + preemptive	1	1.00 (0.71–1.41)	1.000	.	7	0.81 (0.52–1.26)	0.350	56.2
Median age (year)								
> = 40	3	1.18 (0.60–2.32)	0.633	88.0	6	0.60 (0.43–0.84)	0.003	75.7
> = 30 & < 40	0	–	–	–	7	0.62 (0.35–1.09)	0.099	66.6
< 30	2	1.66 (0.47–5.92)	0.435	80.5	3	0.83 (0.40–1.73)	0.619	47.5
Sample size								
> 153	7	1.30 (0.98–1.71)	0.066	84.0	12	0.79 (0.67–0.93)	0.004	77.0
= < 153	3	0.75 (0.43–1.31)	0.312	0.0	9	0.61 (0.37–1.01)	0.053	65.5
Stem cell source								
PB (> 50%)[a]	4	1.06 (0.81–1.38)	0.671	82.3	13	0.67 (0.54–0.84)	0.001	81.0
BM (> 50%)[a]	4	1.62 (0.72–3.67)	0.246	76.5	4	0.75 (0.46–1.23)	0.254	62.9
PB + BM	0	–	–	–	1	1.01 (0.48–2.14)	0.981	.
Cord	2	0.98 (0.70–1.36)	0.884	0.0	2	0.89 (0.73–1.10)	0.256	0.0

Abbreviations: *CMV*, cytomegalovirus; *D−/R−*, CMV-seronegative patients with CMV-seronegative donors; *HR*, hazard ratio; *AML*, acute myeloid leukemia; *CML*, chronic myeloid leukemia; *AL*, acute leukemia; *ALL*, acute lymphocytic leukemia; *MDS*, myelodysplastic syndrome; *Preemptive*, preemptive therapy of CMV infection; *Prophylaxis*, prophylaxis therapy of CMV infection; *Q-PCR*, quantitative real-time PCR of CMV; *MAC*, myeloablative conditioning; *RIC*, reduced-intensity conditioning or non-myeloablative conditioning; *PB*, peripheral blood stem cell; *BM*, bone marrow

[a] The percentage of patients

P = 0.003), and larger sample size (> 153) (HR = 0.79, 95% CI, 0.67–0.93; *P* = 0.004) are associated with decreased relapse after allo-HSCT (Table 2).

Influence of CMV serostatus or CMV replication on transplantation outcome

In the present analysis, CMV replication was an independent risk factor for increased non-relapse mortality (NRM) in patients with AML (HR = 1.64, 95% CI, 1.46–1.85; *P* < 0.001) and ALL (HR = 1.92, 95% CI, 1.57–2.34; *P* < 0.001) (Table 3). We did not observe any association of CMV replication with overall survival (OS) (HR = 0.86, 95% CI, 0.62–1.20; *P* = 0.377) and graft-versus-host disease (GVHD) (*P* > 0.05). D−/R− had no significant impact on NRM (HR = 0.81, 95% CI, 0.51–1.29; *P* = 0.377) in patients with AML, but there was better OS (HR = 0.89, 95% CI, 0.83–0.96; *P* = 0.003) in D−/R− patients.

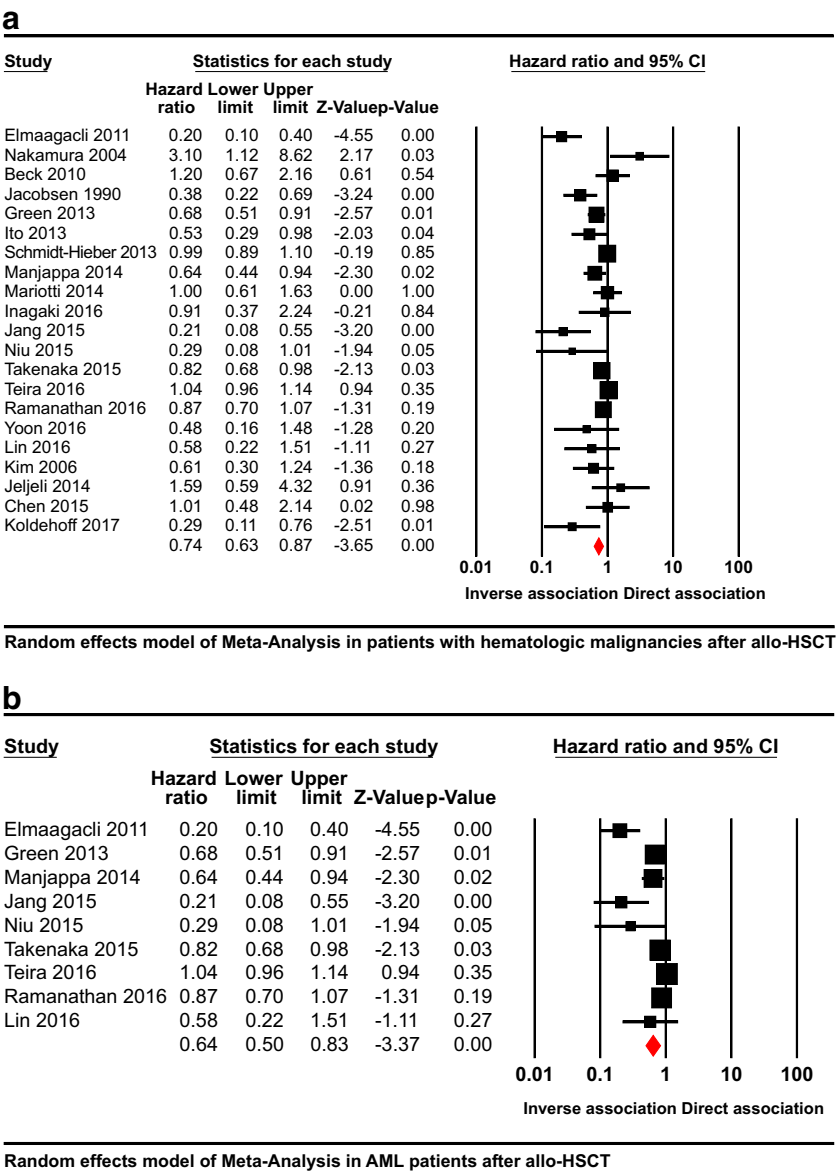

Fig. 2 Cumulative meta-analysis of the risk of disease relapse associated with CMV replication after transplantation. **a** Forest plot for the association between CMV replication and disease relapse; **b** forest plot for the association between CMV replication and disease relapse in patients with AML

Discussion

Recent advances in supportive care and donor selection reduce NRM after allo-HSCT. Nevertheless, little progress has been made to reduce the incidence of relapse. Relapse still represents the main cause for treatment failure [41]. CMV infection, as one of the most common and important complications in the allo-HSCT procedure, has recently been considered the favored factor of relapse based on a possible anti-leukemia effect. The results of the present study revealed the following: (1) There might be a significant protection against relapse in AML patients with CMV replication, but those patients had higher incidence of NRM; and (2) pre-transplant CMV serostatus had no significant impact on disease relapse after transplantation.

Relapse after allo-HSCT is associated with several factors, such as advanced disease status, high-risk cytogenetic, human leukocyte antigen match between graft and recipient, graft composition, GVHD, and delayed immune reconstitution [42–47]. After allo-HSCT, T cells are regenerated through thymic and peripheral pathways, with the thymus generating a more diverse T cell repertoire. In the first months after allo-HSCT, the repopulation of the T cell compartment is facilitated by cytokine- and antigen-driven homeostatic peripheral expansion of T cells that were transplanted with the graft [48]. Early cytomegalovirus replication leaves a specific and dynamic imprint on the reconstituting T cell compartment long-term after allo-HSCT [49]. Among patients who received ganciclovir at engraftment, those who had breakthrough antigenemia had significantly better recovery of T cell

Table 3 HR and 95% CI evaluating D−/R− and CMV replication as a risk factor for transplant outcome

Source (reference)	CMV replication for OS	CMV replication for NRM	CMV replication for GVHD	D−/R− for OS	D−/R− for NRM	D−/R− for GVHD
Elmaagacli et al. [9]	0.4 (0.3–0.7) AML	1.19 (0.68–2.07) AML	0.1 (0.04–0.4) AML-aGVHD	–	–	–
Schmidt-Hieber et al. [36]	–	–	–	0.85 (0.77–0.93) ALL 0.92 (0.86–0.98) AML	0.83 (0.73–0.95) ALL 0.98 (0.81–0.99) AML	–
Manjappa et al. [12]	–	–	0.33 (0.21–0.51) AML-cGVHD	–	–	–
Takenaka et al. [37]	–	1.60 (1.18–2.17) AML 1.74 (1.09–2.75) ALL	–	–	0.60 (0.38–0.96) AML 0.81 (0.38–1.70) ALL	–
Jang et al. [28]	0.22 (0.18–0.88) AML	–	–	–	–	–
Niu et al. [34]	–	–	1.03 (0.65–1.62) AML-aGVHD 2.19 (1.15–4.17) AML-cGVHD	–	–	–
Teira et al. [38]	1.28 (1.17–1.39) AML 1.48 (1.26–1.71) ALL	1.68 (1.46–1.91) AML 1.96 (1.54–2.39) ALL	1.09 (0.9–1.26) AML-aGVHD 1.00 (0.89–1.10) AML-cGVHD 1.14 (0.81–1.52) ALL-aGVHD 0.86 (0.63–1.08) ALL-cGVHD	–	–	–
Ramanathan et al. [35]	1.07 (0.88–1.30) AML	–	1.31 (0.96–1.79) AML-aGVHD 1.38 (0.96–1.98) ALL-aGVHD	–	–	–
Summary hazard ratio	0.68 (0.42–1.11) $P = 0.120$ AML 0.86 (0.62–1.20)[a] $P = 0.377$	1.64 (1.46–1.85) $P < 0.001$ AML 1.92 (1.57–2.34) $P < 0.001$ ALL	0.87 (0.55–1.39) $P = 0.564$ AML-aGVHD 0.88 (0.38–2.03) $P = 0.758$ AML-cGVHD 1.24 (0.98–1.57) $P = 0.078$ ALL-aGVHD	0.89 (0.83–0.96)[a] $P = 0.003$	0.81 (0.51–1.29) $P = 0.377$ AML 0.83 (0.73–0.94) $P = 0.005$ ALL 0.86 (0.73–1.02)[a] $P = 0.083$	–

− indicates not reported

Abbreviations: *HR*, hazard ratio; *D−/R−*, CMV-seronegative patients with CMV-seronegative donors; *CMV*, cytomegalovirus; *AML*, acute myeloid leukemia; *ALL*, acute lymphocytic leukemia; *OS*, overall survival; *NRM*, non-relapse mortality; *aGVHD*, acute graft-versus-host disease; *cGVHD*, chronic graft-versus-host disease

[a] Hematologic malignancies without a definite subtype

function at 3 months compared with patients who remained antigenemia negative [50]. CMV infection is required for the generation and/or maintenance of the CMV-specific T cell pool, and replication of latent virus was identified as the main factor leading to immune reconstitution [29, 51]. In the setting of allo-HSCT and the absence of high-dose steroids, low-level, short-term antigenemia may, in fact, have a protective effect by enhancing late immune function and anti-leukemia effect. On the other hand, CMV-specific CD8+ CTLs play an important role in controlling CMV replication after allo-HSCT, which can also indicate the strength of the donor T cell-mediated anti-leukemia effect [52–54]. It has been hypothesized that virus-specific CTLs may cross-recognize minor histocompatibility, serum and neutrophil elastase, or leukemia-associated antigens expressed on leukemic cells [55, 56].

We also demonstrated that this protective anti-leukemic effect restricted to AML, other than ALL, MDS, CML, or lymphoma. Actually, the primary AML marrow blasts can contain large CMV copy numbers in a significant proportion of affected patients [57]. CMV infection of residual AML marrow blasts may similarly fade to a latent state similar to latent CMV infections in other tissues after allogeneic HSCT. Recent results showed that CMV replication after HSCT can promote an increase in educated NKG2C+ natural killer cells and γδT cells which contribute to malignant disease relapse protection [58, 59]. Furthermore, CMV replication up-regulates the expression of leukocyte fixation antigen-3 on blasts carrying CMV, leading to enhanced NK cell-mediated lysis of the blasts [60]. This effect mediated by NK cell seems to be restricted to patients with myeloid malignancies.

Admittedly, the environment in which this analysis was conducted is not itself an uncontrolled factor in the association being studied. Factors like distributions of demographics, year of study, conditioning regimens, methods of detecting CMV infection, and antiviral therapy have the potential to affect both relapse and non-relapse mortality after allo-HSCT. Where CMV surveillance and preemptive antiviral therapy are implemented especially intensively, patients with CMV-seropositive grafts are likely to have little exposure to CMV; while CMV surveillance is less sensitive and preemptive therapy is applied sparingly, the environment is favorable for detecting an association between CMV and allo-HSCT outcome [61]. In the present study, it appears that the association between CMV replication and disease relapse was found in studies conducted in Asia, published after 2010, T cell replete PBSCT using MAC conditioning without ATG, in studies where CMV detected by real-time PCR with preemptive therapy. Interestingly, we also found that this effect was significant in studies with large sample size (> 153) and in older patients (> = 40). However, the number of AML patients accounted for most of patients in studies during the last 5 years. In fact, this association is restricted to patients with AML. Given that T cell replete, no ATG, MAC, and PB contributes to the beneficial effect in our subset analyses, T cells from donor may play a more important role than NK cells. Because of the CMV prevalence in Asia [62] and increased risk of CMV reactivation in the elderly [63, 64], preemptive antiviral therapy will be administered to patients with CMV reactivation by real-time PCR. In other words, manageable CMV antigenemia after allo-HSCT could be essential to the anti-leukemia effect.

CMV may have a deleterious impact on the overall outcome after allo-HSCT. We then investigated the impact of CMV infection on transplantation outcome. Despite the findings affirming a decreased risk of relapse in patients with CMV replication after transplantation, we continue to observe an association between CMV replication and NRM after HSCT and no significant positive association with GVHD. Therefore, it seems reasonable to assume that CMV replication by itself possibly promotes the strong long-term anti-leukemic effect observed in this study. CMV replication mostly comes from patients who are CMV seropositive, the risk of transmission of CMV from R+ could up to 30% in D−, and D −/R+ patients also have an increased risk of CMV disease [65]. In the present study, we also came to the same results that D+ and/or R+ patients had higher risk of developing CMV replication after transplantation when compared with D−/R− patients (supplementary Tables 1–2). Unexpectedly, there was no association between pre-transplant CMV seronegativity serostatus and disease relapse in the present analysis. Except pre-transplant CMV serostatus, there are other reported predictors of CMV infection including GVHD, corticosteroids use, or antivirals [4, 66]. Indeed, although the pre-transplant CMV serostatus could predict a reduced relapse risk for seropositive donor and/or recipient pairs in some studies, this effect was largely restricted to those patients who actually developed CMV infection post-transplantation.

Several potential limitations and strengths concerning our study findings need to be addressed. In the present meta-analysis, many of the individual patient data were unavailable for its systematic approach, and we used aggregate data as reported in published articles (or as provided by their authors). Thus, many clinical investigations could not be included even if they focused on this topic. Furthermore, observational studies are considered to have greater tendency towards publication bias than randomized clinical trials [67]. However, we conducted a subgroup analysis according to risk factors that may affect outcomes, and the heterogeneity became less evident. The attempts to identify unpublished data, search studies reported in languages other than English, and conduct a detailed assessment of the factors that influence the conclusion are the strengths of our study. Most importantly, based on the NOS, all of the studies included in this meta-analysis were of acceptable or high quality.

In conclusions, these limitations notwithstanding, the present meta-analysis shows that CMV replication may provide a

predictor of disease relapse in AML patients. CMV replication might contribute to a decreased relapse of AML after allo-HSCT. However, this benefit is offset by an increased risk of NRM. Additional studies are needed to confirm these findings and explore possible mechanisms of CMV infection and disease relapse after transplantation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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