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Review Article

Unrelated cord blood transplantation versus haploidentical transplantation in adult and pediatric patients with hematological malignancies-A meta-analysis and systematic review

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Abstract: Several clinical trials have compared the safety and efficacy of umbilical cord blood transplantation (UCBT) with haploidentical transplantation (HIT) in patients with hematological malignancies. To obtain more reliable evidence, we performed a systematic review and meta-analysis. Seven studies were included and there was a combined total of 102 children and 1311 adults undergoing UCBT, along with 94 children and 915 adults undergoing HIT. Pooled comparisons of studies of UCBT and HIT in children found that the incidence of chronic graft-versus-host disease (GVHD) and disease-free survival (DFS) at 2 years (RR 0.34, 95% CI (0.03, 4.53), P=0.41; HR 0.51, 95% CI (0.23, 1.09), P=0.08) were not statistically different. For adults, although the incidence of grade II-IV acute GVHD differ (RR 1.17, 95% CI (1.02, 1.34), P=0.02), but it indicates a very small difference between the groups as the RR is barely above 1. On the other hand, although the incidence of grade III-IV acute GVHD did not differ (RR 1.51, 95% CI (0.78, 2.92), P=0.22), but there is a tendency of higher risk for the UCBT. And the incidence of chronic GVHD did not differ (RR 1.05, 95% CI (0.82, 1.34), P=0.71). There was no difference in relapse, non-relapse mortality (NRM) and DFS at 2 years (HR 0.92, 95% CI (0.74, 1.13), P=0.42; HR 0.87, 95% CI (0.49, 1.52) P=0.62 and HR 0.74 95% CI (0.39, 1.43), P=0.37). In conclusion, UCBT and HIT could be considered as equally effective option for adult patients without HLA-matched donors.

Keywords: Umbilical cord blood transplantation, haploidentical transplantation, meta-analysis

Introduction

Allogeneic hematopoietic stem cell transplantation is considered to be a potentially curative treatment for many hematological malignancies. In the absence of HLA-matched donor, alternative donor sources i.e. unrelated umbilical cord blood (UCB) and haploidentical (haplo) donor, are suitable. Since the first successful umbilical cord blood transplantation (UCBT) performed in 1988 to treat a child with Fanconi anemia [1], cord blood transplantation has been used as an option to treat hematological malignancies. Meanwhile, haploidentical transplantation has also been increasingly used over the past two decades with the improvement of new GVHD prevention strategies, such as T cell depletion with high CD34+ doses to overcome risk of graft failure and high dose cyclophosphamide post transplantation [2-4]. A number of clinical trials have been conducted to evaluate the clinical outcomes of umbilical cord blood transplantation (UCBT) [5-13] for hematological disorders compared with haploidentical transplantation (HIT) [3, 14-17]. Transplantation using haploidentical donors with post-transplantation cyclophosphamide could be considered a valid alternative option for patients, Survival after transplantation was adjusted for potentially confounding transplantation-related variables in some studies [14, 15], Luznik L et al. [3] showed that modified

dose of MMF (increased the frequency of dosing of MMF) achieved reducing the rate of rejection. Presently the best option for patients lacking access to HLA-matched donor remains uncertain. EBMT (European Society for Blood and Marrow Transplantation) data [18] showed a striking increase of clinical cases in haplo transplants compared to UCB grafts, which suggests that UCBT tends to be replaced by HIT [19, 20] even everyone has a donor [21]. However, associated with reduction of transplant related mortality (TRM) and graft failure, another study [22] reported that CBT is potentially a better alternative of HIT. Therefore, the main of this systematic review was to evaluate whether UCBT is equivalent to HIT in treating adult [17, 23-26] and pediatric [27, 28] patients with hematopoietic malignancies, which may help clinicians and patients in choosing hematopoietic stem cell source for allogeneic hematopoietic stem cell transplantation (HSCT).

Methods

We systematically reviewed all data on comparative studies of UCBT versus HIT in which survival was the primary outcome measure. To obtain reliable evidence on the relative effect of UCBT versus HIT in the primary treatment of adults and children with hematological malignancies, and results from studies were integrated to increase statistical power. The secondary outcomes included GVHD, RI and NRM.

Search strategy

Relevant studies were identified through a computerized literature search of the MEDLINE, EMBASE, and the Cochrane Library. The following Medical Subject Headings (MeSH) terms were used for the initial literature search: “cord blood”, “umbilical”, “haploidentical” and the alternate search terms “transplant”, “transplantation” and “transplants”. We included all journal articles and searched these terms in the titles and abstracts. No language restrictions were applied. Full text papers were obtained to extract the data for analysis. References of retrieved articles were also checked for any relevant trials. Studies published before January 2019 were eligible. Our study is in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines issued in 2009 [29].

Selection criteria

All comparative studies of UCBT versus HIT were selected and all selected studies were retrospective, non-randomized and non-blinded. Patients were children and adults (range: 1-76 years) requiring allogeneic HSCT to treat malignant disorders. Data for GVHD, relapse, NRM and overall survival (OS) or disease-free survival (DFS) or GVHD-free relapse-free survival (GRFS) had to be available either in the articles or through personal communication. Each study was critically appraised for validity based on consistency and accuracy between treatment groups. Data were independently abstracted by two reviewers (Duihong Li and Xiaofan Li). Studies without comparable patient data between the 2 comparative groups were excluded.

Quality assessment

The risk of bias (eg. study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting) in each trial was independently assessed by the two authors, using the Quality In Prognosis Studies (QUIPS) tool [30].

Statistical analyses

To estimate the treatment effects, outcomes were calculated as either relative risks (RR) or hazard ratios (HR), with their respective 95% confidence intervals (CIs). HRs were the preferred form of data for calculating OS, DFS, GRFS, relapse and NRM occurring over time. When HRs were not given in an article, data were extracted from the respective Kaplan-Meier curves to estimate HRs. Heterogeneity was explored by the chi-squared test with a significance set at a *P* value of. 10, the quantity of heterogeneity was measured by I^2, with I^2>50% indicating significant heterogeneity. All analyses were calculated using Review Manager (Version 5.2 for Windows). When significant heterogeneity was found, a random effects model was used to estimate the overall treatment effect.

Results

The electronic database search yielded 873 potentially relevant publications, from which

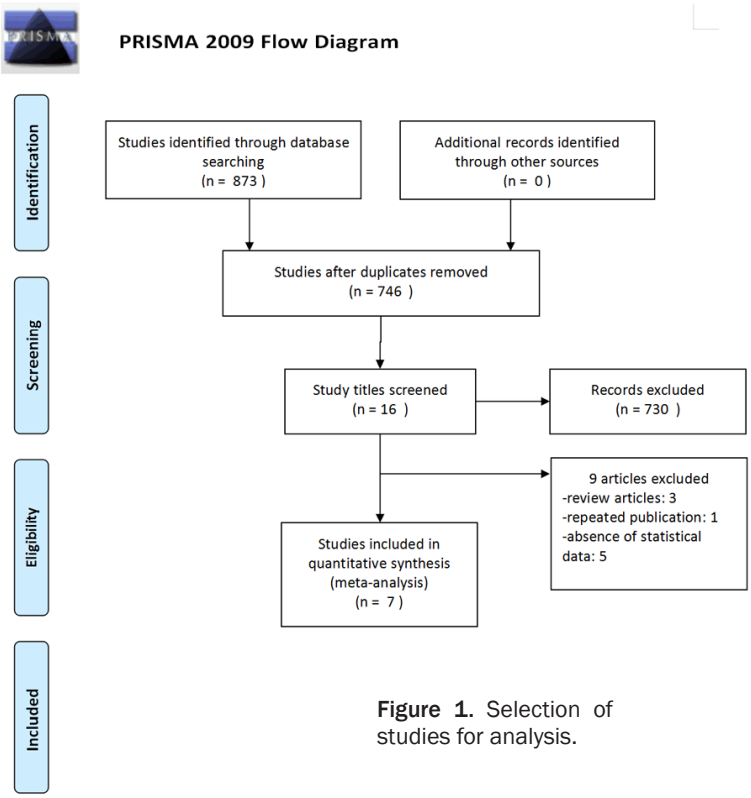


Figure 1. Selection of studies for analysis.

seven trials were identified and included in this meta-analysis [**Figure 1**]. All studies were retrospective, non-randomized and non-blinded. As shown in **Table 1**, two studies were performed in pediatric patients and five studies in adults. These studies in children involved 102 patients receiving UCBT and 94 patients receiving UBMT. There were more adults, with a combined total of 1311 adults undergoing UCBT and 915 undergoing UBMT in the comparative studies. The study by Raiola et al. [17] reported the results of patients who received grafts from five different donor types, and only patients receiving UCBT and HIT were included for our analysis. The study of Ruggeri et al. [24] analyzed the patients separately as AML and ALL, so we pooled the data of the two groups separately.

The risk of bias assessment for the included trials is summarized in **Figure 2**. Three trials had study confounding bias due to the lack of mportant potential confounding factors and 6 trials had attrition bias due to incomplete outcomes data.

Children

The results for children are shown in **Figure 3**. In the two studies, only the study by Mo et al. [28] provided RR for the risk of grade II-IV aGVHD and grade III-IV aGVHD and showed a significantly lower rate of aGVHD in patients with UCBT [RR 0.45, 95% CI (0.29, 0.69), P=0.0003; RR 0.46, 95% CI (0.24, 0.90), P=0.0.02]. The incidence of chronic GVHD was similar between UCBT and HIT when trials were pooled [RR 0.34, 95% CI (0.03, 4.53), P=0.41] [**Figure 3A**]. Only Mo et al. provided HR for the risk of Relapse, NRM and OS and revealed no significant differences between UCBT and HIT[HR 0.62, 95% CI (0.20, 1.90), P=0.40; HR 0.77, 95% CI (0.22, 2.71), P=0.68 and HR 0.90, 95% CI (0.32, 2.52) P=0.84].There were no significant differences in DFS when studies were pooled [HR 0.51, 95% CI (0.23,1.09), P=0.08] [**Figure 3B**].

Adults

The results for adults are shown in **Figure 4**. The rate of grades II-IV aGVHD in the UCBT group was significantly higher than that in the HIT group [RR 1.17, 95% CI (1.02, 1.34), P=0.02]. The risks of experiencing grades III-IV aGVHD, cGVHD, relapse and NRM in UCBT group were similar in two groups [RR 1.51, 95% CI (0.78, 2.92), P=0.22; RR 1.05, 95% CI (0.82, 1.34), P=0.71; HR 0.92, 95% CI (0.74, 1.13), P=0.42 and HR 0.87, 95% CI (0.49, 1.52) P=0.62]. Measures of survival could not be pooled because of different definitions use, one study [23] was +180 d OS, one study [17] was 4-year OS, one study [25] did not mention DFS, therefore only 2 studies [24, 31] had adequate data on DFS in adults. We found DFS at 2 years was similar between the two groups (HR 0.74 95% CI 0.39-1.43; P=0.37). However, Giannotti et al. [26] reported a OS and GRFS at 2 years in favor of HIT (HR 0.46, 95% CI 0.27-0.77, P=0.003; HR 0.42, 95% CI 0.26-0.66, P=0.0002).

Discussion

In this meta-analysis of UCBT versus HIT, UCBT was associated with similar aGVHD (II-IV) and

Table 1. Characteristics of included retrospective, non-randomized and non-blinded Studies

Author/Country	Study population	Number	Median age (range, years)	Gender	Study arm	HLA matching		Conditioning regimen	GVHD prophylaxis	Included Outcomes
						Matched #matched alleles/ all alleles: of patients#	Mismatch #matched alleles/all alleles: of patients#			
Claudio G. Brunstein 2011 [23]/America	Hematologic malignancies/adults	50	58 (16-69)	NR	dUCBT	6/6: 8%	5/6: 22% 4/6: 70%	RIC: 100%	MMF, CsA, Tac	GVHD, NRM, relapse and survival
		50	48 (7-70)		HIT-BM	-	8/10: 2% 7/10: 18% 6/10: 24% 5/10: 56%	RIC: 100%	PTCy, Tac, MMF	
A.M. Raiola 2014 [17]/ Italy	Hematologic malignancies/adults	105	40 (18-64)	NR	sUCBT	-	5/6: 51.4% 4/6: 45.7% 3/6: 2.9%	MAC: 83%	CsA, MMF, ATG	TRM, GVHD, relapse, OS, DFS
		92	45 (17-69)		HIT-BM	-	3-4/8: 100%	MAC: 77%	CsA, MMF	
A Ruggeri 2015-AML [24]/EBMT, EUROCORD	AML/adults	558	45 (18-72)	F: 53%	sUCBT/ dUCBT	NR	NR	MAC: 50%	CsA, Pred, MTX, Tac, MMF, ATG, other	GVHD, relapse, NRM, LFS
		360	44 (18-75)	F: 42%	HIT-BM/ PBSC	NR	NR	MAC: 61%	CsA, Pred, MTX, SIRO, Tac, Cy, MMF, anti-CD25, ATG, other	
A Ruggeri 2015-ALL [24]/EBMT, EUROCORD	ALL/adults	370	35 (8-76)	F: 43%	sUCBT/ dUCBT	NR	NR	MAC: 69%	CsA, Pred, MTX, Tac, MMF, ATG, other	GVHD, relapse, NRM, LFS
		158	30 (18-76)	F: 43%	HIT-BM/ PBSC	NR	NR	MAC: 54%	CsA, Pred, MTX, SIRO, Tac, Cy, MMF, anti-CD25, ATG, other	
Jean El-Cheikh 2015 [25]/France, Italy	Hematologic malignancies/adults	81	47 (18-66)	F: 43%	sUCBT/ dUCBT	>4/6: 100%		NMAC: 100%	CsA, MMF	GVHD, NRM, OS
		69	44 (19-68)	F: 43%	HIT-BM/ PBSC	5-6/8: 100%		NMAC: 100%	PTCy	
Federica Giannotti 2018 [26]/EBMT, EUROCORD	AML/adults	147	42.6 (18-67.9)	F: 55.8%	sUCBT	NR	NR	MAC: 100%	NR	GVHD, relapse, TRM, LFS
		186	44.3 (18.5-66.1)	F: 54.3%	HIT-BM	NR	NR	MAC: 100%	PTCy:71%	
Marta Gonza´lez-Vicent 2011 [27]/Spain	Acute Leukemia/ Children	38	6 (1-18)	F: 52.5%	sUCBT	6/6: 7.9%	5/6: 31.6% 4/6: 52.6% 3/6: 7.9%	MAC: 100%	CsA, ATG, Corticoids	GVHD, relapse, TRM, LFS
		29	9 (1-19)	F: 27.6%	HIT-PBSC	-	3/6: 100%	RIC: 100%	CsA, MTX, Corticoids	
Xiao-Dong Mo 2016 [28]/China	ALL/Children	64	9 (2-14)	F: 49.2%	sUCBT	6/6: 23.4%	5/6: 62.5% 4/6: 14.1%	MAC: 100%	CsA, MMF	GVHD, relapse, NRM, OS, DFS
		65	10 (3-14)	F: 34.4%	HIT-BM+PBSC	-	5/6: 4.6% 4/6: 10.8% 3/6: 84.6%	MAC: 100%	CsA, MMF, MTX	

sUCBT: single umbilical cord blood transplantation; dUCBT: double umbilical cord blood transplantation; HIT: haploidentical transplantation; BM: bone marrow; PBSC: peripheral blood stem cells; NR: not reported. GVHD prophylaxis : PTCy: post-transplant Cyclophosphamide, MMF: mycophenolate mofetil, CsA: Cyclosporine A, Tac: Tacrolimus, MTX: mtheotrexate, Pred: prednisone, SIRO: sirolimus, Cy: cyclophosphamide, TRM: transplanted related mortality, NRM: non-relapse mortality, LFS: leukemia-free survival; DFS: disease-free survival, OS: overall survival. EBMT: European Society for Blood and Marrow Transplantation, EUROCORD: Eurocord is a European Association of Rope, Twine and Netting manufacturers, their suppliers and their affiliate industries.

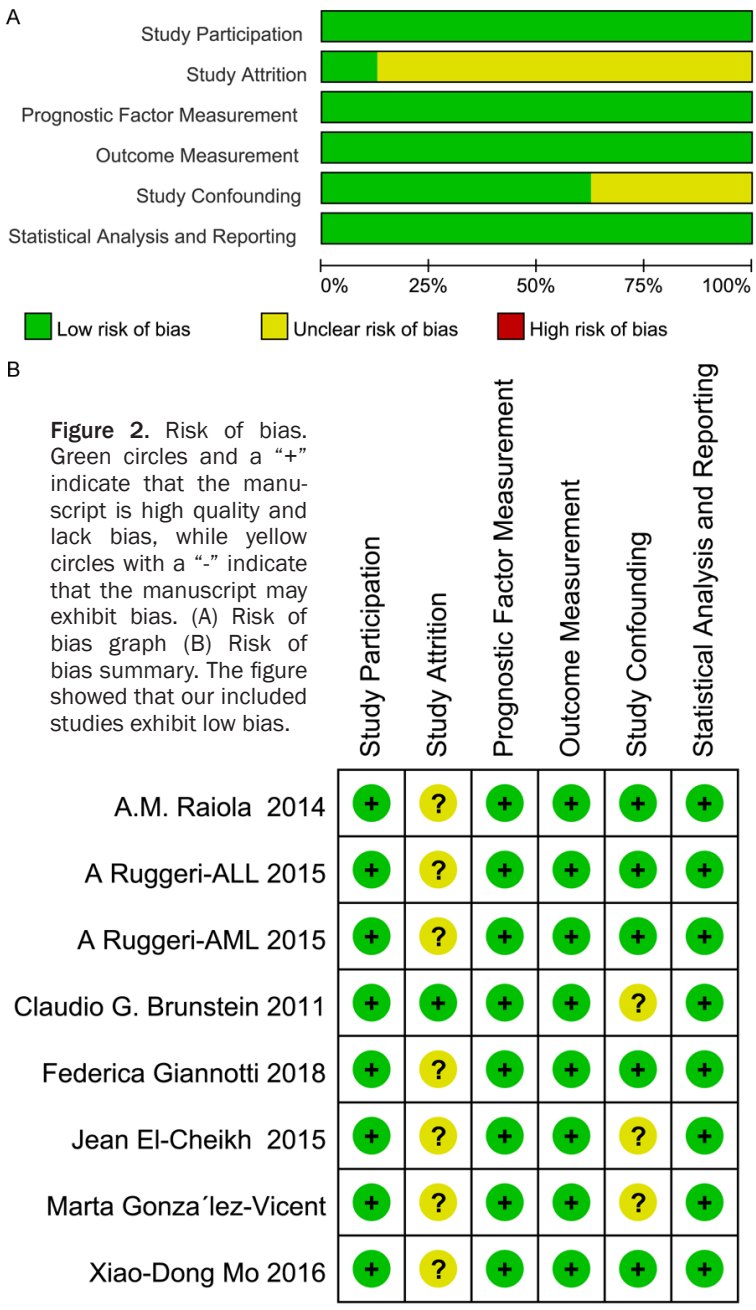


Figure 2. Risk of bias. Green circles and a "+" indicate that the manuscript is high quality and lack bias, while yellow circles with a "-" indicate that the manuscript may exhibit bias. (A) Risk of bias graph (B) Risk of bias summary. The figure showed that our included studies exhibit low bias.

relapse and equivalent survival for adult patients. In the adult studies, although the *p*-value was significant for the aGVHD (II-IV), but the RR is barely above 1 and the lower limit of the 95% CI is almost 1 (And the reason maybe that the studies of Ruggeri and Giannotti were performed by the same group (Eurocord: a European Association) and the inclusion periods of the study may indicate that there is an overlap of the population described in both studies), which indicates a very small difference between the groups. On the other hand, for aGVHD (III-IV), although the *p*-value is not significant, there is a tendency of higher risk for the UCBT. This may be explained by the application of the PTCy-based approach, which has been described in other studies [3, 19, 31-33]. PTCy GVHD prophylaxis, developed by the Baltimore group, prevents the GVHD by targeting alloreactive T cells while sparing regulator T cells [34]. OS and GRFS at 1 year were better in HIT in Giannotti et al.'s study. Inferior engraftment (UCBT vs HIT: 86% vs 96%) and the use of ATG (UCBT vs HIT: 91% vs 28.8%) may explain the difference. No significant difference in cGVHD, relapse rate, non-relapse mortality and disease-free survival between UCBT and HIT was found in this meta-analysis for adults group.

For pediatric patients, Mo et al. reported that UCBT was associated with less aGVHD. This may be due to the difference in the number of HLA disparities as the percentage of patients with 2 or 3 mismatches in UCBT was 14.1%, much lower than that in the HIT group (95.4%). The incidence of cGVHD and disease-free survival were not significantly different between the two groups. For some outcomes such as Relapse, NRM and OS were made base in 1 study only, we could not get decisive conclusion about pediatric groups.

Several limitations should be considered in this meta-analysis. First, randomized controlled studies were not available to date, therefore, only nonrandomized comparative studies were included. However, what encourages us is that a prospective phase III randomized trial (BMT CTN 1101; NCT01597778) comparing UCBT with PTCy-based HIT is currently underway. Second, the amount of included studies was too small for a funnel plot to detect publications bias. Third, cord blood transplantation with both single unit and double cord blood units were included, which may influence the out-

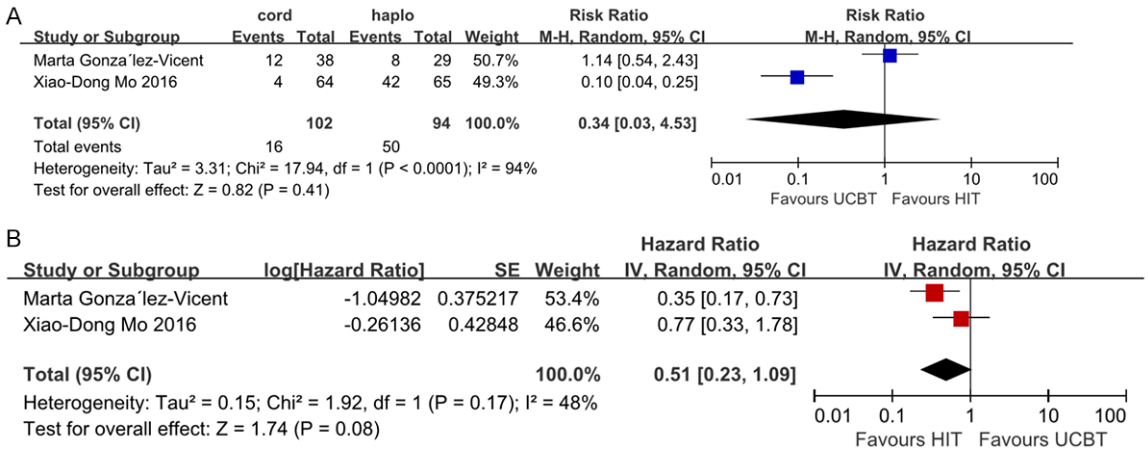
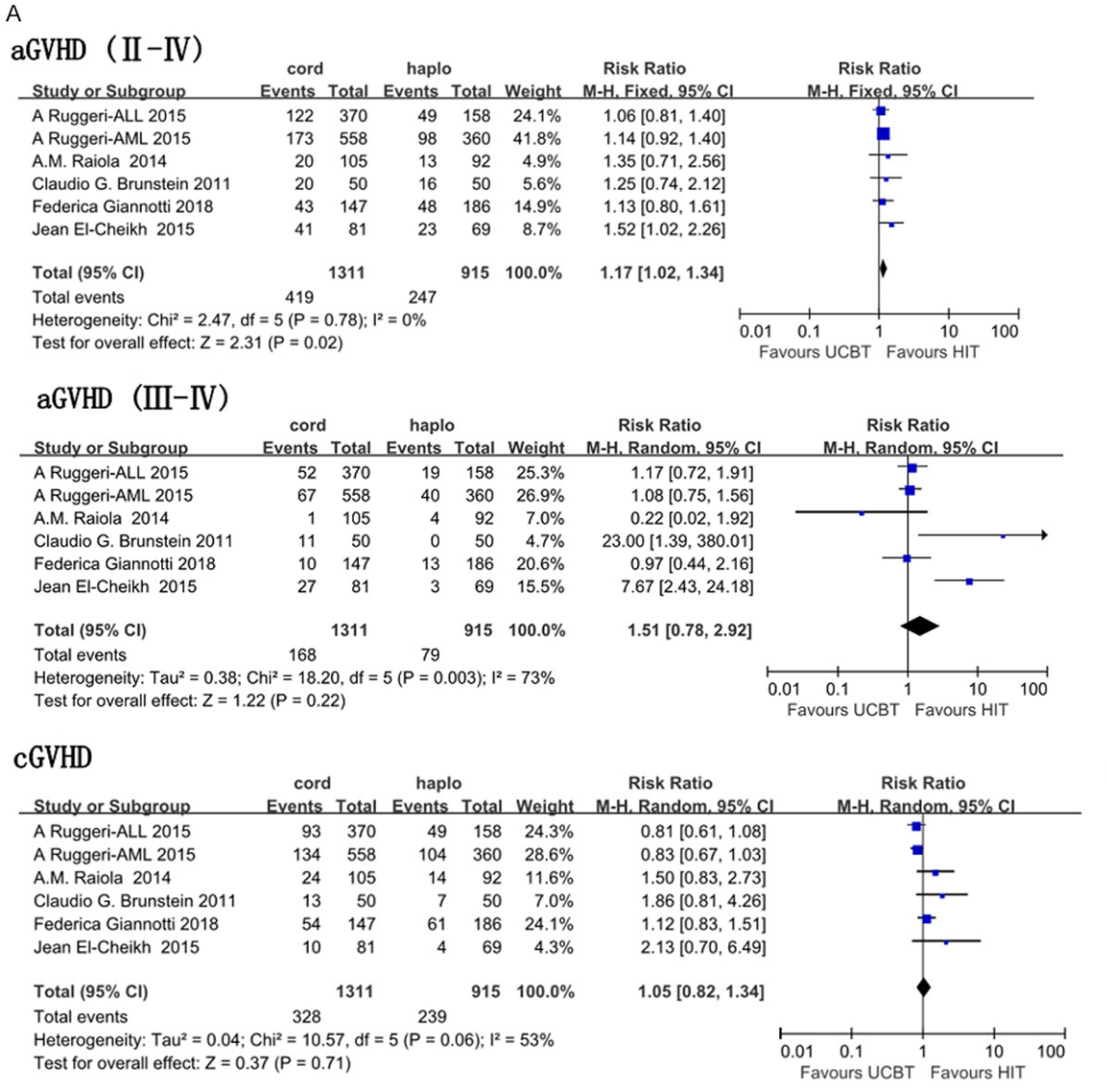


Figure 3. Forest plot of the RR/HR in children group. The size of the squares reflects each study's relative weight and the diamond (◇) represents the aggregate RR/HR and 95% CI. A. cGVHD in children: there were no significant differences in cGVHD when studies were pooled and showed similar incidence of cGVHD between UCBT and HIT group. B. 2-year-DFS in children: P=0.08 in 2-year DFS when studies were pooled.



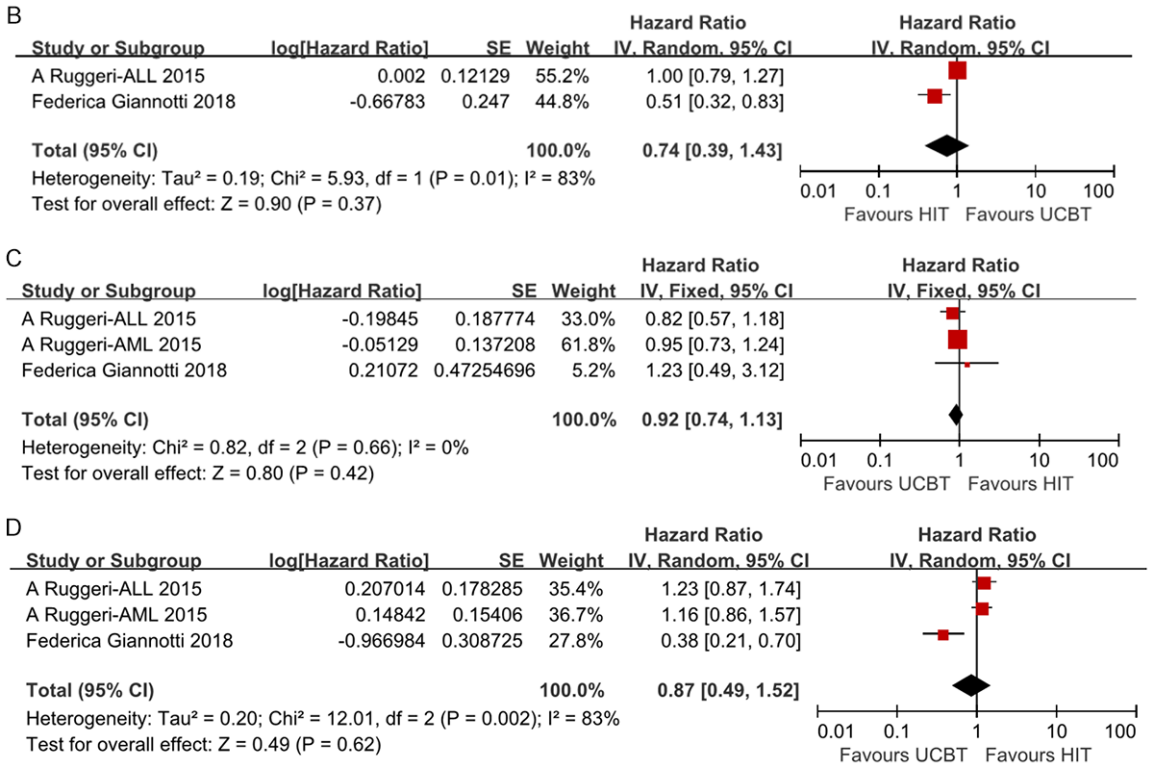


Figure 4. Forest plot of the RR/HR in adults group. The size of the squares reflects each study's relative weight and the diamond (◇) represents the aggregate RR/HR and 95% CI. (A) GVHD in adults: there were significant differences in grades II-IV acute GVHD (aGVHD) when studies were pooled. Although the *p*-value was significant for the aGVHD (II-IV), but the RR is barely above 1 and the lower limit of the 95% CI is almost 1, which indicates a very small difference between the groups. For aGVHD (III-IV), There were no significant differences in cGVHD. (B) 2-year-DFS in adults (C) Relapse in adults (D) NRM in adults: there were no significant differences in 2-year-DFS, relapse and NRM.

comes. A.M. Raiola et al. reported a single cord blood unit showed a trend for less relapse and superior disease free survival as comparend to patients receiving double cord blood units. Fourth, The center experience and the different expertise in the choice of donor sources [23, 25] may exert influence to outcomes. Last, subgroup analysis for peripheral blood and bone marrow graft in haplo transplantation could not be performed because of outcomes of these two grafts were analyzed together in the studies [24, 25, 28].

In conclusion, UCBT and HIT could be considered as equally effective option for adult patients with hematopoietic malignancies. For adult patients without matched related donors, cord blood transplantation can be considered as an alternative. And there is a tendency of equally effective choice in HIT and UCBT for pediatric patients with hematopoietic malignancies.

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Disclosure of conflict of interest

None.

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