# Single versus Double Umbilical Cord Blood Transplants: A Meta-analysis of Comparative Studies Umbilical Cord Blood Transplants

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## Abstract

**Background**: A number of alternatives has been proposed, including umbilical cord blood transplant (UCBT), in patients who do not matched donors for hematopoietic stem cell transplantation (HSCT). However, there are conflicting results regarding the role of the two units UCBT (dUCBT) compared to single unit (sUCBT). The present systematic review and meta-analysis aimed to compare the outcomes of dUCBT versus sUCBT in patients without suitable HLA-matched donor

**Material and Methods**: We performed an electronic search in the following bibliographic databases: Medline via PubMed, SCOPUS, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). Both prospective and retrospective studies which compared sUBCT and dUBCT were included. Data were analysed using RevMan version 5.3 for windows.

**Results**: The present review included 12eligible studies. The overall effect estimates did not favour either of the two groups in terms of neutrophil engraftment (OR =0.92, 95% CI [0.71, 1.19]; p =0.52), palatals engraftment (OR = 1.10, 95% CI [0.79, 1.53]; p =0.59), relapse rates (OR = 1.31, 95% CI [0.82, 2.09]; p =0.26) 5-year disease-free survival (OR = 0.87, 95% CI [0.59, 1.28]; p =0.49), and 5-year overall survival (OR Figure.6). However, the overall effect estimates favoured sUCBT group over the dUCBT group in term of the incidence of grade 2-4 GVHD (OR = 0.66, 95% CI [0.45, 0.97]; p =0.03).

**Conclusion**: In conclusion both sUCBT and dUCBT have comparable results in terms of engraftment success, relapse rates, transplant-related mortality, and overall survival. However, dUCBT is associated with higher risk of acute GVHD which further limit any potential advantages of the dUCBT.

***Keywords**: Umbilical cord transplants; hematological malignances; Meta-analysis*

## Introduction

Over the past few decades, the uses and indications of hematopoietic stem cell transplantation (HSCT) have increased dramatically; HSCT become the cornerstone treatment modality for the management of many hematological disorders and malignancies. Allogenic SCT involves replacement of the immune system of patients with immune dysfunctions or restoration of the bone marrow after total body irradiation for patients with hematological malignancies[1]. However, allogenic-SCT requires the presence of human leukocyte antigen (HLA)-matched siblings as donors in order to be effective and to avoid the hazards of graft rejection[2]; according to previous reports, almost 70% of patientsin

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Western countries, who are indicated for allogenic HSCT, do not have an available HLA-identical sibling [3]. Therefore, a number of alternatives has been proposed including the transplant from unrelated HLA-matched donors,haploidentical donors, and umbilical cord blood transplant (UCBT)[4].Unrelated UCBT are cryopreserved graft source that has emerged as an effective alternative of allogenic-SCT in case of absence of matched-donor; the UCBT are relatively immunologically-free with less risk of immune-mediated complication[5]. Previous retrospective studies have shown that UCBT led to comparable survival to unrelated bone marrow transplants in children with lacking of an acceptable HLA-matched donors[6].

On the other hand, the limited number of T cells in a UCBT product is a major drawback to the technique; it was reported that 10-20% of the UCBT recipients are at increased risk of graft rejection due to low stem cell doses[7,8]. Thus,transplantation of double UCB (dUCBT) units has been proposed in order to increase cell dose, especially in adult patients[9]. Although the dUCBT showed early promising results in terms of graft failure, an increased incidence of graft-versus-graft (GVG) effect was noted among dUCBT recipients, compared to single dose UCBT (sUCBT)[10], which can limit the beneficial role of dUCBT in the case ofinadequate cell dose. In order to compare the effectiveness and safety of both modalities, a growing number of retrospective studies and clinical trials were conducted with conflicting results[11,12].

Therefore, we conducted the present systematic review and meta-analysis to synthesize evidence from the published literature regarding the safety and efficacy of dUCBT versus sUCBT in patients without suitable HLA-matched donor.

## Materials and Methods

We confirm that the presentsystematic review and meta-analysis run in concordance with the recommendations of Preferred Reporting Items of Systematic and Meta-analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements[13,14].

### Inclusion and Exclusion Criteria

In the present study, we included studies that meet the following criteria: (1) studies that included children or adults, who were indicated for unrelated HSCT, with the absence of suitable HLA-matched donor; and (2) studies that compared the efficacy and safety of dUBCT versus sUBCT in this type of patients. There were no restrictions regarding the type of study designs or the characteristics of the included patients. In the case of multiple reports, we included the most completed report. We excluded non-English studies, reviews, thesis, and conference proceeds.

### Search Strategy and Screening

An online bibliographic search of the following databases was conducted from the their inception till December 2018: Medline via PubMed, SCOPUS, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) using different combination of the following keywords:Umbilical cord blood transplant; hematological disorders; and double units. Retrieved citations were imported into EndNote X7 for duplicates removal. Subsequently, unique citations were imported into an Excel sheet and screened by two independent reviewers; the screening was conducted in two steps: title and abstract screening, followed by a full-texts screening of potentially eligible records.

### Data Extraction and Efficacy Measures:

Data entry and processing were carried out using a standardized Excel sheet and two reviewers extracted the data from the included studies. The extracted data included the following domains: (1) Population and methodological characteristics of the included studies; (2) Risk of biasof studied populations, and (3) Study outcomes. The reviewers' independently extracted data from the included articles and any discrepancies were solved by discussion. The outcomes measurements, in studies compared dUBCT versus sUBCT, were: transplant-related mortality, primary engraftment failure, incidence of GVG effect, disease-free survival, and overall survival.

**Risk of Bias Assessment**

The quality of the retrieved randomized controlled trials (RCTs) was assessed according to the Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011 which included the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgments are categorized as 'Low risk', 'High risk' or 'Unclear risk' of bias[15]. On the other hand, the quality assessment of observational study was assessed using new-castle Ottawa scale (NOS) which included the following domains: the selection of the study groups; the comparability of the groups; and the ascertainment of the exposure or outcomes. A sum quality score was calculated for each study (range 1 -9) and the studies were categorized into high (score 1-3), moderate (score 4-6), and low (score 7-9) risk of bias[16].

**Data Synthesis**

We performed a paired comparisons meta-analysis using Review Manager (RevMan) version 5.3 software for windows. Dichotomous data were pooled as odds ratio (OR) with 95% confidence interval (CI) using Mantel-Hansel method. The heterogeneity of the pooled effect estimates was quantified by the $I^2$ and the corresponding p-value.The random-effects modelwas applied based on the assumption of the presence of substantial heterogeneity between the included studies. All reported p values were two-sided, and p-value< 0.05 was considered statistically significant.

## Results

**Literature Search Results**

We retrieved 1121 unique citations after the initial bibliographic search. Then, we retained 42 potentially eligiblerecords afterthe initial title and abstract screening for full evaluation. Finally, 25studies (RCTs=2; Prospective =2; Retrospective =21 studies) were included in the present systematic review and meta-analysis..

**Characteristics of studies**

The present meta-analysis included 25 studies with 6571 patients (sUBCT =3245 patients; dUBCT =3326 patients). All included were retrospective cohort studies, exceptfour studies; two studies were RCTs[11,17] and the other two studies were prospective studies[18,19]. The sample size of the included studies ranged from 19 to 1494 patients with a median follow-up that ranged from 19 to 57.4 months. Notably, there were substantial variations in the characteristics of the patients who received UBCT among the included studies.In addition, the included studies reported conflicting results regarding the efficacy and safety of dUBCT versus sUBCT.

**Risk of Bias Assessment**

The two included RCT exhibited low risk of selection bias, high risk of performance bias, and low risk of bias of other domains inthe Cochrane risk of bias tool. With regard to the included observational studies, the risk of bias ranged from moderate to high according to the NOS; all studies had high risk of bias incomparability and follow-up domains**.**

- Outcomes

**Graft Failure**

Twelve included studies reported the success rate of neutrophils engraftment in sUCBT (N =915 patients) and dUBCT groups (N =1235 patients), the overall effect estimates did not favoureither of the two groups (OR =0.92, 95% CI [0.71, 1.19]; p =0.52); no significant heterogeneity was identified (p =0.43; **Figure.1)**. On the other hand, seven studies reported that the effect of UBCT on the success rate ofplatelets engraftment, the overall effect estimates did not favoursUCBT or dUCBT groups (OR =1.10, 95% CI [0.79, 1.53]; p =0.59); however, significant heterogeneity was identified (p =0.05; $I^2$ =52%).

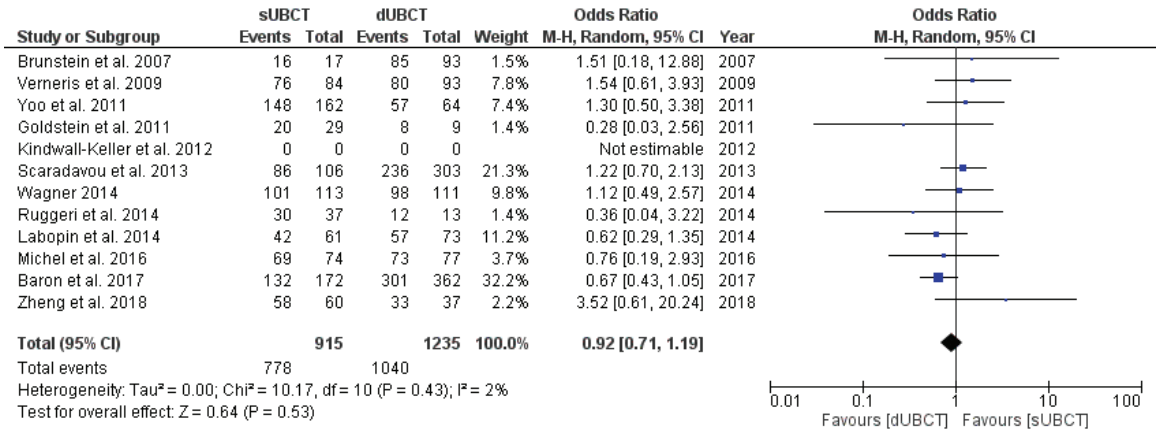


**Figure .1: Forest plots shows the difference in the neutrophil engraftment success rates between sUCBT and dUCBT groups**

### Relapse and Survival

Eight included studies reported the rate of relapse in sUCBT (N =849 patients) and dUBCT groups (N =1435 patients), the overall effect estimates did not favour either of the two groups (OR =1.31, 95% CI [0.82, 2.09]; p =0.26); there was a statistically significant heterogeneity (p <0.001, $I^2$ =78%; **Figure.2)**. In addition the 5-year disease-free survival (OR =0.87, 95% CI [0.59, 1.28]; p =0.49; **Figure 3**) and 5-year overall survival were no significantly different between both groups.

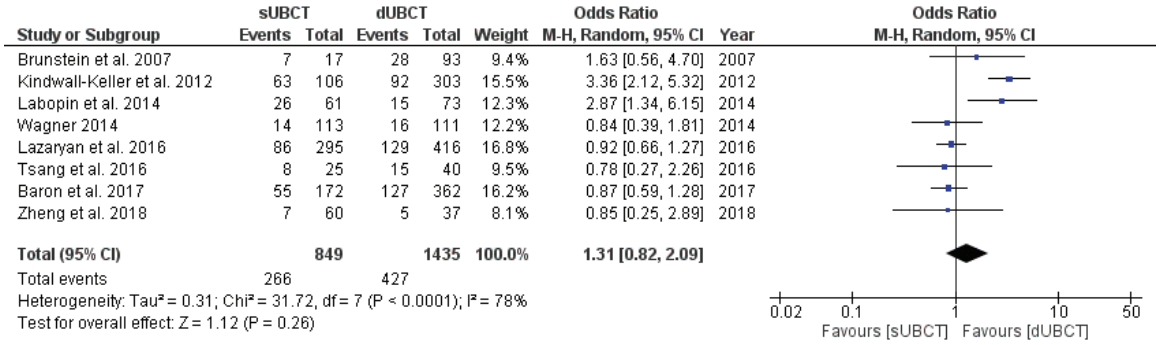


**Figure 2:: Forest plots shows the difference in the relapse rates between sUCBT and dUCBT groups**

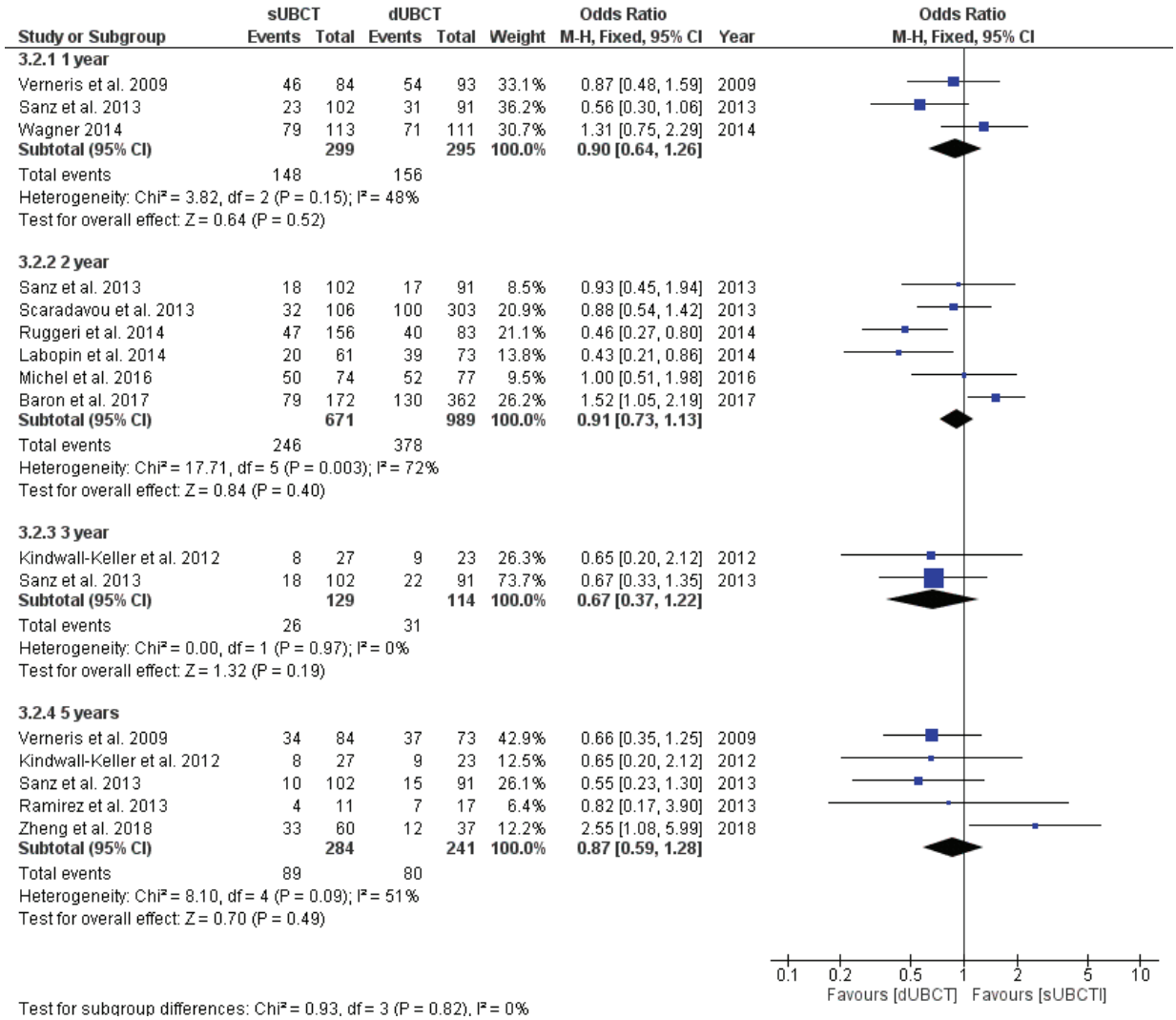


**Figure 3**: **Forest plots shows the difference in the disease-free survival between sUCBT and dUCBT groups**

### GVHD

On the other hand, 11 included studies reported the differences in the incidence of grade 2-4 acute GVHD between sUCBT (N =1866 patients) and dUCBT groups (N =1932 patients), the overall effect estimates favoured sUCBT group over the dUCBT group (OR =0.66, 95% CI [0.45, 0.97]; p =0.03); there was a significant heterogeneity in the pooled effect estimate (p <0.001; $I^2$ =82%. Similarly, 12 studies reported the incidence of grade 3-4 acute GVHD in sUCBT (N =1949 patients) and dUCBT groups (N =2052 patients), the overall effect estimates favoured sUCBT group over the dUCBT group (OR =0.73, 95% CI [0.53, 1.00]; p =0.05); there was a statisticallysignificant heterogeneity (p =0.007; $I^2$ =57%). In contrary, the overall effect estimate did not favour any og the two groups in terms of the incidence of chronic GVHD(OR =0.76, 95% CI [0.54, 1.08]; p =0.12) and any extensive GVHD.

## Discussion

There is no consensus in the published literature regarding the role of administration of two units of UCBT on the engraftment success and survival rates. The present systematic review and meta-analysis showed that there were no statistically significant differences between sUCBT and dUCBT in terms of neutrophils and platelets engraftment. In addition, the 5-year disease-free survival and the overall survival were no significantly comparable between both groups. On the

other hand, the results showed that patients receiving dUCBT are at increased risk of developing grade 2-4 acute GVHD; while the overall effect estimate did not favour any of the two groups in term of the incidence of chronic GVHD. Notably, there were statistically significant heterogeneities in the most of the pooled effect estimates.

Graft failure is a devastating condition that may complicate stem cell transplantation, the failure mainly occurs as a result of graft rejection or severe septicemia and may be manifested by lack or slow engraftment of donor cells[20]. As the UCBT contains limited total nucleated cell and CD34+ cell dose, it carries a higher risk of graft failure than the expected from other transplant options[21]. Therefore, the dUCBT was proposed as a potential guard against graft failure by increasing the cell dose. Our results showed that there were no statistically significant differences between sUCBT and dUBCT groups in terms of success rates of neutrophils and platelets engraftment. In concordance with our findings, a recent systematic review showed that the majority of the published literature reported comparable rates of neutrophil and platelet engraftments after sUCBT and dUBCT[22]. This finding was similar to the results of the only two published RCTs that compared dUCBT with sUCBT[11,17]. Another study reported no difference in engraftment rate between different types conditioning[23]. Nevertheless, other retrospective studies reported higher engraftment rates after sUCBT, compared to dUCBT[24].

The current body of evidence shows that UCBT is associated with lower risk of relapse compared mismatched transplants and haploidentical transplant[25,26]. Moreover, UCBT was reported to have higher 3-years survival than HLA-mismatched unrelated donor transplants[27]. However, there are conflicting results regarding the effect of the number of UCBT units on relapse ratesand overall survival. In the present meta-analysis, there were no statistically significant differences between sUCBT and dUCBT in terms of relapse rates, disease-free survival, and overall survival. Similarly, Wang and colleagues[22] more than half of the published literature showed comparable relapse rates and overall survival between the two groups. In contrary, a previous prospective study reported a lower relapse risk after infusion of dUCBT.

The present systematic review and meta-analysis has a number of strength points. The review run in concordance with the recommendation of the Cochrane handbook and PRISMA, and MOOSE statements. However, we acknowledged the presence of some limitations. The majority of the included studies were retrospective cohorts which may lead to the introduction of many methodological biases including recall bias and misclassification. In addition, there were statistically significant inconsistencies in the pooled effect estimates which may be due to wide variations in the characteristics of studies' population, designs, and transfusion protocols. Moreover, the methodological quality of the included studies was from low-to-moderate which may affect the quality of the present evidence.

In conclusion, the present meta-analysis showed that both sUCBT and dUCBT have comparable results in terms of engraftment success, relapse rates, transplant-related mortality, and overall survival. However, dUCBT is associated with higher risk of acute GVHD which further limit any potential advantages of the dUCBT. However, it should be noted that there were substantial variations in the methodology of the included studies, which led to substantial statistical heterogeneity in the pooled effect estimates. Moreover, only one two RCTs assessed the role of dUCBT, while the rest of included studies were retrospective cohort studies. Thus, it appears that the current evidence is insufficient to support the clinical decision and further well-design studies are still needed.

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**Ethical Clearance:** As the present study is a systematic review of the literature, the need for ethical

approval from the local ethics committee of Princess Nourah Bint Abdulrahman University was waived.

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