**Hematopoietic stem cell transplantation in thalassemia: a systematic review of literature and meta analysis of prospective controlled trials**

**ABSTRACT:**

**Background**: β Thalassemia Major (BTM) is a chronic debilitating hemoglobinopathy characterized by ineffective erythropoiesis and transfusion dependant-anemia. Hematopoietic stem cell transplantation (HSCT) is considered the only curative therapy.

**Purpose:** To compare the benefits and risks of different stem cell sources in this patient population.

**Data Sources:** MEDLINE,Embase, and the Cochrane Database of Systematic Reviews from January 2006 to July 2015.

**Study Selection:** Randomized controlled trials (RCT) comparing HSCT from matched related donor (MRD), matched unrelated donor (MUD), matched sibling donor (MSD), peripheral blood stem cells (PBSC), and umbilical cord ctem cells (UCSC).

**Data Extraction:** Two independent reviewers abstracted data and rated study quality and strength of evidence.

**Data Synthesis:** Seven good-quality studies, met inclusion criteria. No eligible RCTs were identified. OS was comparable in patients receiving bone marrow transplantation (BMT) and those receiving peripheral blood stem cells (PBSC) (RR, 0.94; 95% CI, 0.88-1.02, 4 trials, 602 patients ).There was no significant increase in DFS in BMT recipients compared to PBSC recipients (RR, 1.00; 95% CI, 0.89-1.12, 4 trials, 602 patients ), and no difference in engraftment between both groups (RR, 1.02; 95% CI, 0.94-1.10, 4trials, 602 patients ). There was insufficient data on UCSC transplants. Furthermore, there was no significant difference in OS for MUD-BMT (RR, 0.87; 95% CI, 0.79-1.29, 2 trials 131 patients) and MSD-BMT (RR, 0.87; 95% CI, 0.74-1.03, 2 trials 131 patients) compared to MRD-BMT. Disease-free survival (DFS) was not significantly different for recipients of MUD-BMT (RR, 0.87; 95% CI, 0.69-1.10, 2 trials 131 patients) and MSD-BMT recipients (RR, 0.99; 95% CI, 0.85-1.14, 2 trials 131 patients), compared to MRD-BMT. Similarly, engraftment was not significantly different for MUD-BMT (RR, 1.00; 95% CI, 0.79-1.26, 2 trials 131 patients ) or MSD-BMT (RR, 0.88; 95% CI, 0.80-0.96, 2 trials 131 patients ) compared to MRD-BMT.

**Limitations:** There are no randomized controlled trials on HSCT in BTM.

**Conclusions:** Bone marrow as a source of stem cells has no survival advantage in HSCT for BTM, when compared to PBSCs although it is associated with significantly less morbidity in the post transplant period. MRD-BMT is as effective as MUD-BMT and MSD-BMT.

**BACKGROUND:**

β-thalassemia refers to a group of disorders associated with decreased or absent β globin subunits of hemoglobin (Hb), inherited as pathological alleles of one or more of the globin genes. (reference) (reference)β thalassemia major (BTM) is the severe form of the disease, presenting with transfusion-dependent anemia, during the first year of life. It is characterized by ineffective erythropoiesis and aggressive extension of the rapidly proliferating erythrocytes into intra- and extra-medullary areas, not normally occupied by marrow. (reference)

There have been significant improvements in supportive care available for BTM, thus extending the lifespan of affected patients and allowing the development of long-term complications of the disease [3]. Patients typically die from complications of iron overload if iron chelation is not provided [4]. At present, hematopoietic stem cell transplantation (HSCT) is the only curative treatment for BTM and results have been reported by various centers [5-7]. The first two transplant procedures for the treatment of thalassemia with marrow from matched related donors were performed in December 1981, in Seattle, WA, and in Pesaro, Italy. (reference, reference)The Seattle approach aimed at reducing the risk associated with repeated transfusions including the iron overload and alloimmunization to human leukocyte antigens (HLAs). Thus the transplant recipients were a cohort of young, previously-untransfused BTM patients. The Pesaro protocol did not restrict transplants to untransfused patients and the cohort consisted mainly of previously transfused adults . The Pesaro approach is more clinically applicable,as BTM patients would have received many transfusions by the time they are referred for HSCT. Certainly, freedom from transfusion and its related complications is a distinct advantage in HSCT and in many cases, results in significant improvement of the quality of life.

**OBJECTIVES:**

To evaluate the efficacy and safety of different approaches to HSCT in BTM patients.

**Methodology:**

**Data source**

In collaboration with a master librarian, we developed a search strategy of the databases MEDLINE® (via PubMed®), Embase®, Cochrane Library, and GOVERNMENT CLINICAL TRIAL REGISTRY for peer-reviewed publications comparing different approaches to HSCT in BTM from January 1981 (the year HSCT for BTM was first reported) to July 2015 . Our search strategy used the National Library of Medicine’s medical subject headings (MeSH) keyword nomenclature and text words for HSCT, BTM, and validated search terms for randomized controlled trials {Wilczynski, 2007 #2}

**Selection criteria**

Prospective controlled trials comparing HSCT from allogeneic matched related donor (MRD-BMT), allogeneic matched unrelated bone marrow donor (MUD-BM), allogeneic matched sibling bone marrow donor (MSD-BMT), peripheral blood hematopoietic stem cells (PBHSC), umbilical cord blood (UCBHSC) with each other using various conditioning regimens. Conditioning regimens included are myeloablative, non-myeloablative or both.

**Data collection and analysis**

Two review authors independently screened studies and had planned to extract data and assess risk of bias using standard Cochrane Collaboration methodologies. We included studies on patients with a Pesaro Risk Classification 1, 2 and 3 since most were classified irrespective of associated comorbodities at the time of intervention. Trials were included only once in the analysis using the most updated data. Interventions that were assessed include BMT(MRD-BMT and MUD-BMT and MSD-BMT grouped together as Other BMT), PBHSCT and UCBHSCT.

**Data Extraction and Quality Assessment**

Two reviewers (A.D and A.N), using prespecified eligibility criteria, examined each article; disagreements on inclusion or exclusion were resolved by discussion or by a third reviewer (S.A). For included studies, data describing the study population, interventions, outcomes, quality and applicability were abstracted by a trained reviewer and confirmed by a second reviewer. Study quality was summarized as good, fair or poor after evaluating: adequacy of randomization and allocation concealment, comparability of groups at baseline, blinding, completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, validity of outcome measures, and conflicts of interest. {Agency for Healthcare Research and Quality, #741;Chang, 2011 #9}

**Risk of Bias Assessment**

To avoid risk of bias, all trials that fulfilled the review inclusion criteria were assessed for methodological quality by 3 reviewers (A.F, A.N and A.D). Failure to report of any of the items was considered as a high risk for bias. Since our study included prospective controlled trials, we did not asses the methods used for sequence generation, allocation sequence concealment, blinding, and exclusions from analysis by using standard methods as recommended in the Cochrane Handbook [8,9].We did not consider any violation of ITT as an important risk of bias domain for prospective controlled trials .

The second step was to assess the following domains:

1. Method of tissue typing: Because genetic randomization depends on the assessment of sibling matching, adequate human leukocyte antigen

(HLA) typing and reporting must be ensured.

2. Comparability of potential confounders: The comparability of the study groups was assessed basedon the following confounders: age, patient’s risk

group (Pessaro Risk Class 1, 2 and 3), pre-conditioning and conditioning myeloablative and non-myeloablative regimen , level of mixed chimerism development and post transplant graft versus host prophylaxis.

**Primary outcomes**

1.Overall survival (OS) of the transplanted patients irrespective of the complications of transplantation (either thalassaemia manifestations and transfusion dependant or adverse effects of the transplant procedure like graft failure, grade III/IV acute GVHD, or both) and the quality of life after transplantation. Time period to be reported after at least 1 year of follow-up.

2.Disease-free survival (DFS) (event is defined as either thalassaemia manifestations or adverse effects of the transplant procedure like graft failure, grade III/IV acute GVHD, or both) the interval from time of randomization or study entry to the first recurrence of event or to death of any cause. Time period to be reported after at least 1 year of follow-up.

3.Engraftment (described as the successful implantation of graft and transfusion independent survival) rounds up another important aspect of the outcome.

**Secondary Outcomes**

1.Acute GVHD (aGVHD) (Grade 1-Grade 4) which determines the immediate success of the transplantation and implies the need for second transplantation and is significant controller of the mortality in transplanted patients.

2.Chronic GVHD (cGVHD) (Limited and extensive) which determines the morbidity of the transplanted patients and governs the quality of life post transplant.

3.Transplant Related Mortality(TRM) (Includes both Rejection and non-Rejection mortality) which indicates the efficacy of the transplantation and also indicates at the mortality due to pre-existing comorbidities, conditioning regimen toxicity andtransplantation process.

**Data Synthesis and Analysis**

Dichotomous data were analyzed by calculating the relative risk (RR) for each trial with the 95% confidence interval(CI). We used the Mantel-Haenszel random-effects model to pool RRs throughout the review because of

expected heterogeneity between studies related to different distribution of disease risk characteristics. The random effects model is based on the assumption that different studies are not identical but follow some (usually

normal) distribution. The pooled estimate refers to the center of intervention effects. The confidence intervals describe the uncertainty in the location of this mean. Differences in confounders were assessed using the Student t test or as reported in the primary publication.All analyses were performed using Review Manager (RevManversion 5.3; the Nordic Cochrane Centre, the Cochrane Collaboration, 2012, Copenhagen, Denmark).

**Results:**

The search yielded 91 associated results, and 48 potentially important results, 29 relevant clinical trials which were considered for further investigation; however, 22 of the 29 studies were excluded 2013 that randomized 958 patients fulfilled inclusion criteria [24, 27-28, 30, 34-35, 38].One trial [34] did not report on OS, DFS and Engraftment and cannot be included except in the secondary outcome analysis. Five trials compared PBHSCT to BMT[27, 28, 30, 34, 35], one trial compared MRD-BMT to MUD-BMT[24], one trial compared MRD-BMT to MSD-BMT[38].The definition of Pesaro Risk Classification patients was consistent between trials except in one trial [35].The mean duration of follow-up among all studies was 33 months (range, 24-72 months).All trials used myeloablative or non-myeloablative conditioning regimen as summarized in Table 1. Data regarding demographics and Pesaro Risk Classes are summarized in Table 2. for various reasons (Fig. 1). Seven trials (3 comparisons) conducted between January 2006 and July 2015.

Comparative Prospective Clinical Trial without Primary Outcome (n=1)34

Non-Comparative Prospective Clinical Trials not compatible with inclusion criteria (n=22)10-23,26,29,31-33,36-37

Case Reports, Letter to the Editor, Review and Duplication (n=22)

Results not associated with HSCT in Thalassemia alone (n=40)

Fig1. Trial flow according to quality of reporting Meta-analysis (QUOROM) is shown.Superscript indicate the Clinical Trials.

**Assessment of Risk of Bias**

Seven trials that compared MUD-BMT, MSD-BMT, MRD-BMT, PBHSCT, UCBHSCT were prospective controlled. Most of the studies reported data on potential confounders (Table 2).None of the trials were blinded.

**BMT *Vs.* PBHSCT:**

**Primary Outcomes**

**Overall Survival :**

There was no significant increase in overall survival (OS) in patients undergoing BMT compared to PBHSCT (RR, 0.94; 95% CI, 0.88-1.02, 4 trials, 602 patients) .We considered each of the trials individually . All trials showed an increase in OS for BMT compared to PBHSCT except in IB Resnick 2007, and Chunfu Li 2012, where OS was increased in PBHSCT compared to BMT. On network analysis, there was no significant difference in OS in MUD-BMT (RR, 0.87; 95% CI, 0.79-1.29, 2 trials 131 patients) or MSD-BMT (RR, 0.87; 95% CI, 0.74-1.03, 2 trials 131 patients), compared to MRD-BMT.

**Disease Free Survival (DFS):**

Similarly, there was no significant difference in DFS in patients undergoing BMT compared to PBHSCT (RR, 1.00; 95% CI, 0.89-1.12, 4 trials, 602 patients). In one trial where DFS for BMT was decreased compared to PBHSCT (RR, 0.92; 95% CI, 0.77-1.11, 1 trial, 82 patients). (Reference) On network analysis there was no difference in DFS in MSD-BMT (RR, 0.99; 95% CI, 0.85-1.14, 2 trials 131 patients) or MUD-BMT (RR, 0.87; 95% CI, 0.69-1.10, 2 trials 131 patients), compared to MRD-BMT .

**Engraftment:**

Engraftment, which was the third important factor in primary outcome showed patients undergoing BMT had significantly decreased engraftment than PBHSCT(RR, 1.02; 95% CI, 0.94-1.10, 4trials, 602 patients). Two trials, Chunfu Li 2012, and A. Ghavamzadeh 2008, showed the contrary.Similar results were obtained in recipients of MRD, MSD and MUD-BMT. There was no difference in engraftment in MUD-BMT (RR, 1.00; 95% CI, 0.79-1.26, 2 trials 131 patients ), MSD-BMT (RR, 0.88; 95% CI, 0.80-0.96, 2 trials 131 patients )compared to MRD-BMT.

**Secondary Outcomes:**

**Acute GVHD :**

There was a significant decrease in aGVHD in patients undergoing BMT compared to PBHSCT (RR,0.75; 95% CI, 0.61-.0.92, 5 trials, 827 patients). On network analysis, keeping MRD-BMT as the standard, there was no increase in aGVHD in MUD-BMT (RR, 1.33; 95% CI, 0.76-2.35, 2 trials 131 patients) or any decrease in aGVHD in MSD-BMT (RR, 1.94; 95% CI, 0.67-5.65, 2 trials 131 patients) compared to MRD-BMT.

**Chronic GVHD:**

Similarly, cGVHD was significantly decreased in patients undergoing BMT compared to those undergoing PBHSCT (RR, 0.37; 95% CI, 0.24-0.54, 5 trials, 827 patients). On network analysis, taking MRD-BMT as the standard, cGVHD was not significantly different in MUD-BMT (RR, 0.89; 95% CI, 0.29-2.76, 2 trials 131 patients ) and MSD-BMT (RR, 0.85; 95% CI, 0.19-3.70, 2 trials 131 patients ), compared to MRD-BMT.

**Transplant Related Mortality :**

Transplant related mortality **(TRM)** was significantly decreased in patients undergoing BMT compared to patients undergoing PBHSCT (RR,0.67; 95% CI, 0.34-1.35, 4 trials, 602 patients).Two trials by IB Resnick 2007 and Chunfu Li 2012 disagreed with these results. There was no significant difference in TRM in patients of MSD-BMT (RR, 1.21; 95% CI, 0.15-9.67, 2 trials 131 patients) or increase in MUD-BMT (RR, 2.00; 95% CI, 0.37-10.92, 2 trials 131 patients) can be established when compared to MRD-BMT .

**PUBLICATION BIAS:**

The results of the Begg’s and Egger’s tests showed no signifi­cant indication of publication bias (Figure 4). Therefore, it is unlikely that publication bias had a major influence on the results of the study.

**DISCUSSION:**

Thalassemia is the most common inherited hemoglobinopathy and most patients are treated with blood transfusion and iron chelation. . Hemopoietic stem cell transplantation remains the only curative treatment for β-thalassemia and to date, 3000 BTM patients have received HSCT. {Angelucci, 2014 #15}β-thalassemia patients should be referred for HSCT at an early age as available evidence shows better long-term outcomes for BTM patients who receive HSCT at a young age. The choice of stem cell source for thalassemia ranges from BMT, PBSCT and UCSCT. Furthermore, donors can either be MRD-BMT, MSD-BMT or MUD-BM.The objective of our review is to compare outcomes of HSCT from different sources.We also compared outcomes based on donor type.. Seven randomized control trials, and a total of 958 patients were included.

We observed no increase in OS of patients in BMT to PBHSCT (RR, 0.94; 95% CI, 0.88-1.02, 4 trials, 602 patients ) There was no statistically significant difference in DFS or engraftment in BMT recipients compared to PBHSCT recipients.

When considering aGVHD , BMT patients showed a statistically significant decrease in the incidence of aGVHD and cGVHD, compared to PBSCT .

However, these findings did not affect TRM, which was not dignificantly different in BMT recipients compared to PBSCT.

When analysing data based on donor type, there was no significant difference in OS, DFS and engraftment in patients undergoing MRD-BMT compared to MSD-BMT and MUD-BMT.

Surprisingly, aGVHD was not significantly decreased in MRD-BMT and MSD-BMT , compared to MUD-BMT. Recipients of MUD-BMT and MSD-BMT showed no statistically significant difference in cGVHD and TRM, compared to MRD-BMT patients.

In conclusion; BMT is not superior to PBHSCT as a source of stem cells in HSCT in BTM as it may carry a similar risk of reduced engraftment. Moreover, there is no advantage for BMT in OS and DFS compared to PBSCT in BTM patients. Considering the complications of stem cell transplantation post-transplant, aGVHD and cGVHD are significantly lower in BMT than PBHSCT.

By the same token, there was no significant advantage to MRD-BMT and MSD-BMT compared to MUD-BMT in terms of the OS, DFS and engraftment. The complications of transplantation including aGVHD and TRM is not significantly increased in MUD-BMT compared to MRD-BMT and MSD-BMT. This puts to rest the speculation that MRD-BMT is far superior to MUD-BMT or inferior to MSD-BMT in BTM. Only about one-third of the patients who suffer from thalassemia can find a matched related donor source for their stem cell transplantation. (ref) Thus, matched unrelated donor transplantation offers patients with no available matched related donor a chance for cure without any major compromise in OS, DFS.

**Limitations:**

There are a number of limitations to this systemic review. Firstly, most clinical trials done so far on stem cell transplant in thalssemia are non-randomised and are mainly prospective controlled clinical trials or single arm clinical trials. Thus, no randomized controlled trials were included in this systematic review. Many studies compared only various conditioning regimens leaving aside the topic of stem cell transplantation in thalassemia due to which we could not include them in our systematic review. Also, we could not conduct subgroup analyses according to specific Pessaro Risk Classification. Specifically, we could not conduct a subgroup analysis based on the age of

patients because of the sparse data in many of the trials. The patients who received UCBHSCT cannot be included in subgroup analysis due to paucity of data.

**Implications for Practice and for Research**

This systematic review indicates no overall survival and disease free survival advantage for BMT over PBSCs in BTM,. However, aGVHD and cGVHD are significantly decreased in BMT recipients, compared to PBSCs.

A similar advantage could not be established when comparing types of BMT donors including MRD-BMT , MSD-BMT and MUD-BMT. Thus, β-thalassemia patients, for whom a donor could not be identified, may have a greater opportunity to achieve cure through a MUD-BMT. The role of UCBHSCT should be assessed in future trials.

**CONFLICT OF INTEREST DISCLOSURES:**

The authors declare no conflicts of interest.

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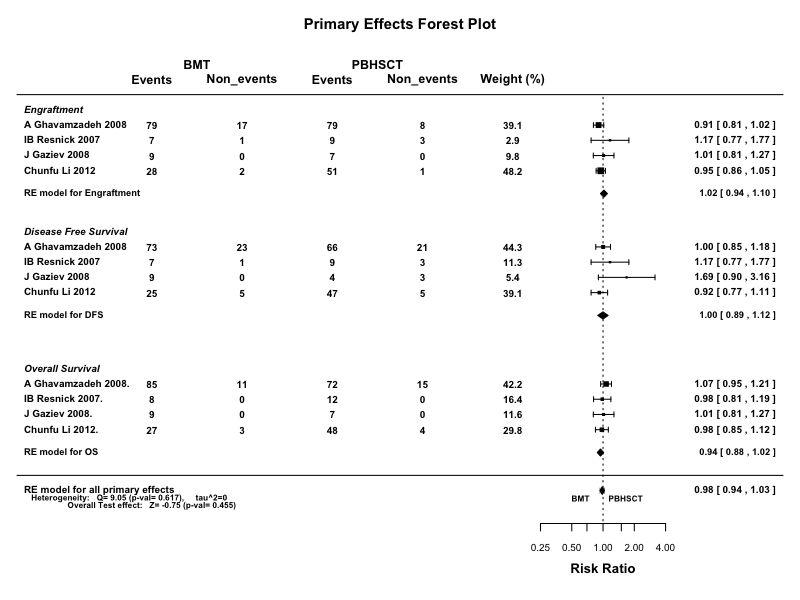
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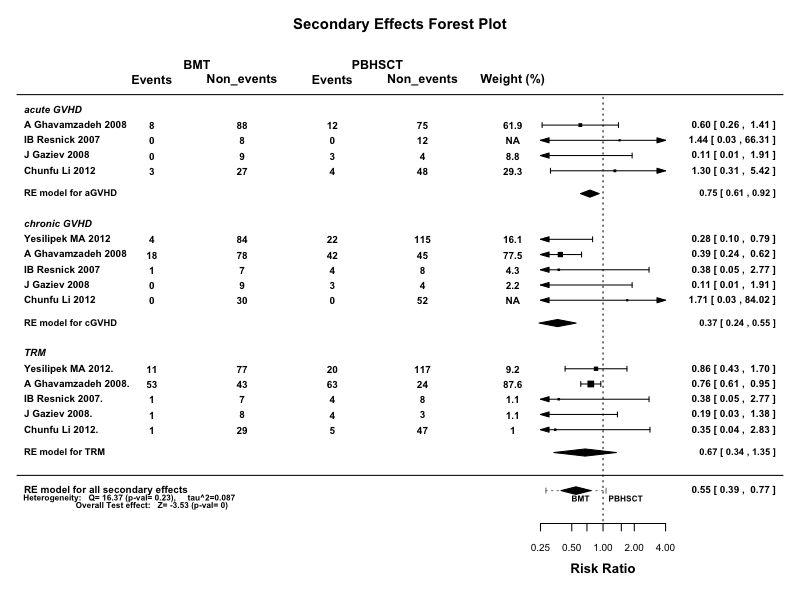
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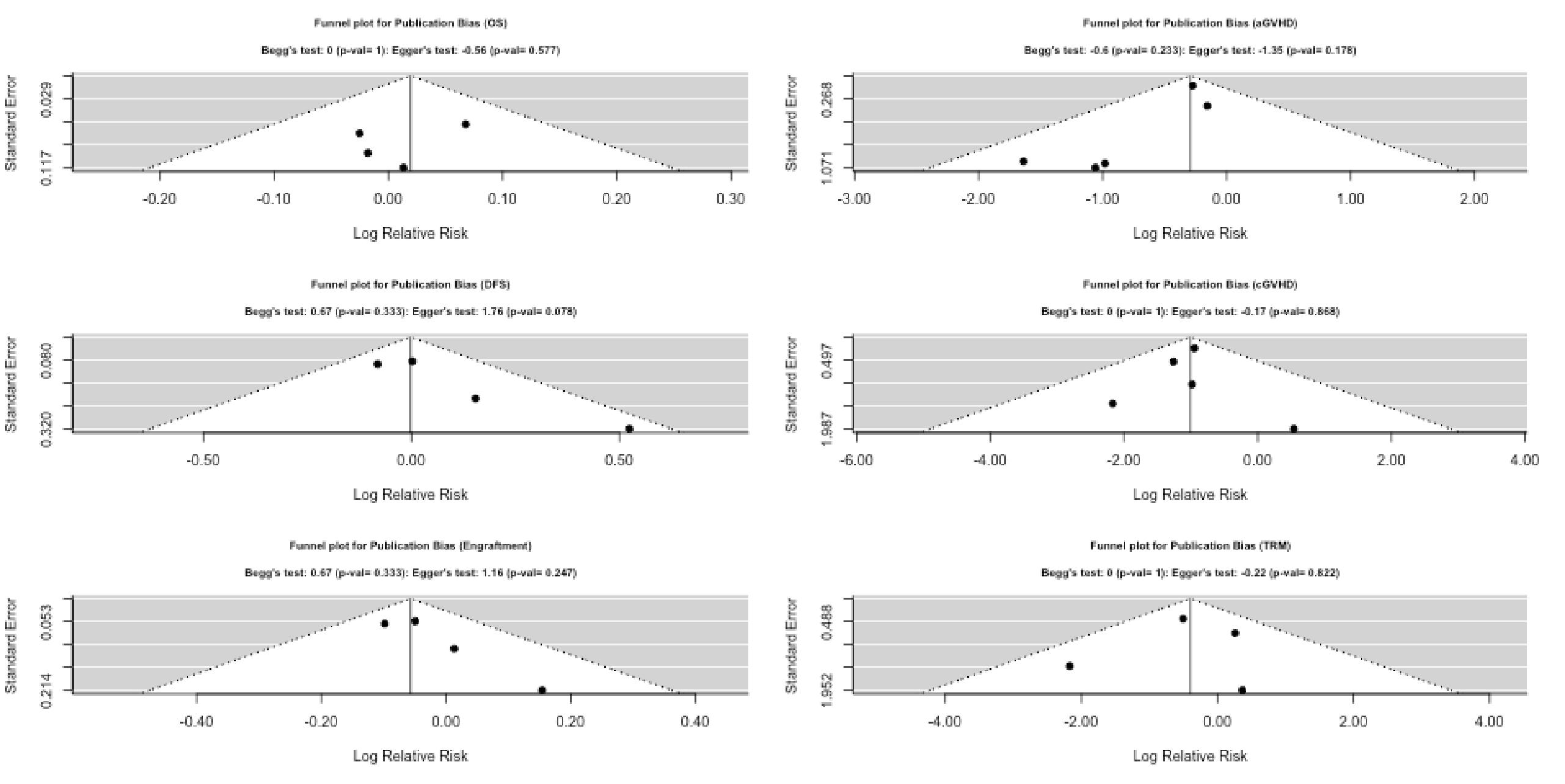
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