Efficacy and Safety of Mesenchymal Stem Cells Co-Infusion in Allogeneic Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis

Teng li (cq179591@163.com)
Third Military Medical University Southwest Hospital
Chengxin Luo
Third Military Medical University Southwest Hospital
Jiasi Zhang
Third Military Medical University Southwest Hospital
Ling Wei
Third Military Medical University Southwest Hospital
Wei Sun
Third Military Medical University Southwest Hospital
Qin Xie
Army Medical University School of Nursing
Yan Liu
Third Military Medical University Southwest Hospital
Yongli Zhao
Third Military Medical University Southwest Hospital
Shuangnian Xu
Third Military Medical University Southwest Hospital
Lihua Wang
Third Military Medical University Southwest Hospital

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Abstract

Background

Hematopoietic stem cell transplantation (HSCT) is a life-saving strategy for severe hematological conditions, but its efficacy and safety need further improvement. Co-infusion of mesenchymal stem cells (MSCs) may bring promise for the overall efficacy in HSCT setting. About that there are increasing studies, while the results from different trials are conflicting. A systematic review and meta-analysis are needed to appraise the real efficacy of MSCs co-infusion in HSCT.

Methods

Five medical databases were searched to identify related controlled studies, which included individuals with hematological diseases receiving allogeneic HSCT (allo-HSCT), and with MSCs co-infusion as intervention arm versus no MSCs as comparison arm. Meta-analysis was performed using RevMan 5.4.

Results

Ultimately, 19 trials met the inclusion criteria. MSCs co-infusion was associated with shorter time both to ANC engraftment (4RCTs: SMD -1.20, p = 0.04; 10nRCTs: SMD -0.54, p = 0.04) and PLT engraftment (4RCTs: SMD -0.60, p = 0.04; 10nRCTs: SMD -0.70, p = 0.01), lower risk of cGVHD incidence (4RCTs: RR 0.53, p = 0.01; 10nRCTs: RR 0.50, p < 0.01), and slightly positive trend towards the risk of aGVHD incidence (3RCTs: RR 0.84, p = 0.33; 9nRCTs: RR 0.74, p < 0.01) and NRM(3RCTs: OR 0.59, p = 0.34; 3nRCTs: OR 0.18, p < 0.01); didn't affect relapse (5RCTs: RR 1.34, p = 0.34; 4nRCTs: RR 0.74, p = 0.24) and overall survival (4RCTs: HR 1.54, p = 0.18; 6nRCTs: HR 0.60, p = 0.06). Subgroup analyses revealed that, when co-transplanted with MSCs, patients younger than 18 or those received HLA-haploidentical grafts had improved engraftment (ANC and PLT and lower risk of NRM and GVHD (acute and chronic forms) incidence. For adults or those received HLA-identical grafts, the risk of cGVHD incidence were reduced. Patients with hematologic malignancies had lower risk of developing GVHD and NRM, patients with non-malignancies showed faster engraftment.

Conclusion

Without increasing the risk of mortality or relapse, MSCs c*o-infusion in* allo-HSCT improved engraftment of platelet and neutrophil, reduced the risk of developing cGVHD. In terms of aGVHD and NRM, the effect of MSCs co-infusion was not quite significant with current evidence.

Background

Throughout the past decades, hematopoietic stem cell transplantation (HSCT) has been the best choice for patients suffering from hematological disorders or malignancies, providing a chance for the complete recovery of blood cellular constituent and graft versus tumor effects. Before the infusion of hematopoietic stem cells (HSCs), recipients routinely need to receive an intensive (total body irradiation-based or chemotherapy-based) conditioning regimen according to the patient's physical condition, disease type, stage, and donor options, which can completely wipe out the immune system and tumor cells. Successful engraftment of HSCs is the precondition for the therapeutic effect of HSCs. However, lots of factors can result to treatment failure or delay of the HSC engraftment, thus raising the transplant-related mortality (TRM). Graft versus host disease (GVHD), either in its acute or chronic forms, is a specific and potentially fatal complication in patients following allogeneic hematopoietic stem cell transplantation (allo-HSCT). For acute GVHD(aGVHD), skin damage is the most common form, second by the gastrointestinal mucous membrane and liver, but other organs may also be affected. Chronic GVHD (cGVHD), characterized by a progressive injury of tissue, could result in fibrosis, susceptibility to infections, reduced quality of life and even overall survival (OS) [1]. Other complications include relapse and infections, such as adenovirus, epstein-barr virus (EBV), cytomegalovirus (CMV) and opportunistic bacterial or fungal infections, all of which can cause significant morbidity and mortality in HSCT recipients [1].

Recently, numerous studies have been carried out to improve the efficacy of HSCT, including the research and application of mesenchymal stem cells (MSCs) [2–6]. As a kind of multipotent stem cells, MSCs are well known to prop up bone marrow stroma and promote hematopoietic reconstruction; besides, MSCs exhibit anti-inflammatory and immune modulating abilities [7–9]; it is therefore considered to have the potential to improve the outcome of HSCT. Although many researchers [10–14] have investigated the effect of MSCs co-infused in HSCT setting, controversy remains yet. Given this, it is necessary to perform a systematic review by pooling those related studies together to clarify this issue, providing an up-to-date clinical evidence for clinicians and patients.

Methods

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15]. There was no need to require ethics approval as it was a systematic review of published summary data [16].

Review objective

The specific research question was: "Are the outcomes of MSCs co-transplantation with allo-HSCs more effective than allo-HSCT alone in people with hematologic disease?" The Eligibility Criteria was defined and listed in Additional file 1.

Data sources and searches

We searched literature systematically in PubMed, Embase, Web of Science, SinoMed and Cochrane Library from date of record to 10 June 2020. The search strategies were shown in Additional file 2.

Study selection

The titles and abstracts of articles identified by the search strategies were screened by 2 reviewers independently. Duplicates were eliminated electronically. All potentially relevant publications were retrieved in full, and then the eligibility criteria were applied to the full text of these studies. At last, the two reviewers discussed and reached a consensus on the papers that should be included. The flow diagram of the literature search and selection is shown in Fig. 1.

Definition of outcomes

We chose engraftment and incidence of GVHD as primary outcomes; relapse rate (RR), overall survival (OS), treatment related mortality or non-relapse mortality (TRM/NRM), and immune reconstitution as secondary outcomes. (I) Engraftment: neutrophil engraftment is defined as the time point of the first 3 consecutive days post-HSCT that the patient reaches an absolute neutrophil count (ANC) of $\geq 0.5 \times 10^9$ cells/L; platelet engraftment is defined as the first day that the patients did not have a platelet transfusion and had a platelet count (PLT) of $\geq 20\times10^9$ cells/L for 7 consecutive days [17]. (II) GVHD: the incidence and severity of GVHD were determined according to a National Institutes of Health (NIH) consensus conference [18]. (III) RR: relapse rate is defined as the recurrence of disease [19]. (IV) OS: overall survival is defined as the time from transplantation until death from any cause [19]. (V) TRM/NRM: death in the absence of persistent relapse is categorized as non-relapse mortality or treatment related mortality [20]. (VI) Immune reconstitution: the recovery of natural killer cells, monocytes, dendritic cells, B cells, T cells and immunoglobulin level [21, 22].

Data extraction

Study basic information, patient characteristics, source of HSCs and MSCs, donor type of HSCs and MSCs, HSCs HLA matching, MSCs dose, median follow up time and major clinical outcomes (Engraftment, GVHD, RR, OS, NRM/TRM and immune reconstitution) were isolated from each included study by 2 investigators independently with specially designed forms. We resolved discrepancies by discussion and consensus. The primary characteristics of the included studies were demonstrated in Table 1. Additional file 3, 4 and 5 contained all the outcomes extracted from each study.

Methodological quality assessment

Methodological quality of studies was critically assessed in collaboration between the first two authors. For the RCTs, the Cochrane Collaboration's tool for assessing the risk of bias (RoB) in randomized trials was applied [23], and an adapted RoB form adjusted to fit the non-randomized design was used for the nRCTs [19]. Random sequence generation and allocation concealment were appraised for RCTs while comparison between groups and selection criteria of participants were evaluated for nRCTs [19]. All studies were appraised for the blinding, selective reporting and incomplete outcome data with a three-point scale (low RoB, high RoB or unclear). Inconsistencies between investigators were resolved by discussion.

Statistical analysis

This meta-analysis was performed with Review Manager (RevMan) Version 5.4. Considering the apparent heterogeneity, we performed it separately for the 6 RCTs and 13 nRCTs. It was considered statistical significance when a two-sided p value ≤ 0.05. To the outcome of engraftment, we chose standard mean differences (SMD). As only median values were attributed in most articles except for studies by Xiang 2017 [10] and Xiao 2013 [24], we used the range and total number to calculate the mean day of engraftment with the way described by Luo [25]. For OS, the log HRs and standard errors were drawn from the studies directly, or transformed from the presented p value and events, or converted from the displayed Kaplan–Meier curves indirectly [26]. We merged the log HRs and corresponding 95 % CIs of each study by the generic inverse-variance method. Statistical heterogeneity across studies was evaluated by Chi-square-based Q test with a significant level at $p < 0.1$ and quantified with I^2 statistic ($I^2 > 50\%$ indicated high heterogeneity) [27]. If heterogeneity was not significant fixed-effect model was adopted for synthesis, otherwise random-effect model was employed [16]. At last, subgroup analyses were conducted based on patients' clinical characteristics, including type of disease, HLA matching and average age.

Results

Search results and Characteristics of the studies

As shown in figure 1 and table 1, totally 734 records were screened by title and abstract. Of which 35 publications were selected for full-text review and appraised for eligibility. As well cited references in these articles were inspected to identify additional reports. At last, 19 studies with 728 participants met the selection criteria for this review [3, 5, 10-13, 17, 20, 24, 28-37]. These studies comprised 16 full publications and 3 meeting abstracts. Among which, 10 were conducted in China, 5 in Europe, 1 in the USA, 2 in Iran, and 1 in Korea. Six of the 19 studies were RCTs with 234 participants, and the remaining 13 trials were sorted as nRCTs, including 7 prospective controlled studies with a total of 203 patients, and 6 historical controlled studies contained 291 participants. Ten trials were in adolescents or children, seven were in adults, one trial involved patients aging from 3 to 48 years old and 1 trial did not mention the average age of participants. Two trials were in patients with β-thalassaemia, one in severe aplastic anemia (SAA), thirteen trials were in patients with hematological malignancies, the remaining 3 trials contained patients with malignant or non-malignant hematonosis together. Six trials administered umbilical cord blood (UCB) HSCs, six trials delivered peripheral blood (PB) HSCs, four trials included patients received UCB, PB or bone marrow (BM) HSCs, whereas 3 trials didn't report the source of HSCs. Four trials infused HLA-identical HSCs, thirteen trials delivered HLA haploidentical HSCs, the remaining 2 trials failed to mention. MSCs were extracted from BM in 9 trials, UCB in 8 trials, and two trials failed to cover the source of MSCs. In the intervention arms, MSCs were administered at a dose of less than 1×10^6 cells/kg in 4 trials, between 1×10^6 and 5×10^6 cells/kg in 11 trials, more than 5×10^6 cells/kg in 2 trials, and other 2 trials didn't give information about this. The median durations of follow-up were within 1-year in 2 trials, between 1 and 2 years in 7 trials, between 2 and 3 years in 4 trials, 3 years and more in 4 trials, in the remaining two trials, the durations of follow-up varied greatly between groups, which were (3-28) and 7.4(1-22) months in MSCs groups, (32-110) and 24(1-107) months in control groups, respectively.

All patients received intensive conditioning regimens, GVHD prophylaxis and supportive care. Patients in the control groups underwent HSCT alone. Patients in the experimental groups received co-infusion of MSCs with allogeneic HSCs, both of which were administrated within day '0' whenever allowed by the patient's

condition, otherwise within the coming 24h. The main outcomes were engraftments of platelet and neutrophil, acute and chronic GVHD, secondary outcomes included relapse rate, overall survival, non-relapse mortality or treatment related mortality, and immune reconstitution.

Risk of Bias analysis

Figure2 showed the quality assessment results for each study. No trial included more than 100 participants and some trials recruited participants even less than 20 [11, 24, 33-35]. Most studies in the 6 RCTs were at low risk of bias, but the 13 nRCTs were with higher risk according to the predefined methodological quality assessment tool.

Engraftment

Four RCTs and 10 nRCTs provided sufficient information of the neutrophil engraftment that differed from 10.5 to 29.82 mean days for the experimental group and from 12.31 to 28.1 mean days for the control group. We estimated the mean and standard deviation (SD) from the given sample size, median and range [25], Ghavamzadeh 2010 [37] and Kang 2017 [30] were not included in meta-analysis of this results as they only supplied the median values. Data from Baron 2010 [3] were ruled out for it defined neutrophil count of $\geq 1.0\times10^9$ cells/L as the standard of neutrophil engraftment. Results from Liu 2011 [17] and Ghavamzad 2017 [5] were not included because they monitored white blood cell (WBC) engraftment instead of neutrophil engraftment. Both meta- analysis of RCTs with 130 participants and nRCTs with 341 participants indicated that patients received MSCs co-infusion had a shorter time of reaching neutrophil recovery compared with the control group (4 RCTs: SMD -1.20, 95% CI -2.32 to -0.08, p = 0.04, I^2 = 86%; 10 nRCTs: SMD -0.54, 95% CI -1.05 to -0.03, p = 0.04, I^2 = 74%; Fig. 3a&b).

With regard to the platelet engraftment, we did not include the study by Ghavamzadeh 2010 [37] and Kang 2017 [30] for lack of usable data; data from the studies by Baron 2010, Ning 2008 and MacMillan 2009 [3, 20, 31] were not included because they defined platelet count of $\geq 100\times10^9$ cells/L or $\geq 50\times10^9$ cells/L as the standard of platelet recovery. As a result, only 4 RCTs and 10 nRCTs were selected for synthesis, the engraftment time differed from 8.71 to 52.05 mean days for MSCs co-infused groups and from 16.02 to 78.94 mean days for the controlled groups. Both RCTs with 157 participants and nRCTs with 381 participants revealed that the patients from the MSCs co-infusion group had a faster recovery of platelet than those from HSCT alone group (4 RCTs: SMD -0.60, 95% CI -1.17 to -0.02, p = 0.04, I^2 = 63%; 10 nRCTs: SMD -0.70, 95% CI -1.24 to -0.16, p = 0.01, I^2 = 79%; Fig. 3c&d).

According to the funnel plot as showed in Additional file 6, publication bias was obvious for the outcomes of ANC and PLT engraftment. Meanwhile, statistical heterogeneity existed as indicated by the Tau^2、Chi^2 and I^2 tests (Fig. 3a,b,c&d). Thus, we adopted random-effect model and performed sensitivity one-out analyses to estimate the relative contribution of each single study to the overall heterogeneity. When the study of Wu 2013b [35] was abandoned, the score of I^2 sharply decreased from 63% to 0% in the meta-analysis of PLT engraftment in RCTs, which may be accounted by that it was the only trail that used MSCs in excess of 5×10^6 cells per kilogram; no significant I^2 changes were observed in the other 3 meta-analysis.

In addition, we conducted subsets analyses (details were shown in Additional file 7) according to the dose of MSCs where all the studies were sorted into three groups. The study of Xiao 2013 [24] was excluded as it failed to document the dosage of MSCs. These analyses manifested that with the increase of MSCs dose, hematopoietic recovery was more effective. Although the results of subsets in nRCTs with MSCs among 1×10^6 to 5×10^6 cells per kilogram were not obvious, which may partly be attributed to the potential confounders of the study design. However, as the number of included studies and sample size in some subgroups were limited, all these results should be explained with caution.

GVHD

The incidence of grade Ⅱ-Ⅳ aGVHD was reported in 3 studies [17, 20, 35]. Study of Ghavamzad 2010 [37] only provided the data of grade Ⅱ-Ⅳ aGVHD; Mareika, 2016 [32] covered the occurrences of grade Ⅱ-Ⅳ and grade Ⅲ-Ⅳ aGVHD; the study of Xiang 2017 [10] wasn't included as it did not report this outcome. Among the 13 nRCTs, nine studies reported the incidence of overall aGVHD; two [3, 31] provided only the data of grade Ⅱ-Ⅳ aGVHD; and the remaining 2 studies [24, 29] did not mention this outcome.

Regarding the incidence of grade Ⅱ-Ⅳ aGVHD, no statistical significance was observed in the meta-analysis including 3 RCTs with 98 cases (RR 0.84, 95% CI 0.59 to 1.19, P = 0.33, I^2 = 0%; Fig. 4a). Whereas in the meta-analysis including 9 nRCTs with 377 participants, it showed that patients with MSCs co-infusion had a significantly lower rate of grade Ⅱ-Ⅳ aGVHD incidence than the control group (RR 0.74, 95% CI 0.60 to 0.91, P = 0.005, I^2 = 0%; Fig. 4b). No difference was found between groups in outcomes of grade Ⅱ-Ⅳ, grade Ⅲ-Ⅳ and grade Ⅳ aGVHD, from neither meta-analysis with RCTs nor that with nRCTs (Fig.4a&b).

Among the19 candidate studies, three [3, 29, 37] did not provide information about cGVHD incidence, two [11, 32] presented only the incidence of extensive cGVHD without data about the number of people who developed limited cGVHD. As a result, 4 RCTs with 156 participants (RR 0.53, 95% CI 0.33 to 0.87, P = 0.01, I^2= 25%; Fig. 5a) and 10 nRCTs with 380 participants (RR 0.50, 95% CI 0.33 to 0.75, P = 0.001, I^2=0%; Fig. 5b) were separately included in meta-analysis for the overall occurrence of cGVHD, both results of RCTs and nRCTs suggested that MSCs co-infusion could significantly reduce the overall incidence of cGVHD.

Specifically, in the outcome of limited cGVHD, no statistical significance was found between groups. However, patients in the MSCs group had a lower risk of extensive cGVHD compared with the control groups, as demonstrated by the meta-analysis with 8 nRCTs (RR = 0.37, 95% CI 0.17, 0.81, I^2 = 0%, P = 0.01; Fig 5b), meanwhile, there was a slightly trend from meta-analysis with 4 RCTs (RR = 0.44, 95% CI 0.17, 1.09, I^2= 0%, P = 0.08; Fig. 5a).

Both funnel plots for aGVHD and cGVHD (Additional file 8) showed asymmetry, indicating the existence of publication bias. The statistical heterogeneity was not significant as indicated by the Tau^2、Chi^2 and I^2 tests.

Overall Survival

Totally, there are 14 trials estimated the effect of MSCs co-infusion on overall survival of HSCT recipients, of which four studies were excluded [11, 5, 12, 13] for they failed to provide sufficient information that could be transformed into logHR and SE. With the rest of 4RCTs (164 participants) and 6 nRCTs (231 participants), the outcomes of meta-analysis (HR 1.54, 95% CI 0.81 to 2.93, P = 0.18, I^2 = 0%, Fig. 6a; HR 0.60, 95% CI 0.35 to 1.02, P = 0.06, I^2 = 34%, Fig. 6b; respectively) suggested no statistically significant difference of OS between groups. Publication bias was not obviously visualized from the funnel plot of OS, which was shown in Additional file 9a. Statistical heterogeneity was not significant as indicated by the Tau^2、Chi^2 and I^2 tests.

Relapse Rate

Eleven studies reported the occurrence of relapse in both the MSCs group and the control group, but studies by Ball 2007 [13] and Daganzo 2009 [28] were excluded for reason of varied follow-up time between groups. Both the meta-analysis for 5 RCTs with 186 participants and 4 nRCTs with 184 participants (RR 1.34, 95% CI 0.74 to 2.43, P = 0.34, I^2 = 13%, Fig. 7a; RR 0.74, 95% CI 0.45 to 1.22, P = 0.24, I^2 = 0%, Fig. 7b; respectively) suggested no difference between patients given MSCs co-transplantation and those were not. Apparent publication bias was observed from the funnel plot of RR (Additional file 9b) and statistical heterogeneity was not significant as indicated by the Tau^2、Chi^2 and I^2 tests.

TRM/NRM

For the non-relapse mortality or treatment related mortality (TRM/NRM), the meta-analysis results varied between the 3 RCTs with 100 participants and the 3nRCTs with 97 participants (OR 0.59, 95% CI 0.20 to 1.73, P = 0.34, I^2 = 0%, Fig. 7c; OR 0.18, 95% CI 0.06 to 0.54, P = 0.002, I^2 = 0%, Fig. 7d; respectively). But all of the odds ratios are no more than 1 and no statistical heterogeneity was observed, we could draw that there was still a slightly trend that patients infused with MSCs may have a lower risk of TRM/NRM. Of which the funnel plot was not applicable for the small number of studies. The statistical heterogeneity was not significant as indicated by the Tau^2、Chi^2 and I^2 tests.

Immune reconstitution

Multiple studies had investigated the effect of MSCs co-transplantation in allo-HSCT on the immune reconstitution. However, it was difficult to combine all these data from each trial because of varied parameters and time points, we just made a qualitative description.

In the study of Ball 2007, the recovery time of natural killer cells at 28 days post transplantation was faster in recipients received MSCs co-infusion compared with the controls [13]. The research by Xiang 2017 [10] showed that the levels of lymphocytes subpopulations and immunoglobulins in patients treated with MSCs were statistically higher than the control group at 1st, 3rd and 6th month post transplantation. While the other seven trials [3, 5, 11, 17, 28, 32, 34] found no differences in the time of lymphocyte recovery post transplantation between two groups (details were shown in Additional file 5).

Analyses of patient subgroups

In the end, we conducted subgroup analysis based on the type of disease (malignant versus nonmalignant), HLA matching (HLA identical versus haploidentical) and average age (children and adolescents versus adults) by combining all the RCTs and nRCTs together (details were presented in Additional file 10-15; merged results were shown in table 3).

For malignant patients, risks of developing aGVHD, cGVHD and NRM were significantly reduced with MSCs co-transplantation; while for those with nonmalignant disorders, MSCs co-transplantation could accelerate hematopoietic recovery in both aspects of ANC and PLT engraftment.

Recipients who received HLA-identical grafts could benefit in outcomes of cGVHD and OS from receiving MSCs co-transplantation. Whereas for those who undergoing HLA-haploidentical HSCT, MSCs co-transplantation could play a significant positive role in the outcomes of hematopoietic reconstitution (both ANC and PLT engraftment), significantly reduce the risk of developing GVHD (both aGVHD and cGVHD) as well as TRM/NRM.

For adults, people received MSCs co-transplantation could have a lower incidence of cGVHD than those were not. While for individuals younger than 18, the intervention of MSCs co-transplantation could improve hematopoietic reconstitution (both ANC and PLT engraftment), and reduce the risk of developing GVHD (both aGVHD and cGVHD) as well as TRM/NRM obviously.

Discussion

Allogeneic HSCT is the curative method for a lot of hematological disease, the perfection of its whole process is a hot project. The main objective of our study was to determine whether MSCs co-transplantation with allo-HSCT in patients with hematological conditions could improve transplantation outcomes, including engraftment, GVHD, TRM, relapse and survival of patients. The outcomes of our meta-analyses (shown in table 2) indicated that the use of MSCs co-infusion, without influencing the risk of mortality or relapse, could facilitate engraftments of ANC and PLT, reduce the risk of cGVHD incidence. As for aGVHD incidence and NRM, the effect of MSCs was still unclear with current evidence. Subgroup analyses revealed that, when co-transplanted with MSCs, patients younger than 18 or those received HLA-haploidentical grafts had improved engraftment（both ANC and PLT）and lower risk of NRM and GVHD (both acute and chronic forms) incidence. For adults or those received HLA-identical grafts, the risk of cGVHD incidence were reduced. Patients with hematologic malignancies had lower risk of developing GVHD and NRM, patients with non-malignancies showed faster engraftment.

Although we have found advantage for MSCs co-transplantation with HSCT in our meta-analysis, but there may be some potential limitations. Firstly, it was notable of the heterogeneity across studies, including the type and stage of diseases, sources and dosage of HSCs and MSCs, HLA matching, definitions of outcomes, varied follow-up time and study designs, although we have performed subgroup analysis and sensitivity analysis trying to resolve it. But also note

that, in the subgroups of non-malignant disorders and HLA-identical matching, there were no more than 3 trials with small sample sizes involved in each meta-analysis. Secondly, publication bias was possible due to 2 ongoing trials (ChiCTR-OCN-15006595, ChiCTR-IIR -16007806) [38, 39], which were initiated in 2015 and 2016, but we failed to find any related publications. Thirdly, we restricted the language of literature only to Chinese and English, which may result some relevant studies fail to be retrieved. Fourthly, 3 trials [5, 32, 37], which were published in a form of abstract on poster session, failed to provide us enough information to fully evaluate sources of bias. Last, it was also important to think about the limitations of I^2. Despite most of the I test scores were below 50%, particularly if there is a limited number of trials or few events involving in a meta-analysis, actually I^2 values are likely to be underestimated [40, 41].

The role of MSCs in HSCT is constantly a hot issue, several meta-analyses have been conducted to evaluate the efficacy and safety of MSCs co-transplantation or infusion after HSCT. A systematic review with 9 studies published in 2016 found no significant statistical difference in effects of MSCs co-transplantation with HSCs [19]. Whereas it didn't exam the outcome of PLT engraftment. In their meta-analysis for the risk of cGVHD, Kallekleiv and colleagues included only 3 RCTs and 3 nRCTs, which were also involved in our study. But we included an additional RCT (Xiang 2017) and 7 nRCTs (including Ghavamzadeh 2017, Daganzo 2009, Kang 2017, Xiao 2013, Zhang 2015, Wang 2015 and MacMillan, 2009) because of the time reason and the inclusion of Chinese papers. In our review with much larger sample sizes and with recently published studies, both meta-analysis in 4 RCTs and 10 nRCTs suggested that MSCs co-infusion could significantly lower the risk of cGVHD when compared with the control group. Another meta-analysis conducted by Wang [42], which adopted random effects analysis, showed no significant difference in the outcome of cGVHD in subgroup analysis (RR 0.52, 95% CI 0.24 to 1.14, P = 0.259, participants = 156). With an I^2 score of 25%，we chose the fixed effects model in our meta-analysis. As a result, our meta-analysis with the same 4 RCTs which were included in Wang's meta-analysis for cGVHD, indicated that MSCs co-infusion could significantly reduce the incidence of cGVHD (RR 0.53, 95% CI 0.33 to 0.87, P = 0.01, participants = 156). Furthermore, we obtained consistent findings from the meta-analysis with 10 nRCTs (RR 0.50, 95% CI 0.33 to 0.75, P < 0.01, participants = 380).

Recent large cohort studies have also confirmed our results. One multi-center trial [43] demonstrated that it was efficacious and safe for children with SAA to infuse BM-MSCs combined with haplo-HSCT, in terms of promoting hematopoietic implantation, controlling against severe aGVHD and prevention for cGVHD. Which was consistent with our findings that for individuals younger than 18 or underwent haploidentical HSCT, MSC co-transplantation could play a significant positive role in the outcomes of hematopoietic reconstitution, graft versus host disease. As well as for those with nonmalignant disorders, MSCs co-infusion could accelerate hematopoietic recovery.

When determining the optimal treatment schedule of MSCs co-transplantation in HSCT, issues such as the cell type and dose, administration timing and the subjects of MSCs are also very important. In this review, we focused only on the timing and the patient of MSCs infused, while the other variables of MSCs have not been well define yet. Although there were two systematic reviews [42, 44] that had analyzed the role of different dose and sources of MSCs infused in HSCT, they included a mixture of studies both MSCs co-infusion and late-infusion. In order to address the limitations of HSCT much better, which including infection, relapse of disease, engraftment and complications of GVHD [45], we should also consider selecting the appropriate source of MSCs to match specific type of HSCs. To our knowledge, there is no clinical trials that specifically studied this issue in the setting of MSCs co-transplantation. Therefore, high-quality researches focusing on these aspects are needed in the future.

In addition, a single cell RNA sequencing study of equine MSCs reveals that there are both inter- and intra-source heterogeneity across different sources of MSCs, indicating that some MSCs subgroups may have advantageous biological function. These findings provide us a clue for improving the therapeutic potential of MSCs and HSCT outcomes through adopting different MSCs subgroups [46].

Conclusion

Collectively, the treatment strategy of MSCs c*o-infusion with* allo-HSCT could generally improve engraftment and reduce the risk of developing cGVHD without increasing the risk of mortality or relapse; in terms of aGVHD and NRM, the effect of MSCs co-infusion was not quite significant. Specifically, children, adolescents or those received haploidentical HSCT might benefit most from this intervention.

Inevitably, potential confounders existed across the studies included in this review. Thus, to avoid harming patients, it's imperative to conduct more well-powered randomized controlled trials to validate our findings and clarify certain issues such as the appropriate sources and dosage of MSCs co-transplanting in patients with specific clinical conditions.

Abbreviations

HSCT: Hematopoietic stem cell transplantation；MSCs: Mesenchymal stem cells；GVHD：Graft versus host disease; OS: Overall survival; RR: Relapse rate; TRM/NRM: Treatment related mortality or non-relapse mortality; ANC: Absolute neutrophil count; PLT: Platelet; EBV: Epstein-barr virus；CMV: Cytomegalovirus; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SMD: Standard mean difference; RR: Risk ratio; OR: Odds ratio; HR: Hazards ratio; CI: Confidence interval; HLA: Human leucocyte antigen; SAA: Severe aplastic anemia; UCB: Umbilical cord blood; PB: Peripheral blood; BM: Bone marrow

Declarations

Acknowledgments

Not applicable

Authors' contributions

SNX and LHW contributed to the conception, design and supervision of this study. SNX and TL were responsible for collection of data, risk of bias, performing the statistical analysis and manuscript preparation. CXL and TL were responsible for checking the data and data conversion. JSZ, LW, WS, QX, YL and YLZ participated in the data interpretation, illustration making or manuscript preparation. CXL, SNX and TL involved in revising the manuscript critically for important intellectual content. All authors were responsible for drafting the manuscript and read and approved the final version.

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Availability of data and materials

All supporting data and materials were included in the article and its additional files.

Ethic approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declared no conflicts of interest.

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Tables

Table1. Characteristics of included studies in systematic review (N = 19)

First author, year and country	Study	Disease	No. (MSCs+/MSCs-)	Median /MeanAge (year) (MSCs+/MSCs-)	HSCs source (Donor Type)	HSCs HLA matching	MSCs Source (Donor type)	MSCs dose (10^6/kg)	Median follow up time (month) (MSCs+/MSCs-)
Ning, 2008, China	RCT	HM	25(10/15)	38/ 37	BM, PB（BM +PB）RD）	Identical	BM（RD）	0.34 (0.03-1.53)	36.6 (0.6–44.0)
Ghavamzad, 2010, Iran	RCT	NMD	48(25/23)	17/16	PB, BM（RD）	Identical	NA (NA)	1.45-1.80	10(1-28)
Liu,2011, China	RCT	HM	55(27/28)	30/31.5	BM+PB（RD）	HID	BM（RD, TPD）	0.3-0.5	23.7 (0.7-33.5)
Wu,2013b, China	RCT	HM	20(8/12)	9.8/8.5	UCB（URD）	HID	UCB（URD）	7.19 (2.44-10.12)	16.5(11-27)/ 18.5(12–31)
Mareika, 2016, Belarus	RCT	HM	22(10/12)	13(5-24)	NA（NA）	NA	BM (NA)	1.56±0.4	38 (5.7-59.4)
Xiang,2017, China	RCT	HM	64(32/32)	5.5±1.4/ 5.2±1.2	PB（URD）	Identical	UCB（URD）	1.0	24
Ball, 2007, Netherlands	HCT	HM& NMD	61(14/47)	8(1-16)/ 7.1(1-17)	PB（RD）	HID	BM（RD）	1.6 (1.0-3.3)	(3-28)/ (32-110)
Daganzo, 2009, Spain	PCT	HM	55(9/46)	32/35	UCB（URD）	HID	BM（URD）	1.2 (1.04-2.22)	7.4(1-22)/ 24(1-107)
MacMillan, 2009, U.S.A.	HCT	HM	30(7/23)	7.5(0.2-16)	UCB（URD）	HID	BM（RD）	2.1 (0.9–5.0)	81.6
Baron,2010, Belgium	HCT	HM	36(20/16)	58/55	PB（URD）	HID	BM（URD）	NA	18.7 (13.3-30.3)
Hou, 2010 China	PCT	HM	35(15/20)	32(14-45）/ 28.5(12-48)	NA（RD）	HID	BM (RD:2, TPD:13)	0.41 (0.22-0.52)	6
Bernardo, 2011, Italy	HCT	HM	52(13/39)	2/4	UCB（URD）	HID	BM (RD)	1.9 (1–3.9)	36(28/42)
Lee, 2013, Korea	HCT	HM	16(7/9)	6.9/9.5	UCB（URD）	HID	UCB（URD）	1.0 in 4 pts 5.0 in 3 pts	24
Wu, 2013a, China	PCT	HM& NMD	14(5/9)	8.8/7.8	UCB（URD）	HID	UCB（URD）	5.76 (3.12-8.21)	27 (24-31)
Xiao,2013, China	PCT	HM& NMD	15(7/8)	30(12-60)/ 35.5(16-54)	PB（URD）	NA	UCB（URD）	NA	15
Wang,2015, China	PCT	NMD	14(7/7)	28(22-43)	PB（RD）	HID	UCB（URD）	Total:30.0	14.5(6-74)
Zhang,2015, China	HCT	HM	49(22/27)	22.5（3-48）/23（3-43）	PB（URD）	HID	UCB（URD）	1.0	22(1-98)

Kang,2017, China	HCT	HM	47(34/13)	7(1.5 - 13)	PB, BM （RD）	HID	UCB （URD）	1.0	20(0.5-67)
Ghavamzad, 2017, Iran	PCT	NMD	70(41/29)	NA	NA （RD）	Identical	NA （URD）	1.0-2.0	35.76/31.44

RCT: randomized controlled trial; PCT: prospective controlled trial; HCT: historical controlled trial;

HM: hematological malignancies; NMD: nonmalignant disorders; PB: peripheral blood; BM: bone marrow; UCB: umbilical cord blood; RD: related donor; URD: unrelated donor; NA: not available; Pts: patients. HID: haplo-identical donor

Table 2. Merged outcomes of the meta-analysis

Outcome	Study Design	Number of Trials	Sample Size	SMD/RR/ OR/ HR	95%CI	*P*	I^2
ANC	RCTs	4	130	SMD: -1.20	-2.32, -0.08	0.04*	86%#
	nRCTs	10	341	SMD: -0.54	-1.05, -0.03	0.04*	74%#
PLT	RCTs	4	157	SMD: -0.60	-1.17, -0.02	0.04*	63%#
	nRCTs	10	381	SMD: -0.70	-1.24, -0.16	0.01*	79%#
aGVHD	RCTs	3	98	RR: 0.84	0.59, 1.19	0.33	0%
	nRCTs	9	377	RR: 0.74	0.60, 0.91	0.005*	0%
cGVHD	RCTs	4	156	RR: 0.53	0.33, 0.87	0.01*	25%
	nRCTs	10	380	RR: 0.50	0.33, 0.75	0.001*	0%
OS	RCTs	4	164	HR: 1.54	0.81, 2.93	0.18	0%
	nRCTs	6	231	HR: 0.60	0.35, 1.02	0.06	34%
RR	RCTs	5	186	RR: 1.34	0.74, 2.43	0.34	13%
	nRCTs	4	184	RR: 0.74	0.45, 1.22	0.24	0%
NRM	RCTs	3	100	OR: 0.59	0.20, 1.73	0.34	0%
	nRCTs	3	97	OR: 0.18	0.06, 0.54	0.002*	0%

* the difference was statistical significance.

significant heterogeneity needed to conduct subgroup analysis.

Table 3. Merged outcomes of the subgroup analysis

Not reported	>18 years	≤18 years	Average age	Not reported	Non-identical	Identical	HLA matching	Mixed
0	6	8		2	10	2		3
0	192	279		37	346	88		90
NA	-0.37(-1.00, 0.26)	-1.07(-1.84, -0.31)		-1.30(-2.03, -0.57)	-0.63(-1.18, -0.07)	-0.79(–3.02, 1.45)		-1.39(-2.86,0.07)
NA	0.25	<0.01*		<0.01*	0.03*	0.49		0.06
1	6	7		2	10	2		3
70	219	249		37	367	134		90
-1.67(-2.22, -1.11)	-0.35(-0.86, 0.17)	-0.71(-1.22, -0.19)		-1.02(-1.77, -0.26)	-0.50(-0.93, -0.07)	-0.94(-2.36, 0.49)		-1.41(-2.79, -0.03)
<0.01*	0.19	<0.01*		<0.01*	0.02*	0.2		0.05*
1	5	6		0	10	2		2
70	196	209		0	381	94		75
0.86(0.59,1.25)	0.85(0.65,1.12)	0.64(0.47,0.87)		NA	0.76(0.61,0.94)	0.79(0.56,1.11)		0.53(0.21,1.33)
0.42	0.25	<0.01*		NA	0.01*	0.18		0.17
1	6	7		1	10	3		3
70	189	276		15	365	155		90
0.58(0.28,1.21)	0.54 (0.36,0.81)	0.43 (0.23,0.84)		0.16(0.01,2.66)	0.56(0.39,0.81)	0.43(0.22,0.84)		0.38(0.11,1.28)
0.15	<0.01*	0.01*		0.20	<0.01*	0.01*		0.12
0	5	5		0	8	2		1
0	220	175		0	306	89		14
NA	1.01(0.44,2.30)	0.94(0.39,2.22)		NA	0.70(0.45,1.10)	2.95(1.05,8.25)		1.68(0.27,10.44)

NA	0.98	0.88	NA	0.12	0.04*	0.58
0	4	5	1	6	2	0
0	165	205	22	259	89	0
NA	1.25(0.68,2.31)	0.79(0.49,1.30)	3.55(0.16,78.56)	0.81(0.51,1.28)	1.34(0.29,6.25)	NA
NA	0.47	0.36	0.42	0.37	0.71	NA
0	3	3	0	5	1	1
0	116	81	0	172	25	14
NA	0.46(0.18,1.18)	0.19(0.05,0.68)	NA	0.31(0.14,0.68)	0.72(0.06,9.22)	0.27(0.01,6.89)
NA	0.11	0.01*	NA	<0.01*	0.80	0.43

Figures

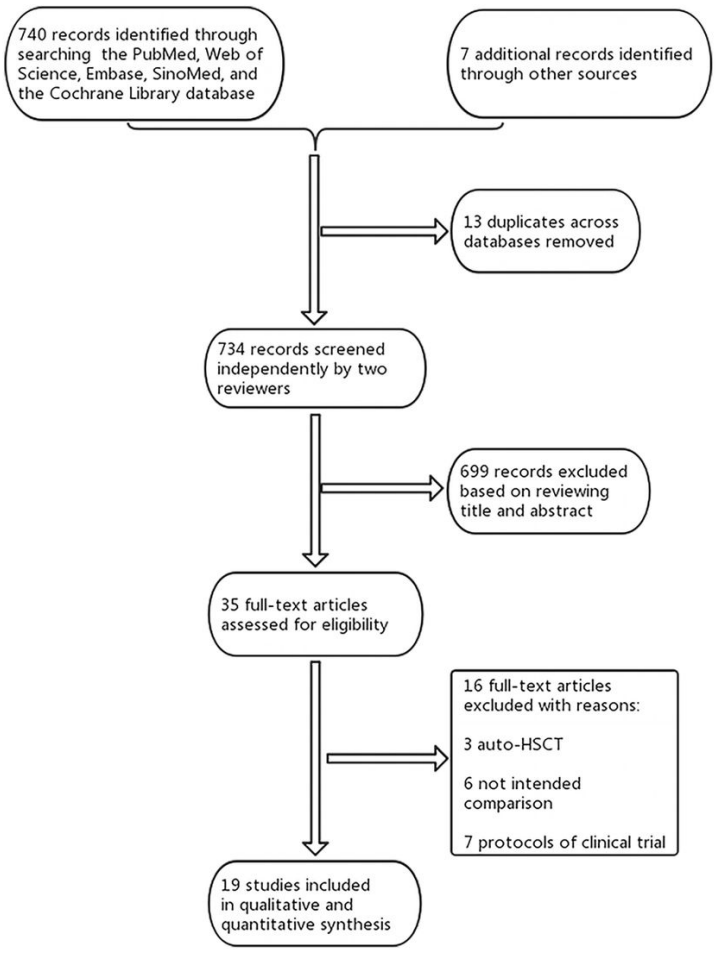

Figure 1

Flow diagram of the selection process.

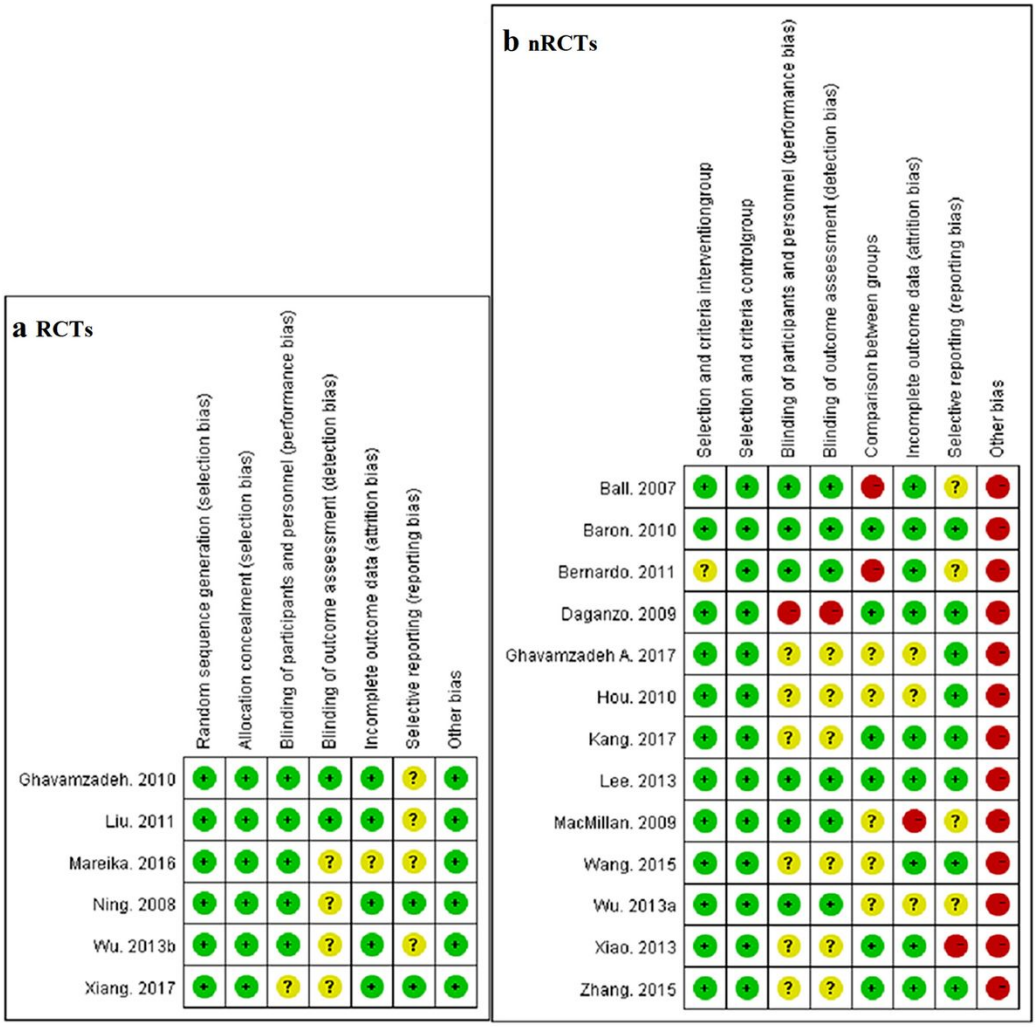

Figure 2

Risk of Bias. (a) for 6 RCTs. (b) for 13 nRCTs.

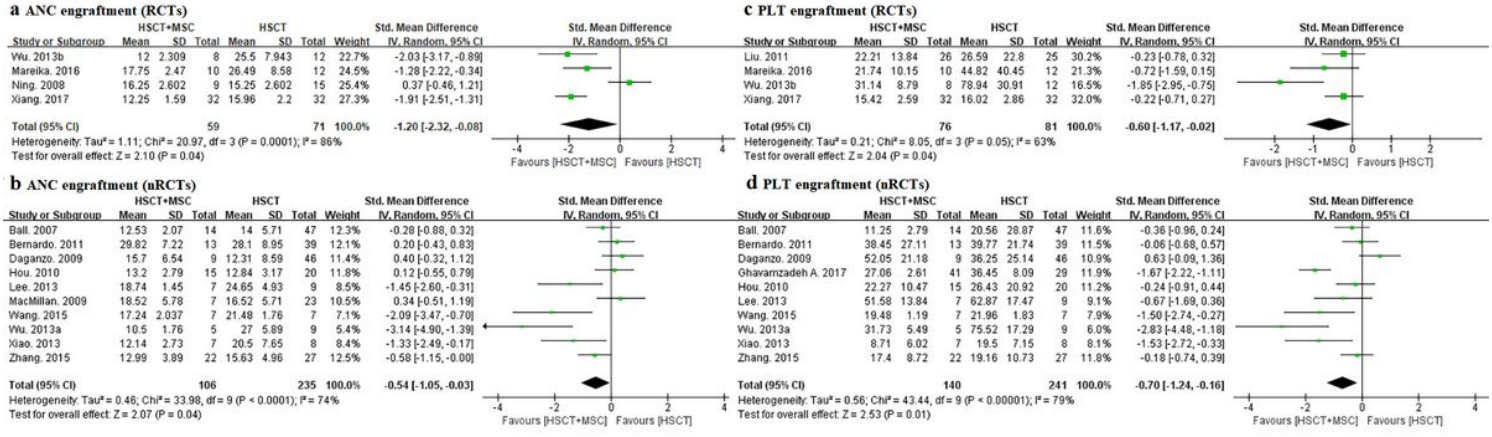

Figure 3

Meta-analysis of comparison for engraftment between HSCT+MSC group and HSCT alone group. (a) ANC engraftment in RCTs. (b) ANC engraftment in nRCTs. (c) PLT engraftment in RCTs. (d) PLT engraftment in nRCTs.

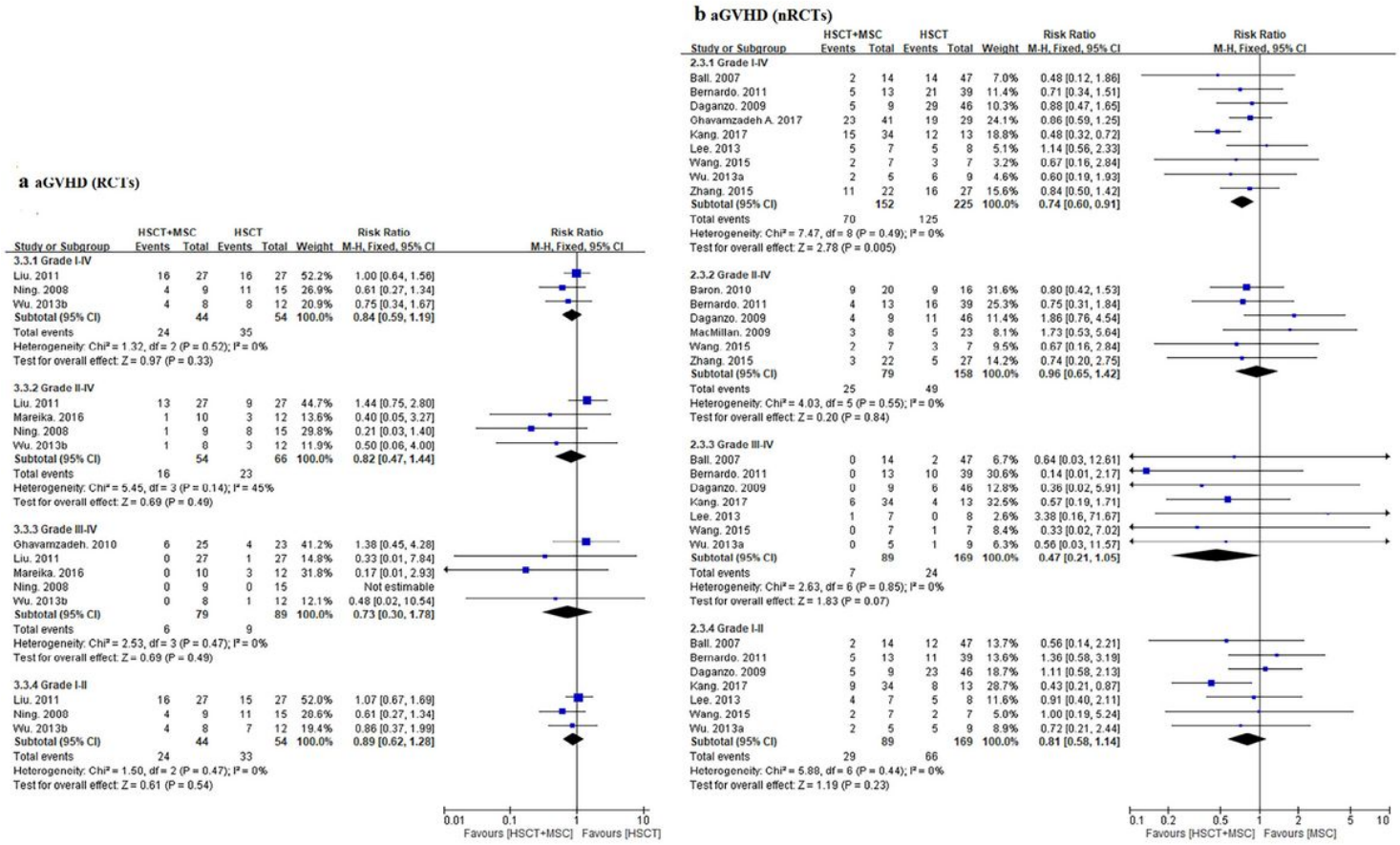

Figure 4

Meta-analysis of comparison for overall and graded incidence of aGVHD between HSCT+MSC group and HSCT alone group. Analysis was performed for (a) RCTs and (b) nRCTs separately.

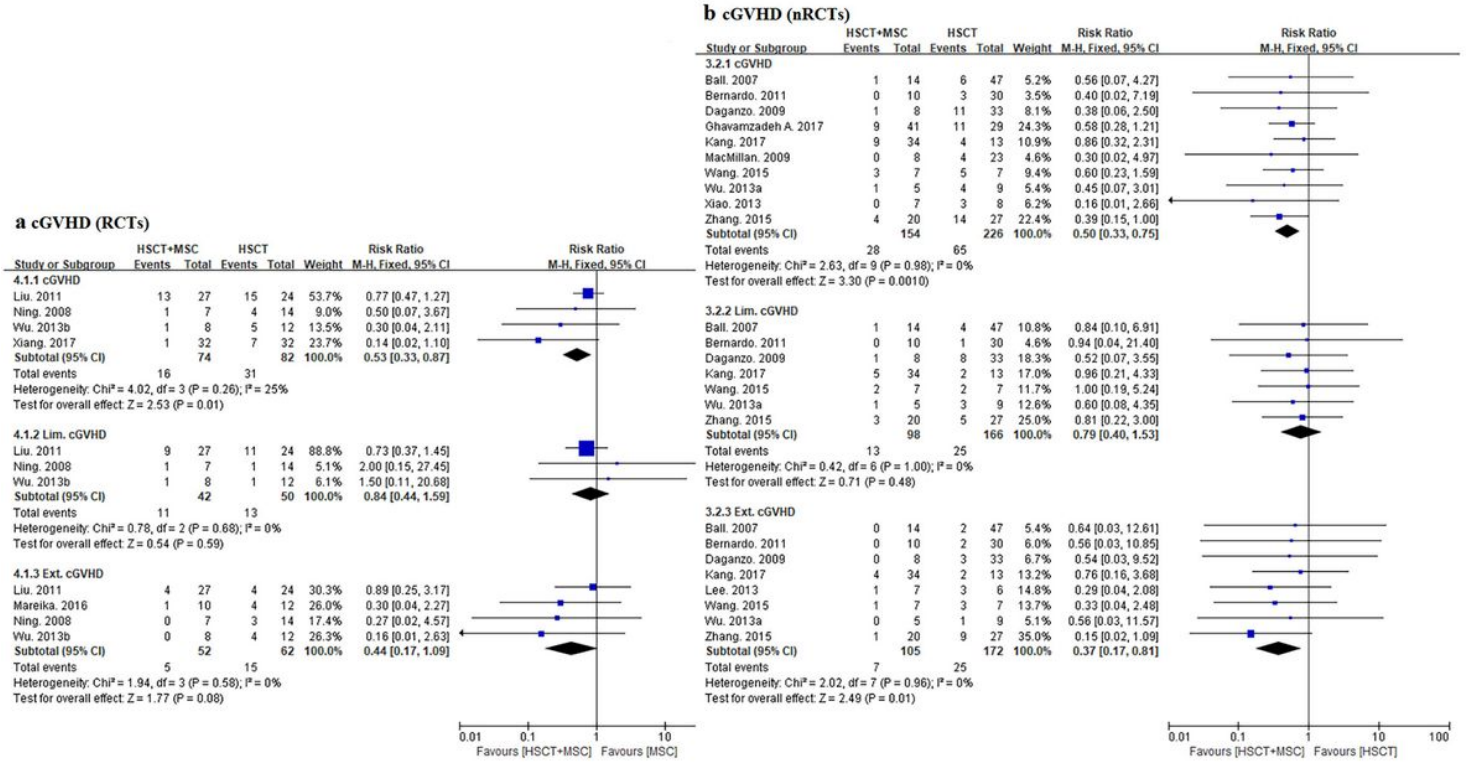

Figure 5

Meta-analysis of comparison for overall and graded incidence of cGVHD between HSCT+MSC group and HSCT alone group. Analysis was performed for (a) RCTs and (b) nRCTs separately. Lim.: limited; Ext.: extensive.

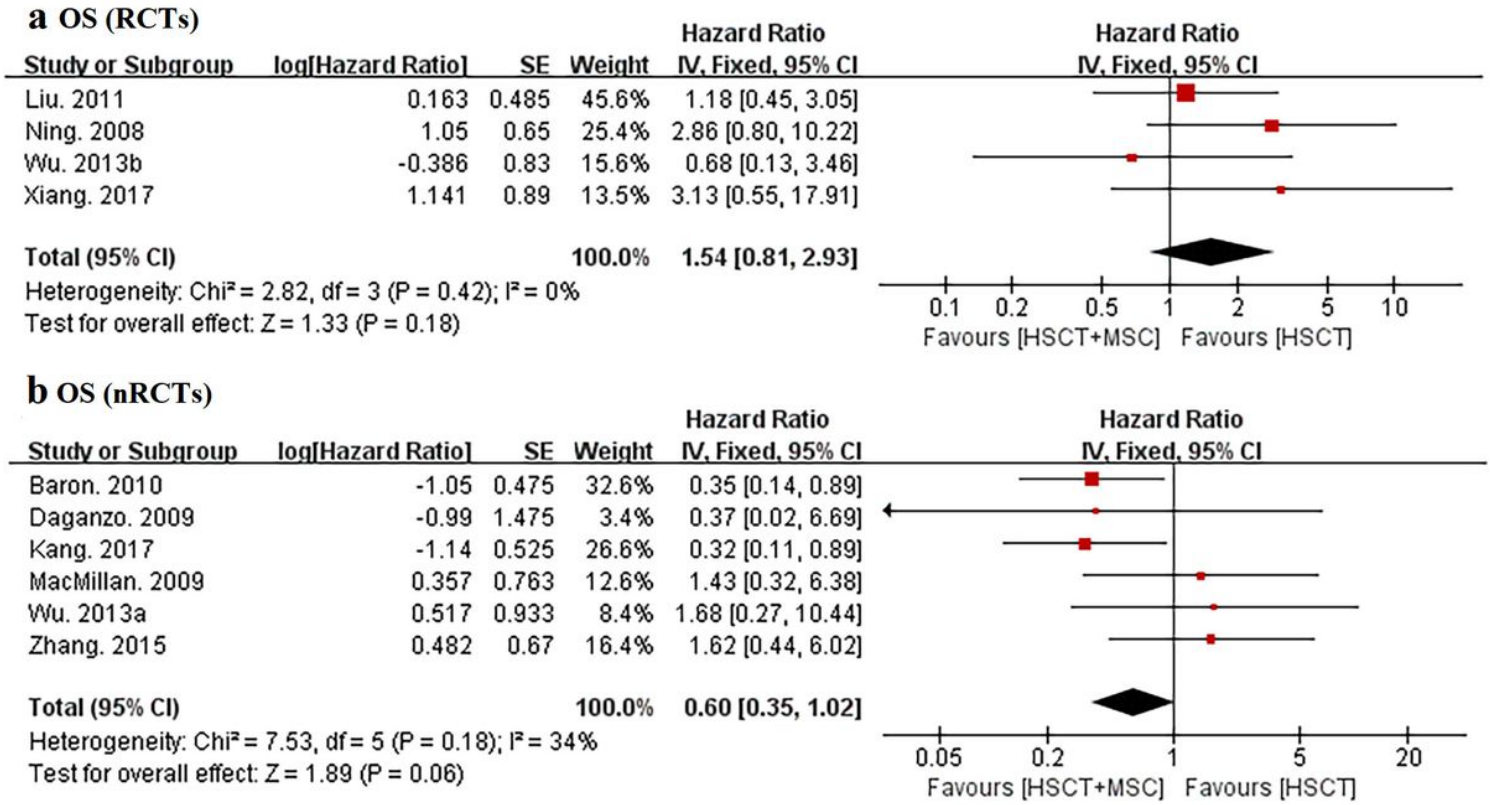

Figure 6

Meta-analysis of comparison for OS between HSCT+MSC group and HSCT alone group. Analysis was performed for (a) RCTs and (b) nRCTs separately.

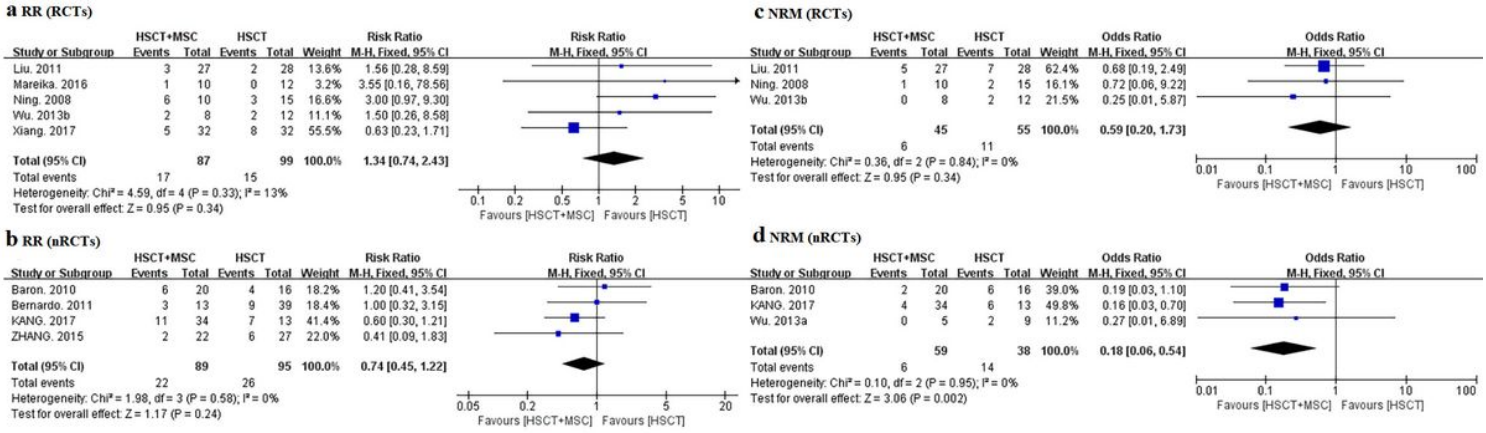

Figure 7

Meta-analysis of comparison for RR and NRM between HSCT+MSC group and HSCT alone group. Analysis was performed for RCTs and nRCTs separately.

Supplementary Files

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- Additionalfile15Fig.S10..tif
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