

Mesenchymal Stromal Cells as Prophylaxis for Graft-versus-host Disease in Haplo-identical Hematopoietic Stem Cell Transplantation Recipients With Severe Aplastic Anemia? - A Systematic Review and Meta-analysis

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Research

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Abstract

Background: Mesenchymal stromal cells (MSCs) are an emerging prophylaxis option for graft-versus-host disease (GVHD) in haplo-identical hematopoietic stem cell transplantation (haplo-HSCT) recipients with severe aplastic anemia (SAA), but studies have reported inconsistent results. This systematic review and meta-analysis evaluates the efficacy of MSCs as prophylaxis for GVHD in SAA patients with haplo-HSCT.

Methods: Studies were retrieved from PubMed, EMBASE, Cochrane, Web of Science and <http://clinicaltrials.gov> from establishment to February 2020. Twenty-nine single-arm studies (n = 1456) were included, eight (n = 241) studies combined with MSCs and eleven (n = 1215) reports without MSCs in haplo-HSCT for SAA patients. The primary outcomes were the incidences of GVHD. Other outcomes included 2-year overall survival (OS) and the prevalence of cytomegalovirus viremia (CMV). Odds ratios (ORs) were calculated to compare the results pooled through random or fixed effects models.

Results: Between MSCs and no MSCs groups, no significant differences were found in the pooled incidences of acute GVHD (56.0%, 95%CI: 48.6%-63.5% vs. 47.2%, 95%CI: 29.0%-65.4%; OR 1.43, 95%CI: 0.91-2.25; p = 0.123), grade II-IV acute GVHD (29.8%, 95%CI: 24.1%-35.5% vs. 30.6%, 95%CI: 26.6%-34.6%; OR 0.97, 95%CI: 0.70-1.32; p = 0.889), chronic GVHD (25.4%, 95%CI: 19.8%-31.0% vs. 30.0%, 95%CI: 23.3%-36.6%; OR 0.79, 95%CI 0.56-1.11; p = 0.187). Further, there was no obvious differences in 2-year OS (OR 0.98, 95%CI 0.60-1.61; p = 1.000) and prevalence of CMV (OR 0.61, 95%CI 0.40-1.92; p = 0.018).

Conclusions: Our meta-analysis indicates that the prophylactic use of MSCs co-transplantation is not an effective option for SAA patients undergoing haplo-HSCT. Hence, the general co-transplantation of MSCs for SAA haplo-HSCT recipients may lack of evidence-based practice.

Introduction

Severe aplastic anemia (SAA) is a life-threatening bone marrow failure syndrome characterized by pancytopenia and hypoplastic bone marrow. Hematopoietic stem cell transplantation (HSCT) was considered as a first-line therapy for young adults¹. However, only 20–30% acquired SAA patients realistically hope to find a human leukocyte antigen (HLA)-matched sibling donor. With the improvement of conditioning regimens, like “Beijing protocol”, haplo-identical HSCT (haplo-HSCT) has recently been widely used to treat SAA patients as an alternative strategy². However, the main challenges facing current haplo-HSCT usage included the risk of graft-versus-host disease (GVHD) and a higher graft failure (GF) rate^{3–5}. Therefore, improving the haplo-HSCT outcomes in SAA patients is of great concern.

Mesenchymal stem cells (MSCs) are multipotent stem cells characterized by modulating immune and inflammation response, supporting hematopoiesis and repairing tissues, which are widely used in haplo-HSCT^{6,7}. MSCs can be isolated from many tissues, including bone marrow (BM), cord blood and umbilical cord (UC) tissues, periosteum, adipose tissue, and fetal liver^{8,9}. According to several previous clinical studies, the application of MSCs in haplo-HSCT can decrease the incidence and severity of acute or chronic GVHD, promote facilitation of HSC engraftment and improve OS^{10–15}. However, others also found that MSCs may make little or no difference in reducing the risk of GVHD and death^{16–18}. Thus, these conflicting results need to be addressed urgently¹⁹.

To the best of our knowledge, there have been some excellent clinical studies about proposing haplo-HSCT as the first-line therapy for SAA patients^{20–22}. Therefore, it's of great importance to clarify key factors related to the outcomes of SAA with haplo-HSCT. For example, some meta-analyses compared different donor sources in haplo-HSCT, evaluating whether PB or BM as graft source produces a more satisfactory outcome in SAA patients²³, others sought the optimal conditioning regimen for haplo-HSCT in patients with SAA^{24–26}. In addition, several meta-analyses have approved the efficacy of MSCs in haplo-HSCT recipients with haematological conditions, mostly in haematologic malignancies^{27,28}. Nevertheless, no meta-analysis has been done to evaluate the efficacy of MSCs combined with haplo-HSCT in SAA patients so far. Therefore, we performed the first systematic review and meta-analysis to investigate the efficacy of MSCs co-transplantation following HSCT in patients with SAA.

Methods

Literature Search

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines issued in 2009²⁹. We performed a systematic literature search in PubMed, EMBASE, OVID, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to January 2020 with the search terms “haplo-identical hematopoietic stem cell transplantation”, “mesenchymal stem cells” and “severe aplastic anemia”. In addition, we searched clinical trials in <http://clinicaltrials.gov> with “severe aplastic anemia [condition/disease] AND (haplo-identical hematopoietic stem cell transplantation [other terms])”.

Study Selection

Articles in the literature were identified and data were extracted by two investigators, independently. Disagreements were resolved through discussion. The reference lists of relevant studies were also hand-searched. These searches were limited to the ‘first generation’ reference lists. We removed duplicates and reviewed titles or abstracts. Studies were included that met the following criteria: (1) phase 2 or 3 clinical trials or retrospective studies evaluating efficacy of MSCs co-transplantation following HSCT in patients with severe aplastic anemia; (2) cases with > 5 patients; (3) studies with a consistent criteria of observation items; (4) the study reported a quantitative outcome of interest. Exclusion criteria were the following: (1) review papers or expert opinions; (2) individual case reports; (3) the study did not report a quantitative outcome of interest. (4) the studies were reported in a language other than English. Meta-analyses do not involve human subjects and do not require Institutional Review Board review.

Data Extraction

Data extraction from the eligible studies was carried out independently by 2 authors. We used a standardized extraction form to extract information about the first author; year of publication; study design; number of patients; median Age; median intervals from diagnosis to treatment; the prophylaxis of GVHD; the conditioning regimen; acute GVHD (aGVHD); grade II-IV aGVHD; chronic GVHD (cGVHD); engraftment rate; all-cause mortality rate and cytomegalovirus(CMV) viremia. Because there are differences in study design, we extracted information in accord with the following criteria: (1) if data were used in two or more studies, data from the latter study were extracted on the basis of subtracting data published in the formal study; (2) we also summarized haematologic reconstitution time without performing a meta-analysis.

Quality Assessment

Two authors worked independently on quality assessment. If disagreements occurred, an adjudicator was consulted. Single-arm studies were assessed using the Newcastle-Ottawa Scale modified for cohort studies without controls, as previously used by Lopez-Olivoa³⁰. Potential scores ranged from 0 to 6, with higher scores indicating higher quality. The following components were assessed: selection, which includes the representativeness of the exposed cohort; ascertainment of exposure; demonstration that the outcome of interest was not present at the start of the study; and outcome, which consists of an assessment of outcome, followed-up long enough for outcomes to occur, and adequacy of the follow-up of cohorts. Because it was a meta-analysis of single proportions, publication bias was not advisable in this study.

Statistical Analysis

Data manipulation and statistical analyses were performed using Stata statistical software version 15.0 (StataCorp, College Station, TX, USA) and R software (version 3.6.3). We conducted separate analyses for single-arm retrospective researches studying the treatment outcomes of haplo-HSCT with MSCs or without MSCs. Heterogeneity between studies was evaluated via I-squared statistic and p value. When heterogeneity was significant ($p < 0.05$ or I-squared $> 50\%$), a random-effects model was adopted to pool the results. Then, χ^2 tests were applied to find if there are statistical differences of pooled estimates between groups, the effect measure was the adjusted odds ratio (OR) with 95% confidence intervals (CIs) and $p < 0.05$ was defined as statistically significant. The results of the meta-analysis were graphically displayed by forest plots and heterogeneity was further explored by subgroup analysis and sensitivity analysis. Notably, the event rates can be zero or one from some studies yet they still need to be included in the analysis to represent the whole population. In such cases, the resulting distribution of proportions tends to be 0 inflated. We made good use of the Freeman-Tukey double arcsine transformation to perform normalization and variance, which can be achieved by using the metaprop module to perform fixed and random effects meta-analysis of proportions.

Results

Search results

We initially identified 478 potentially eligible papers from the electronic databases. After excluding 53 duplicates, records ($n = 425$) were screened by reviewing titles and abstracts and excluded according to the exclusion criteria. Finally, the remaining 61 studies were further filtrated by reading full text. As a result, 32 records were excluded, and 29 studies met the inclusion criteria. The included studies were divided into two groups (MSCs³¹⁻³⁸; no MSCs^{22, 25, 39-57}) based on whether they applied the MSCs or not. The selection process is illustrated in Fig. 1. Screening and evaluation were conducted independently by two reviewers with resolution of disagreement by consensus or adjudication by a third reviewer.

Quality assessment

The results of risk of bias for each study are shown in Table 1-2. All studies had a score ≥ 5 , which indicates a relatively high research quality. The subjects included were representative, and ascertainment of exposure was confirmed by secure record. Outcome assessment was based on medical records, and the follow-up period was sufficient for outcomes to occur.

Table 1
Characteristics of included studies in the meta-analysis (MSCs group)

Author (Publication year)	Study Design	Recruitment period	Number of patients	Median Age	Sex(M/F)	Type	Conditioning regimen	GVHD prophylaxis	Inte dia trea
Wang Z- K ³¹ (2019)	Single- arm study	2014/01 -2016/12	35	11.5 (3-18)	18/17	SAA/VSAA(19/16)	busulfan(Bu) + cyclophosphamide (Cy) + antithymocyte globulin (ATG)	CsA + MMF + MTX	NA
Yue C ³² (2018)	cases	2014/01 -2017/01	6	23(15- 31)	3/3	VSAA(6)	busulfan(Bu) + cyclophosphamide (Cy) + antithymocyte globulin (rATG)	CsA + MMF + MTX	2(1-
Liu Z ³³ (2017)	Single- arm study	2013/03 -2015/08	44	24 (8- 47)	29/15	SAA/VSAA(31/13)	busulfan(Bu) + cyclophosphamide (Cy) + antithymocyte globulin (ATG)	CsA + MMF + MTX	31(.
Xu L ³⁴ (2018)	Single- arm study	2010/06 -2013/08	24	16.5(5- 55)	14/10	SAA(24)	cyclophosphamide (Cy) + antithymocyte globulin (rATG) + Flu or	CsA + ATG + CD25Ab+ mycophenolate material.	NA
Wu Y ³⁵ (2017)	Single- arm study	2011/01 -2016/06	77	9(1- 46)	39/38	SAAVSAA/SAA& PNH(72/5)	cyclophosphamide (Cy) + antithymocyte globulin (ATG) + Flu ± busulfan	CsA + MMF + MTX + CD25Ab	7(2-
Li XH ³⁶ (2014)	Single- arm study	2006/10 -2012/10	17	19 (4- 29)	10/7	SAA/VSAA(8/9)	cyclophosphamide (Cy) + antithymocyte globulin (ATG) + Flu	CsA + MMF + CD25Ab	3(1-
Wu Y ³⁷ (2014)	Single- arm study	2007/01 -2013/06	21	18(4- 31)	11/10	SAA/VSAA/SAA&PNH(7/12/2)	cyclophosphamide (Cy) + antithymocyte globulin (rATG) + Flu or	CsA + MMF + CD25Ab + rATG	6(1-
Wang Z ³⁸ (2014)	Single- arm study	2010/03 -2013/04	17	10(4- 19)	6/11	SAA/VSAA/2 HSCT(11/5/1)	BU + fludarabine + CY + ATG	CsA + MMF + MTX + CD25Ab	12 (

Abbreviations: SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; ATG, antithymoglobulin; CsA, cyclosporin A; MSCs, mesenchymal stem cells; transplantation; BU, Busulfan; Cy, cyclophosphamide; MMF, Mycophenolate mofetil; FLU, fludarabine; MTX, methotrexate; GVHD, graft-versus-host disease

Table 2
Characteristics of included studies in the meta-analysis (no MSCs group)

Author (Publication year)	Study Design	Recruitment period	Number of patients	Median Age	Sex(M/F)	Type	Conditioning regimen	GVHD prophylaxis	Interval from diagnosis to treatment(M)
Zhang YY ⁵⁷ (2020)	Single- arm study	2013/01 -2018/09	35	43 (40- 54)	23/11	SAA/VSAA(19/16)	BU + CY + ATG	CsA + MMF + MTX	NA
Ma YR ⁵⁶ (2020)	Single- arm study	NA	199	NA	106/93	NA	BU + CY + ATG	CsA + MMF + MTX	NA
Liu LM ⁵⁵ (2020)	Single- arm study	2010/09 -2018/09	16	32 (8- 55)	9/7	NA	ATG + rituximab	NA	NA
Yang SW ²² (2019)	Single- arm study	NA	32	NA	21/11	NA	NA	NA	NA
Xu LP ⁵⁴ (2019)	Single- arm study	2006-2018	392	NA	223/167	NA	BU + CY + ATG	CsA + MMF + MTX	NA
Hyery Kim ⁵³ (2019)	Single- arm study	2008-2017	32	12.7 (1.4- 21.7)	22/10	SAA/VSAA(20/12)	FLU, CY, ATG ± TBI	CsA + MMF	5.2 (1.2- 106.8)
Lu Y ⁵² (2018)	Single- arm study	2012/09 -2016/09	41	13 (4- 42)	25/16	SAA/VSAA(28/13)	FLU, CY, ATG	CsA + MMF + MTX	25 (6-45)
Sung-Eun Lee ⁵¹ (2018)	Single- arm study	2012/06 -2016/12	34	31.5(17- 59)	20/14	SAA/VSAA(11/23)	ATG + TBI + Flu	CsA + MTX	NA
Cheng YF ⁵⁰ (2018)	Single- arm study	2007/12 -2016/09	28	NA	NA	NA	NA	NA	2.75(1-8)
Cao LQ ⁴⁹ (2018)	Single- arm study	2006/01 -2016/12	131	16 (2- 45)	70/61	NA	NA	NA	NA
Zhang P ⁴⁸ (2017)	Single- arm study	2014/06 -2015/12	8	14(5- 26)	5/3	NA	FLU, CY, ALG/TBI	CsA + MMF + MTX	NA
Zhang Y ⁴⁷ (2017)	Single- arm study	2010/06 -2014/12	18	NA	NA	NA	NA	NA	NA
Pei XY ⁴⁶ (2017)	Single- arm study	2008/01 -2015/12	81	14 (3- 45)	50/31	SAA/VSAA(63/18)	NA	NA	NA
Sarita Rani Jaiswal ⁴⁵ (2017)	Single- arm study	2015/01 -2016/05	20	NA	NA	NA	FLU, CY, ATG,Melphalan	PTCy + sirolimus + CsA + MMF(Abatacept)	NA
Amy E. DeZern ⁴⁴ (2017)	Single- arm study	2011/07 -2016/08	13	33(11- 69)	9/5	NA	FLU, CY, ATG ± TBI	PTCy + MMF + FK506	NA
Zhu H ⁴³ (2016)	Single- arm study	2002/07 -2013/11	38	NA	12/24	SAA/VSAA(8/28)	FLU, CY, ATG ± TBI/BU	CsA + methotrexate (MTX) (n = 12) CsA + MTX + Mycophenolate mofetil (MMF) (n = 22)MTX + Tacrolimus (n = 4)	NA
Liu L ⁴² (2016)	Single- arm study	2005/07 -2013/12	26	26 (10- 54)	15/11	SAA/VSAA/(16/6)	NA	NA	NA

Abbreviations: SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; ATG, antithymoglobulin; CsA, cyclosporin A; MSCs, bone marrow-mesenchymal hematopoietic stem cell transplantation; BU, Busulfan; Cy, cyclophosphamide; MMF, Mycophenolate mofetil; FLU, fludarabine; MTX, methotrexate; GVHD, graft

Author (Publication year)	Study Design	Recruitment period	Number of patients	Median Age	Sex(M/F)	Type	Conditioning regimen	GVHD prophylaxis	Interval from diagnosis to treatment(M)
Ho Joon Im ⁴¹ (2015)	Single-arm study	NA	21	14 (3–21)	NA	NA	FLU, CY, ATG ± TBI	NA	NA
Esteves I ²⁵ (2015)	Single-arm study	2010/07–2014/08	16	17(5–39)	11/5	NA	CY + FLU+ TBI ,Flu + ATG(2)	MMF, CsA, Cy	NA
Gao L ⁴⁰ (2014)	Single-arm study	2007/06–2010/12	26	25.4(18–41)	NA	SAA/VSA(16/10)	FLU, CY, ATG	CsA + MMF + MTX + ATG	NA
Jennifer Clay ³⁹ (2014)	Single-arm study	NA	8	NA	NA	NA	CY + FLU+ TBI	MMF + FLU+ PTCY	NA

Abbreviations: SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; ATG, antithymoglobulin; CsA, cyclosporin A; MSCs, bone marrow-mesenchymal hematopoietic stem cell transplantation; BU, Busulfan; Cy, cyclophosphamide; MMF, Mycophenolate mofetil; FLU, fludarabine; MTX, methotrexate; GVHD, graft

Incidence of GVHD

The pooled results of aGVHD, grade II–IV aGVHD and cGVHD in MSCs group and no MSCs group are summarized in Table 3. Our meta-analysis revealed no significant heterogeneity in aGVHD (I-squared = 8.3%, $p = 0.365$), grade II–IV aGVHD (I-squared = 0.0%, $p = 0.841$) and cGVHD (I-squared = 18.1%, $p = 0.287$) in MSCs group, so fixed models were applied. By pooling studies with no significant heterogeneity, we learned that the overall incidences of aGVHD (Fig. 2a), grade II-IV aGVHD (Fig. 2c) and cGVHD (Fig. 2e) were 56.0% (95% CI, 48.6–63.5%), 29.8% (95% CI 24.1–35.5%) and 25.4% (95% CI, 19.8–31.0%) in MSCs group respectively. While random models were applied in no MSCs group with heterogeneity in aGVHD (I-squared = 88.6%, $p = 0.000$), grade II–IV aGVHD (I-squared = 43.1%, $p = 0.022$) and cGVHD (I-squared = 81.2%, $p < 0.001$). The overall incidences of aGVHD (Fig. 2b), grade II-IV aGVHD (Fig. 2d) and cGVHD (Fig. 2f) were 47.2% (95% CI, 29.0–65.4%), 30.6% (95% CI, 26.6–34.6%) and 30.0% (95% CI, 23.3–36.6%) respectively. Results showed that there was insufficient evidence to detect a difference in the risk of aGVHD in the comparison of MSCs and no MSCs (OR 1.43, 95% CI 0.91 to 2.25; $p = 0.123$), the same situation was detected in grade II–IV aGVHD (OR 0.97, 95% CI 0.70 to 1.32; $p = 0.889$) and cGVHD (OR 0.79, 95% CI 0.56 to 1.11; $p = 0.187$) (Table 3). Subgroup analysis demonstrated that no significant heterogeneity in subgroup between the use of UC-MSCs and BM-MSCs in MSCs group (Fig. 2c, 2e).

Table 3
Pooled estimates in MSCs group and no MSCs group

Pooled estimates	Pooling model	Number of studies	haplo-HSCT	haplo-HSCT	OR(95% CI)	p Value
			haplo-HSCT + MSCs/haplo-HSCT alone	+MSCs (95% CI)		
aGVHD	Fixed/Random	7/9	56.0% (48.6%, 63.5%)	47.2% (29.0%, 65.4%)	1.43(0.91–2.25)	0.123
Grade II–IV aGVHD	Fixed/Random	8/20	29.8% (24.1%, 35.5%)	30.6% (26.6%,34.6%)	0.97(0.70–1.32)	0.889
cGVHD	Fixed/Random	8/18	25.4% (19.8%, 31.0%)	30.0% (23.3%,36.6%)	0.79(0.56–1.11)	0.187
2-year OS	Fixed/Fixed	8/12	84.9% (80.4%, 89.3%)	85.2% (81.6%,88.8%)	0.98(0.60–1.61)	1.000
Engraftment rate	Fixed/Fixed	8/17	98.9% (96.4%, 100.0%)	98.6% (96.5%,99.8%)	1.02(0.66–1.54)	1.000
Cytomegalovirus	Random/Random	5/10	52.4% (31.6%–73.1%)	64.1% (52.9%–75.2%)	0.61(0.40–1.92)	0.018

Abbreviations: GVHD, graft-versus-host disease; aGVHD, acute GVHD; cGVHD, chronic GVHD; MSCs, mesenchymal stromal cells; haplo-HSCT, haploidentical hematopoietic stem cell transplantation; OR, odds ratio; OS, overall survival; CI, confidence interval

Overall survival

2-year OS were reported in 8 studies in MSCs group and 12 studies in no MSCs group respectively without significant heterogeneity in both groups (MSCs: I-squared = 24.0%, $p = 0.238$; no MSCs: I-squared = 20.4%, $p = 0.243$) (Fig. 3a, 3b), so fixed models were applied. The pooled results of 2-year OS were 84.9%

(95% CI, 80.4–89.3%) and 85.2%(95% CI, 81.6–88.8%) respectively (Fig. 3). There was no significant difference in 2-year OS in the comparison of MSCs and no MSCs (OR 0.98, 95% CI 0.60 to 1.61; $p = 1.000$) (Table 3).

Engraftment rate and CMV viremia

Our meta-analysis revealed no significant heterogeneity in engraftment rate (MSCs: I-squared = 0%, $p = 0$; no MSCs: I-squared = 46.8%, $p = 0.018$). Four of eight studies achieved 100% hematopoietic reconstitution and full donor chimerism after haplo-HSCT with the administration of MSCs. The pooled results of engraftment rate were 98.9% (95% CI, 96.4–100.0%) and 98.6% (95% CI, 96.5–99.8%) respectively (Fig. 4). No significant difference was detected which compared MSCs to no MSCs (OR 1.02, 95% CI 0.66 to 1.54; $p = 1.000$). Random models were applied to pool the incidences of CMV viremia because of significant heterogeneity detected in both groups, the pooled results were 52.4% (95% CI, 31.6–73.1%) and 64.1% (95%CI, 52.9–75.2%) respectively (Fig. 5). Likewise, no significant difference was observed (OR 0.61, 95% CI 0.40 to 1.92; $p = 0.018$) (Table 3).

Discussion

This up-to-date meta-analysis comprehensively examined the published literature to evaluate the efficacy of co-transplantation of MSCs and haplo-HSCT in patients with SAA. To the best of our knowledge, this is the first meta-analysis to compare the clinical outcomes of MSCs with no MSCs in haplo-HSCT in patients with SAA. The results of our study are partially consistent with previous a meta-analysis examining the effects of MSCs post-transplantation of haplo-HSCT in haematological malignancies¹⁵.

Our study demonstrated no significant difference with regard to the pooled incidences of GVHD between MSCs and no MSCs group. It's well known that GVHD remains the common and life-threatening complication limiting the widespread use of haplo-HSCT, as it associates with a high mortality and morbidity⁵⁸. Since there were no controlled studies, we compared the incidence of aGVHD, grade II-IV aGVHD and cGVHD in MSCs group and no MSCs group. Although the incidence of aGVHD was higher than no MSCs group, the incidences of grade II-IV aGVHD and cGVHD were lower than the pooled results in no MSCs group. But no significant differences were found between these two groups pooled results. Which is different from previous studies supported a role of MSCs in reducing the incidence of GVHD. Despite these previous studies showing that MSCs are effective in GVHD prophylaxis or treatment, most of them were conducted in vitro or in haematological malignancies. Moreover, the conclusions were drawn in HSCT area without highlighting on haplo-HSCT^{59–61}. Hence, MSCs may make little or no difference to the risk of GVHD compared to no MSCs in haplo-HSCT for SAA patients.

Among MSCs group, four of eight studies achieved 100% hematopoietic reconstitution and full donor chimerism after the application of MSCs in haplo-HSCT, which is higher than no MSCs group (4/17). Although MSCs were higher than no MSCs group with regard to the pooled results of 2-year OS and engraftment rates in our report, no statistically significant differences were found. Furthermore, it's reported that infections are the other major causes of death after haplo-HSCT in addition to GVHD⁶². We calculated the rates of death due to infection. The pooled result was 9.5% (95% CI, 5.8–13.1%) in the included studies in MSCs group, which was much lower than those reported by Center for International Blood and Marrow Transplant Research (CIBMTR), for all haplo-HSCT transplants conducted between 2009 and 2010 (infection: 13–18%)⁶³. CMV infections are opportunistic infections caused by low immune function. A reduction in CMV infection after allo-HSCT can be achieved by hastening post-transplant immune reconstitution. Therefore, co-transplantation of MSCs and haplo-HSCT seemed like making no contribution to immune reconstitution in SAA patients.

It's reported that MSCs produce growth factors to aid tissue regeneration and accelerate the haematologic reconstitution⁶⁴. The median post-HSCT times to neutrophil greater than $0.5 \times 10^9 /L$ and platelet greater than $20 \times 10^9 /L$ were summarized and listed in Table 1–2. The shortest and longest median time to achieve neutrophil engraftment and platelet engraftment were (11–14 days) and (13–21 days) respectively in MSCs group; (10–19 days) and (13–28 days) respectively in no MSCs group. Remarkably, all studies in MSCs group reported results descriptively and stated that they observed either rapid engraftment³⁷ or a similar speed of engraftment after adding MSCs^{31,32}, which may demonstrate a role for MSCs in the enhancement of engraftment in SAA patients who underwent haplo-HSCT.

According to the published papers, the treatment efficacy of MSCs varies among clinical trials, and MSCs source might influence this⁶⁵. The studies included in this meta-analysis used only BM-MSCs or UC-MSCs. Therefore, we conducted a subgroup meta-analysis for GVHD prevention according to MSC source. Consequently, the incidence of GVHD shows no significant difference with regard to the use of UC-MSCs versus BM-MSCs. Besides, we conducted “influence analysis” in Stata to explore the source of heterogeneity in no MSCs group. We could reasonably infer that studies (Jennifer *et al*⁶⁹ and Gao *et al*⁴⁰) were one of the most important sources resulting in the heterogeneity of aGVHD and cGVHD respectively. Both of them were conducted in earlier years with different conditioning regimes and prophylaxis measures.

There are some limitations in our meta-analysis. First, there may be a risk of confounding biases because various baseline characteristics or co-interventions including age, gender, donor type, conditioning regimen and MSCs originals may affect the treatment outcomes in SAA patients after haplo-HSCT, they were not fully controlled in this study. In addition, patients in no MSCs group usually had high heterogeneity. Although we tried to decrease the bias through statistical methods, sometimes errors were unavoidable. Second, because SAA is a rare disorder, few prospective control trails between the MSCs and no MSCs group are available so far, and all the included studies had small sample sizes. Besides, all were single-arm studies and case series that lacked a control group and likely suffered from a high risk of selection bias. Last but not least, we could not assess publication bias using funnel plots because we only had single-arm studies and case series.

In conclusion, our meta-analysis indicates that the prophylactic use of MSCs co-transplantation does not reduce the incidence of GVHD and improve 2-year OS in patients with SAA undergoing haplo-HSCT. Hence, the general co-transplantation of MSCs in routine clinical practice for SAA haplo-HSCT recipients is

not recommended. However, since there is no direct evidence from comparative study to support this conclusion, more prospective, randomized controlled trials (RCTs) are needed to confirm whether MSCs convey a definite benefit for haplo-HSCT for SAA patients.

Declarations

Acknowledgements

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Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All supporting data are included in the article and Additional file

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Authorship contributions

R.L., J.T., and J. S. conceived the study. R.L. collected and analyzed the data, and wrote the paper. J.Z., H.P., and L.F., contributed to the data collection and analysis. J.S. designed the research and give an approval of the final manuscript

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Figures

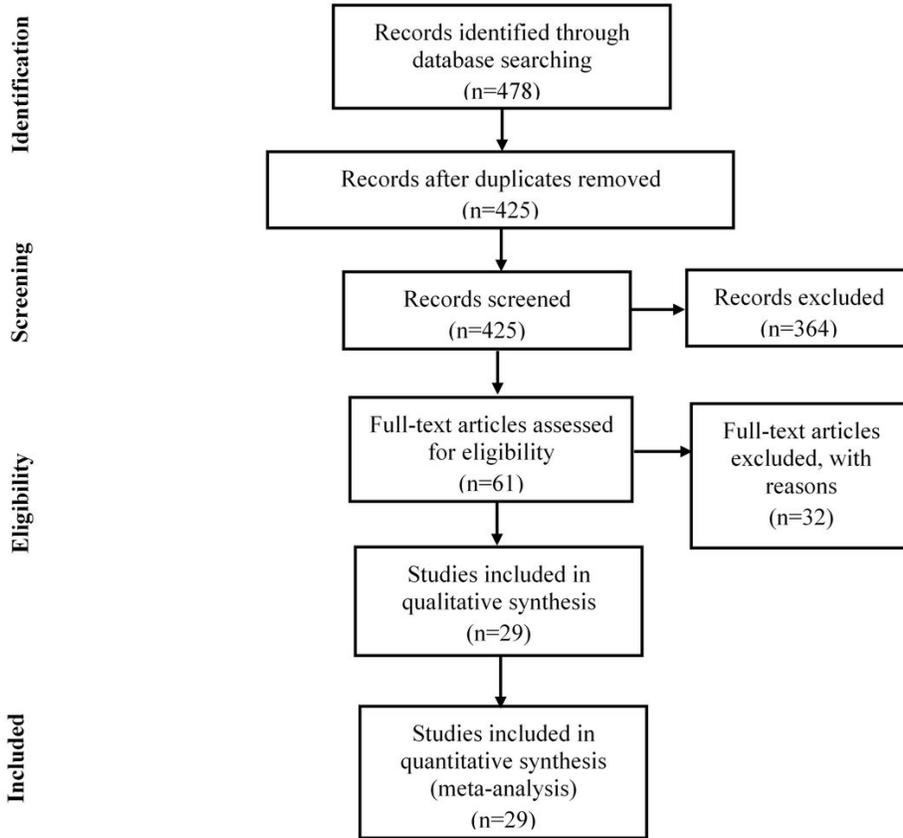


Figure 1

PRISMA flow diagram of the systematic literature search process



Figure 2

Forest plots for the pooled incidence of acute GVHD (a: MSCs group; b: No MSCs group); grade II-IV acute GVHD (c: MSCs group; d: No MSCs group); chronic GVHD (e: MSCs group; f: No MSCs group)

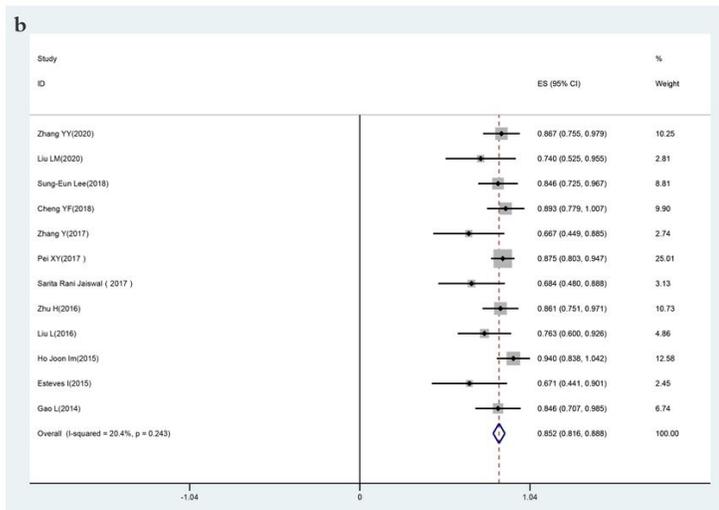
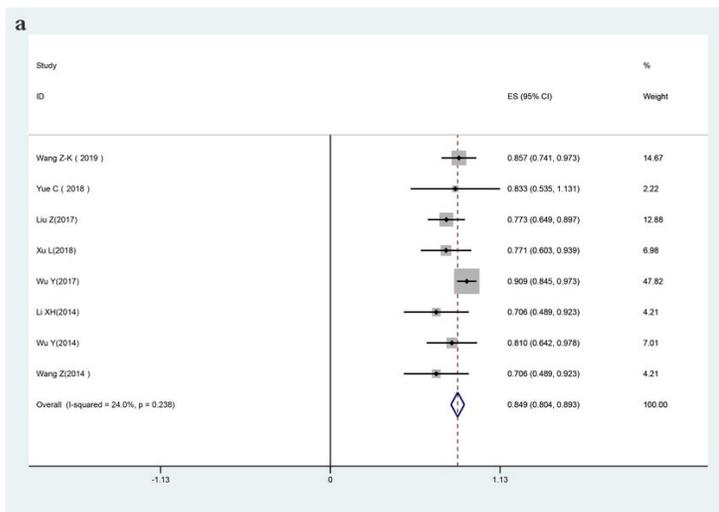


Figure 3

Forest plots for the pooled 2-year overall survival (a: MSCs group; b: No MSCs group)

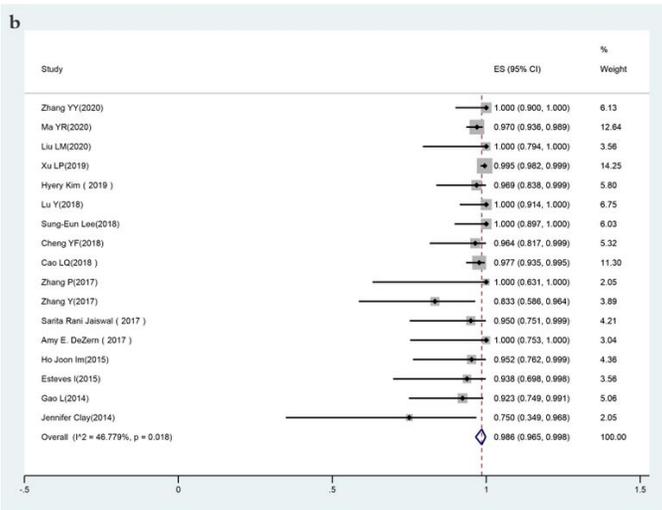
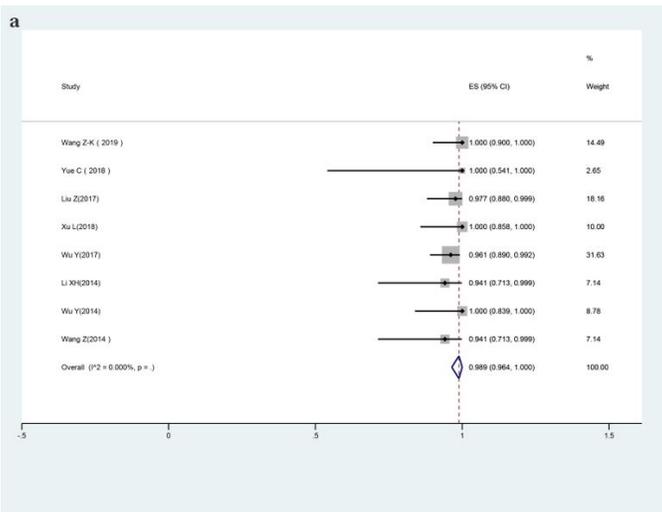


Figure 4

Forest plots for the pooled engraftment rate (a: MSCs group; b: No MSCs group)

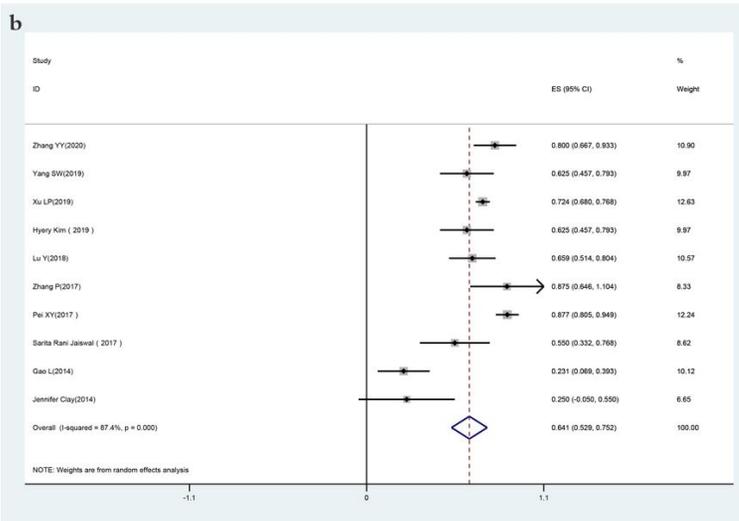
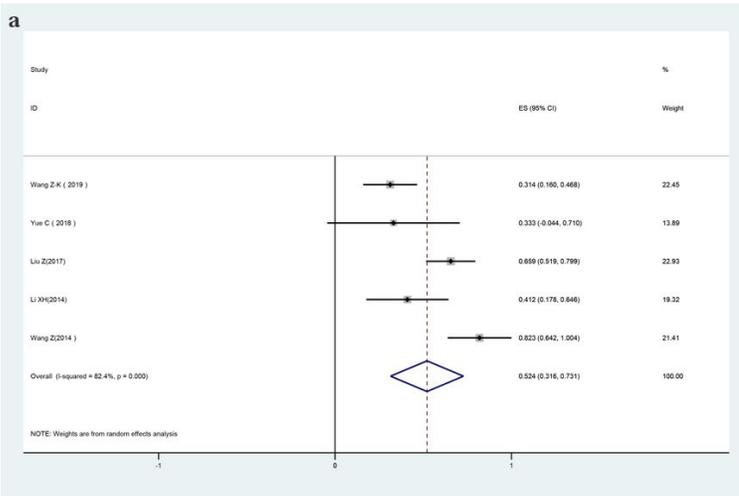


Figure 5

Forest plots for the pooled incidences of CMV viremia (a: MSCs group; b: No MSCs group)