

# Efficacy and safety of stem cells transplantation in patients with type 1 diabetes mellitus—a systematic review and meta-analysis

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**Abstract.** Stem cells (SCs) therapy is a new promising therapeutic modality for type 1 diabetes (T1DM). We performed a systematic review and meta-analysis to evaluate the efficacy and safety of stem cells transplantation (SCT) in patients with T1DM. We searched five literature databases (MEDLINE, EMBASE, Web of Science, WanFang and CENTRAL) up to 31 October 2019. 29 studies (487 patients with T1DM) were included in our meta-analysis. There was no substantial publication bias. Meta-analysis showed the SCT had significant effect to decrease HbA1c (SMD, 1.40; 95% CI, 0.93 to 1.86;  $p < 0.00001$ ;  $I^2 = 89\%$ ) and to improve C-peptide levels (SMD,  $-0.62$ ; 95% CI,  $-1.22$  to  $-0.02$ ;  $p = 0.04$ ;  $I^2 = 92\%$ ) at 1 year follow-up. Subgroup analyses showed the heterogeneity level of the results was high. Significant improvement of metabolic outcomes was observed in the subgroups of mesenchymal stem cells (MSCs) combined with hematopoietic stem cells (HSCs) and HSCs. The older age showed significant association with the efficacy in HSCs subgroup. The higher GADA positive rate before treatment also significantly associated with the decrease of daily insulin requirement. The transient insulin independence rate at last follow-up was 9.6 per 100 person-years (95% CI: 5.8–13.5%). The mean length of insulin independence was 15.6 months (95% CI: 12.3–18.9). The mortality of SCT was 3.4% (95% CI: 2.1–5.5%). Therefore, SCT is an efficacious and safe method for treating patients with T1DM especially in the subgroups of MSCs + HSCs and HSCs. Well designed, double blind and randomized controlled trails with large sample size and long-term follow-up are needed for further evaluation.

**Key words:** Systematic review, Meta-analysis, Stem cells transplantation, Type 1 diabetes mellitus

**TYPE 1 DIABETES MELLITUS (T1DM)** is an autoimmune disease resulting from the destruction of islet  $\beta$  cells, leading to a deficiency of insulin secreting and hyperglycemia. In severe cases, it can also lead to multi-organ diabetes-related dysfunction, especially hypercoagulability, neuropathy, kidney disease, retinopathy, and sometimes organ failure. The annual increment of T1DM was about 3%, which has highlighted the serious concerns of health care professionals worldwide.

Individuals with T1DM need insulin replacement for life. In addition, current therapies such as the cell-based therapies and immune therapies are also being used clinically [1]. As a method of the cell-based therapies, islets

transplantation has been developed in the past decades for the replacement of damaged  $\beta$  cells [2]. However, the development of autoantibodies, immunosuppression toxicity, limited donor supply, and high costs limit this therapy to patients with T1DM.

Due to the intrinsic regenerative potential and immunomodulatory abilities, the stem cells (SCs) therapy has opened up a breakthrough approach to cure autoimmune disease. Meta-analyses of studies on SCs therapy indicated a certain potential to treat liver cirrhosis [3–5], chronic liver disease [6], inflammatory bowel disease [7] and ischemic heart disease [8]. SCs therapy also showed a potential effect to halt or abolish the autoimmune destruction of  $\beta$  cells and to generate functional  $\beta$  cells which could achieve optimized glycemic control in T1DM [9–13]. Our systematic review and meta-analysis aims to explore the efficacy and safety of stem cells transplantation (SCT) in patients with T1DM.

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## Materials and Methods

### *Literature and search strategy*

Databases MEDLINE, EMBASE, Web of Science, WanFang and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1977 to 31 October 2019. We used the Medical Subject Headings (MeSH) and key words to construct our search strategy. The search strategy was #1: Mesenchymal Stem Cell Transplantation; #2: Hematopoietic Stem Cell Transplantation; #3: Bone Marrow Stem Cell Transplantation; #4: Peripheral Blood Stem Cell Transplantation; #5: Multipotent Stem Cells; #6: Cord Blood Infusion; #7: Umbilical Cord Mesenchymal Stromal Cell; #8: type 1 diabetes; #9: T1D; #10: Insulin dependent diabetes mellitus; #11: IDDM; #12: ((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9 OR #10 OR #11)). We imported the literature results into Endnote X7 and deleted duplicated studies. We also browsed the references of included studies and relevant systematic reviews.

### *Inclusion and exclusion criteria*

Studies were identified carefully by two investigators working independently to determine whether an individual study was eligible for inclusion in the meta-analysis. When agreement could not be reached, a third researcher decided if the study was eligible, based on the same criteria of inclusion and exclusion. Inclusion criteria: individuals of any age, gender and population with T1DM according to the criteria of the American Diabetes Association before SCT. Exclusion criteria: Patients with malignancy, any acute or chronic infection, pregnancy, positive serology for human immunodeficiency virus, hepatitis B or C, underlying hematologic, nephrologic, cardiac, psychiatric, or hepatic disease, mental disorders, inborn or adaptive immunodeficiency and hypersensitivity. Case reported studies were excluded. Studies that did not report the detail data related to the efficacy or safety of SCT were also excluded.

### *Data extraction*

Data were independently extracted by two investigators who reached a consensus on all of the items. Information extracted from each study was considered as follows: first author, year of publication, descriptions of patients, mode of injection and the outcomes we interested in, such as the daily insulin requirement, glycosylated hemoglobin (HbA1c) and C-peptide level in treatment group before and after treatment as well as the adverse and mortality effect. We defined severe complications contains bilateral pneumonia and pseudomonas aeruginosa sepsis, which may cause damage to vital organs. Dealing with missing data: we contacted original authors

to clarify missing data or data which were not clearly reported.

### *Quality assessment of included studies*

Two reviewers assessed methodological quality independently according to the Newcastle-Ottawa Scale (NOS). Any discrepancies were resolved by discussion, if disagreements cannot be resolved, a third reviewer were consulted.

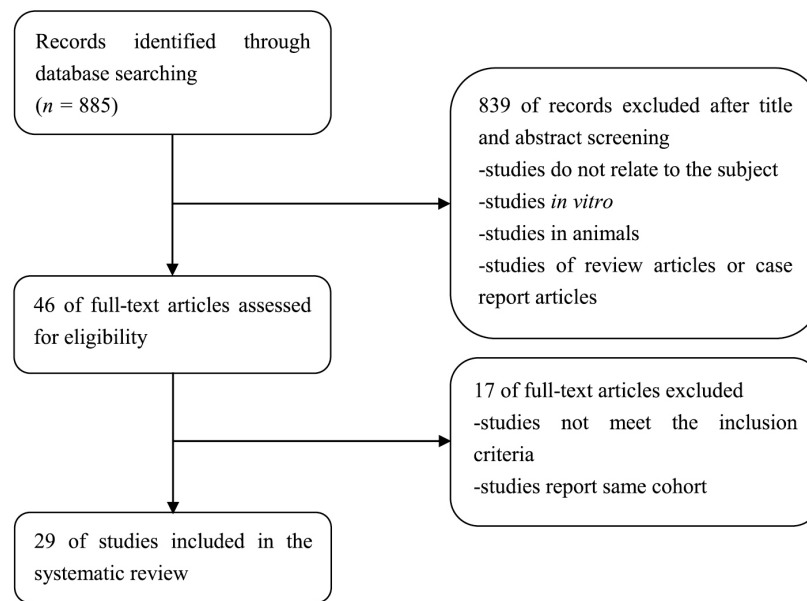
### *Statistical analysis*

Review Manager 5 and Comprehensive Meta Analysis software were used to perform the analyses. For studies reported quantitative data, a meta-analysis was undertaken when studies were sufficiently homogenous. If only two or three studies were to be identified, we performed a fixed-effects model meta-analysis. If more than three studies were to be identified, we performed random-effects analysis. Publication bias was assessed by the funnel plots. Statistical heterogeneity was assessed by the forest plots. Subgroups were classified based on various sources of SCs, including mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), MSCs combined with HSCs (MSCs + HSCs), umbilical cord blood (UCB) and bone marrow mononuclear cells (BM-MNCs). We investigated the heterogeneity using the  $I^2$  statistic which means the proportion of the unexplained heterogeneity by the estimates variability among studies.  $I^2$  values of <25%, 25–50% and >50% represent minimal, moderate and substantial heterogeneity, respectively [14]. If the heterogeneity was high, meta-regression analyses were performed to test the association between the factors and the outcomes. All summary effects were presented with 95% CI [15].

## Results

### *Characteristics of studies*

We retrieved 885 references from the electronic database, as showed on the flow diagram (Fig. 1). The 29 eligible studies met the inclusion and exclusion criteria [16–44]. Main study characteristics were described in Table 1. In general, the total number of patients who underwent SCT was 487. Among them, 5 studies (including 45 participants) underwent MSCs transplantation, 13 studies (including 275 participants) underwent HSCs transplantation, 3 studies (including 52 participants) underwent MSCs + HSCs transplantation, 6 studies (including 83 participants) underwent UCB transplantation, and 2 studies (including 32 participants) underwent BM-MNCs transplantation. The ages of T1DM patients receiving SCT ranged from 3.02 to 40.3 years. These patients had less than 2 months to 11 years of disease



**Fig. 1** Flow diagram of the references selection

duration before SCT. The follow-up periods ranged from 3 to 60 months. The overall quality of the included studies was optimal (Table 2). There was no substantial publication bias be observed (Fig. 2).

### Outcomes of MSCs for T1DM

#### Metabolic outcomes

Fig. 3 and Table 3 showed the meta-analysis of daily insulin requirement (U/kg per day), HbA1c (%) and C-peptide (ng/mL) in patients accepting SCT after 12 months follow-up. The overall analysis demonstrated that SCT had significant effect to decrease HbA1c (SMD, 1.40; 95% CI, 0.93 to 1.86;  $p < 0.00001$ ;  $I^2 = 89\%$ ) and to improve C-peptide levels (SMD,  $-0.62$ ; 95% CI,  $-1.22$  to  $-0.02$ ;  $p = 0.04$ ;  $I^2 = 92\%$ ). SCT showed no significant effect to reduce daily insulin requirement (SMD, 0.55; 95% CI,  $-0.01$  to 1.10;  $p = 0.05$ ;  $I^2 = 90\%$ ), but the  $p$  was on the critical value.

Due to the high heterogeneity, we performed subgroups analysis. The subgroups analysis demonstrated that SCT decreased the daily insulin requirement with statistically significance when compared with baseline after 1 year in the subgroups treated with MSCs + HSCs (SMD, 1.45; 95% CI, 1.01 to 1.89;  $p < 0.00001$ ;  $I^2 = 0\%$ ) and HSCs (SMD, 1.51; 95% CI, 1.02 to 2.00;  $p < 0.00001$ ;  $I^2 = 74\%$ ). There was no significant reduction on the daily insulin requirement in the subgroups of MSCs (SMD, 0.5; 95% CI,  $-0.18$  to 1.18;  $p = 0.15$ ;  $I^2 = 20\%$ ) and BM-MNC (SMD, 0.26; 95% CI,  $-0.25$  to 0.77;  $p = 0.32$ ;  $I^2 = 0\%$ ) when compared with baseline. On the contrary, daily insulin requirement was increased with statistically significance after treatment in UCB group

(SMD,  $-1.96$ ; 95% CI,  $-3.65$  to  $-0.27$ ;  $p = 0.02$ ;  $I^2 = 93\%$ ) (Fig. 3A).

The analysis indicated that SCT significantly decreased HbA1c levels at 1 year in the MSCs group (SMD, 1.08; 95% CI, 0.36 to 1.80;  $p = 0.003$ ;  $I^2 = 51\%$ ), the MSCs + HSCs group (SMD, 0.95; 95% CI, 0.38 to 1.52;  $p = 0.001$ ;  $I^2 = 43\%$ ), the HSC group (SMD, 2.42; 95% CI, 1.45 to 3.38;  $p < 0.00001$ ;  $I^2 = 94\%$ ) and the BM-MNC group (SMD, 1.24; 95% CI, 0.44 to 2.04;  $p = 0.002$ ;  $I^2 = 33\%$ ). While patients treated by UCB did not show significant decreasing on the HbA1c levels (SMD, 0.25; 95% CI,  $-0.06$  to 0.56;  $p = 0.12$ ;  $I^2 = 0\%$ ) (Fig. 3B).

When evaluating the effect of SCT on C-peptide levels, the MSCs + HSCs group (SMD,  $-1.28$ ; 95% CI,  $-1.71$  to  $-0.85$ ;  $p < 0.00001$ ;  $I^2 = 0\%$ ) and HSCs group (SMD,  $-1.64$ ; 95% CI,  $-2.72$  to  $-0.57$ ;  $p = 0.003$ ;  $I^2 = 95\%$ ) showed statistically significant effects. However, there were no statistically significant effects in MSCs, UCB and BM-MNCs groups (SMD,  $-0.20$ ; 95% CI,  $-1.17$  to 0.77;  $p = 0.69$ ;  $I^2 = 74\%$ ; SMD, 0.75; 95% CI,  $-0.54$  to 2.04;  $p = 0.25$ ;  $I^2 = 91\%$ ; SMD,  $-0.31$ ; 95% CI,  $-0.82$  to 0.19;  $p = 0.22$ ;  $I^2 = 0\%$  respectively) (Fig. 3C).

Because of the high heterogeneity still observed in HSCs group, we further used meta-regression analysis to investigate the factors which might affect the efficacy of HSCs transplantation. The results showed that the older age and the higher GADA positive rate before treatment were significantly associated with the decrease of daily insulin requirement ( $p = 0.00017$  and  $p = 0.00041$  respectively) (Fig. 4A and Fig. 4B). The older age was associated with the decrease of HbA1c and the improvement of C-peptide levels ( $p = 0.00077$  and  $p = 0.00065$

**Table 1** General characteristics of the included studies

Studies	SB	Country	No. of patients	Female %	Mean age of patients (years)	Mean duration of T1DM (month)	GADA + (%)	Type of SCs	Mean dose of transplanted (cells/kg)	Mean length of follow-up (month)	Mode of injection
Couri 2009		Brazil	23	26.1	18.4	0.62	87	HSCs	$10.52 \times 10^6$	29.8	IV
Haller 2009		USA	15	46.7	5.5	4.1	NA	UCB	$1.5 \times 10^7$	12	IV
Gu 2010		China	18	66.7	18.4	<6	NA	HSCs	NA	13.8	IV
Vanikar 2010		India	11	36.4	21.1	98.4	45.4	MSCs + HSCs	$3.15 \times 10^6$ NA	23	IP
Feng 2011		China	16	56	13	9.9	NA	HSCs	$5.1 \times 10^6$	7	IV
Haller 2011		USA	24	58.3	5.1	4	NA	UCB	$1.88 \times 10^7$	12	IV
Yu WL 2011		China	6	50	19.67	<3	NR	MSCs	$1 \times 10^7$	9	IV
Gu 2012		China	28	50	17.6	3	93	HSCs	$1 \times 10^6$	23	IV
Li 2012		China	13	23.1	14.1	<12	54	HSCs	$4 \times 10^6$	42	IV
Zhang 2012		China	9	44	17.6	2	100	HSCs	$10.49 \times 10^6$	12	IV
Zhao Y 2012	A <sup>1</sup>	China	6	66.7	30	72	100	UCB	$1 \times 10^6$	6	IV
	B <sup>2</sup>	China	6	83.3	27	132	66.7	UCB	$1 \times 10^6$	6	IV
Haller 2013		USA	10	20	7.2	3.96	NA	UCB	$1.1 \times 10^7$	12	IV
Hu JX 2013		China	15	40	17.6	<6	73.3	MSCs	$2.6 \times 10^7$	24	IV
Mesples 2013		China	2	100	7	<2	100	BM-MNCs	$180 \times 10^6$	12	IP
Wang 2013		China	22	54.5	18.0	<6	100	HSCs	NA	24	IV
Giannopoulou 2014		Germany	7	29	3.02	3.36	NA	UCB	$1.27 \times 10^6$	12	IV
D'Addio 2014		China	65	37	20.4	<3	90.7	HSCs	$5.8 \times 10^6$	48	IV
Gu 2014		China	14	64	8.04	<3	NA	HSCs	NA	36–60	IV
Hou T 2014		China	15	46.7	18.95	4.22	NA	HSCs	$>3 \times 10^6$	14	IV
Carlsson 2015		Sweden	9	11.1	24	<0.75	67.7	MSCs	$2.75 \times 10^6$	12	IV
Jia XL 2015		China	10	90	8–31	<12	80	MSCs	$1 \times 10^6$	12	IV
Thakkar 2015	A <sup>3</sup>	India	10	10	20.2	97.2	100	MSCs + HSCs	$2.65 \times 10^4$ NA	33.1	IP
	B <sup>4</sup>	India	10	40	19.7	118.8	NA	MSCs + HSCs	$2.07 \times 10^4$ NA	33.1	IP
Delgado 2015	A <sup>1</sup>	Spain	6	33.3	33.8	6.5	NA	UCB	$1.0 \times 10^6$	12	IV
	B <sup>2</sup>	Spain	9	33.3	40.3	12.4	NA	UCB	$1.0 \times 10^6$	12	IV
Cai 2016		China	21	57	18.29	111	66.7	MSCs + HSCs	$1.1 \times 10^6$ $106.78 \times 10^6$	12	IP
Snarski 2016		Poland	24	29	26.5	2.03	100	HSCs	$4.19 \times 10^6$	52	IV
Ye 2017		China	8	62.5	18.86	<6	100	HSCs	$2 \times 10^5$	12	IV
Gu 2018		China	20	75	18	2.26	NA	HSCs	NA	48	IV
Mohamed 2018	A <sup>5</sup>	Egypt	15	46.6	22.3	11.9	NA	BM-MNCs	$1 \times 10^6$	3	IP
	B <sup>6</sup>	Egypt	15	53.3	22.3	11.9	NA	BM-MNCs	$1 \times 10^6$	3	IP
Ulyanova 2019		Kazakhstan	5	20	20–42	NA	NA	MSCs	$96 \times 10^6$	3	IV

GADA+(%), GADA positive rate before treatment; SB, subgroup of studies; SCs, stem cells; HSCs, hematopoietic stem cells; UCB, umbilical cord blood; MSCs, mesenchymal stem cells; BM-MNC, bone marrow mononuclear cells; NA, not applicable; 1, subgroup A of patients having some residual islet  $\beta$  cell function; 2, subgroup B of patients with no residual islet  $\beta$  cell function; 3, subgroup A of patients transplanted with autologous cells; 4, subgroup B of patients transplanted with allogenic cells; 5, subgroup A of patients combined with exercise program; 6, subgroup B of patients without exercise program; IP, intra-pancreatic; IV, intravenous.

**Table 2** Quality of included studies

Studies	Selection	Comparability	Exposure	Total
Couri 2009	4	0	3	7
Haller 2009	4	0	3	7
Gu 2010	4	0	3	7
Vanikar 2010	4	0	3	7
Feng 2011	4	0	2	6
Haller 2011	4	0	3	7
Yu WL 2011	4	2	2	8
Gu 2012	4	0	3	7
Li 2012	4	0	3	7
Zhang 2012	4	0	3	7
Zhao Y 2012	4	2	2	8
Haller 2013	4	2	3	9
Hu JX 2013	4	2	3	9
Mesples 2013	3	1	3	7
Wang 2013	4	2	3	9
Giannopoulou 2014	4	2	3	9
D'Addio 2014	4	0	3	7
Gu 2014	4	2	3	9
Hou T 2014	4	2	3	9
Carlsson 2015	4	2	3	9
Jia XL 2015	4	0	3	7
Thakkar 2015	4	2	3	9
Delgado 2015	4	0	3	7
Cai 2016	4	2	3	9
Snarski 2016	4	0	3	7
Ye 2017	4	2	3	9
Gu 2018	4	2	3	9
Mohamed 2018	4	0	2	6
Ulyanova 2019	4	0	2	6

respectively) (Fig. 4C and Fig. 4D). However, the number of transplanted cells and the duration of T1DM showed no significant association with the outcomes in HSCs group (Table 4).

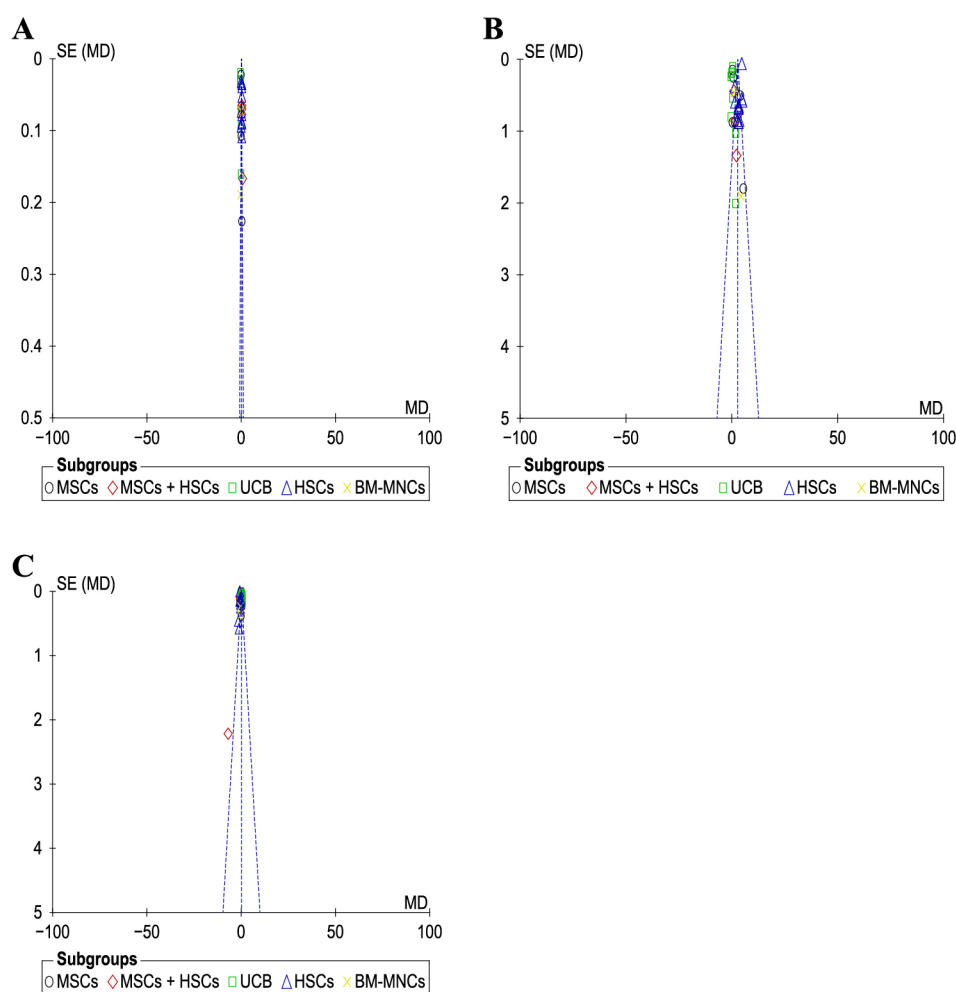
#### Insulin independent rate

The incidence of patients who obtained transient insulin independence after SCT was 9.6 per 100 person-years (95% CI: 5.8 to 13.5%,  $I^2 = 72$ ). 10 studies reported the mean period of transient insulin independence after SCT [16, 20, 23-25, 28, 31, 33, 40, 42] which was 15.6 months (95% CI: 12.3 to 18.9,  $I^2 = 95$ ) (Table 5). Yu WL *et al.* [22] also observed 3 patients achieving insulin independence after SCT, but did not reported the mean

period. Among the 11 studies, only 4 were randomized controlled trials (RCT) [22, 28, 33, 42], the others were self-controlled trails. When analyzing the insulin independence rate in the 4 RCT studies, the SCT showed the significant effects to improve the insulin independence rate compared to control group which treated with insulin (risk ratio (RR), 9.67; 95% CI, 2.62 to 35.62;  $p = 0.001$ ;  $I^2 = 0\%$ ).

#### Adverse events assessment

The common adverse events contained alopecia, fever, vomiting, nausea, gastric tract symptoms, leucopenia, rash and diarrhea. The incident rate of severe adverse events, as bilateral pneumonia and pseudomonas aerugi-



**Fig. 2** Funnel plots of comparing the individual results of administrating stem cells transplantation in T1DM: (A) daily insulin requirement (U/kg per day); (B) HbA1c (%); (C) C-peptide (ng/mL). (MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; UCB, umbilical cord blood; BM-MNCs, bone marrow mononuclear cells; HbA1c, glycosylated hemoglobin)

nosa sepsis, was 3.9% (95% CI: 2.4–6.2%). Two patients died due to the pseudomonas aeruginosa sepsis reported in two studies [31, 40]. The incidence rate of mortality was 3.4% (95% CI: 2.1% to 5.5%,  $I^2 = 0$ ) (Table 5).

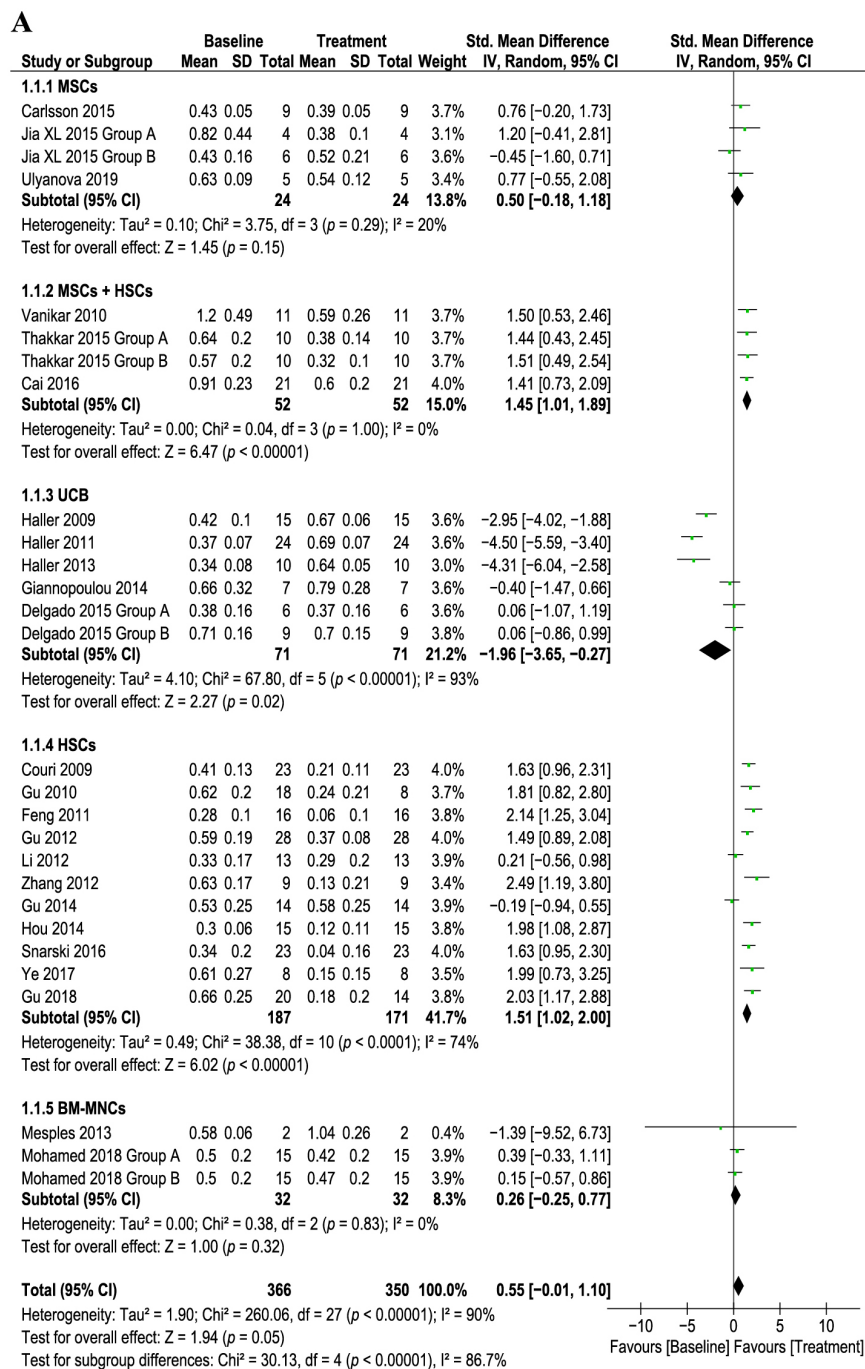
## Discussion

The prevalence of T1DM has been increasing steadily over the past decades. Although the rapid developments of modern diabetes treatment have improved the life quality of T1DM patients, the long-term complications of T1DM cannot be completely avoided. More than a decade ago, a new research field named SCs therapy emerged in health science. Many medical research institutes began nearly a decade research on SCT in patients with T1DM.

To draw a more definitive conclusion of the efficacy and safety of SCT in T1DM, we performed a meta-analysis of 29 published articles. As indicated by the

pooled effect in our meta-analysis, MSCs + HSCs and HSCs groups showed significant effects to reduce daily insulin requirement and HbA1c levels, as well as to improve C-peptide levels at 1 year follow-up compared to the baseline. Whereas the MSCs group only showed significant effect to decrease HbA1c levels but no significant effect to reduce daily insulin requirement or to improve C-peptide levels, which was different from the meta-analysis conducted by Gan J *et al.* [45]. As we know that,  $\beta$  cells function will decrease rapidly within years during the natural course of T1DM. The analysis suggest that MSCs, MSCs + HSCs and HSCs groups could be effective in maintaining  $\beta$  cells function at 1 year follow-up. However, further studies are needed to confirm the long-term effectiveness. Our data also showed that the older age was significantly associated with the decrease of daily insulin requirement, the decrease of HbA1c and the improvement of C-peptide levels in the HSCs subgroup. We further explored the



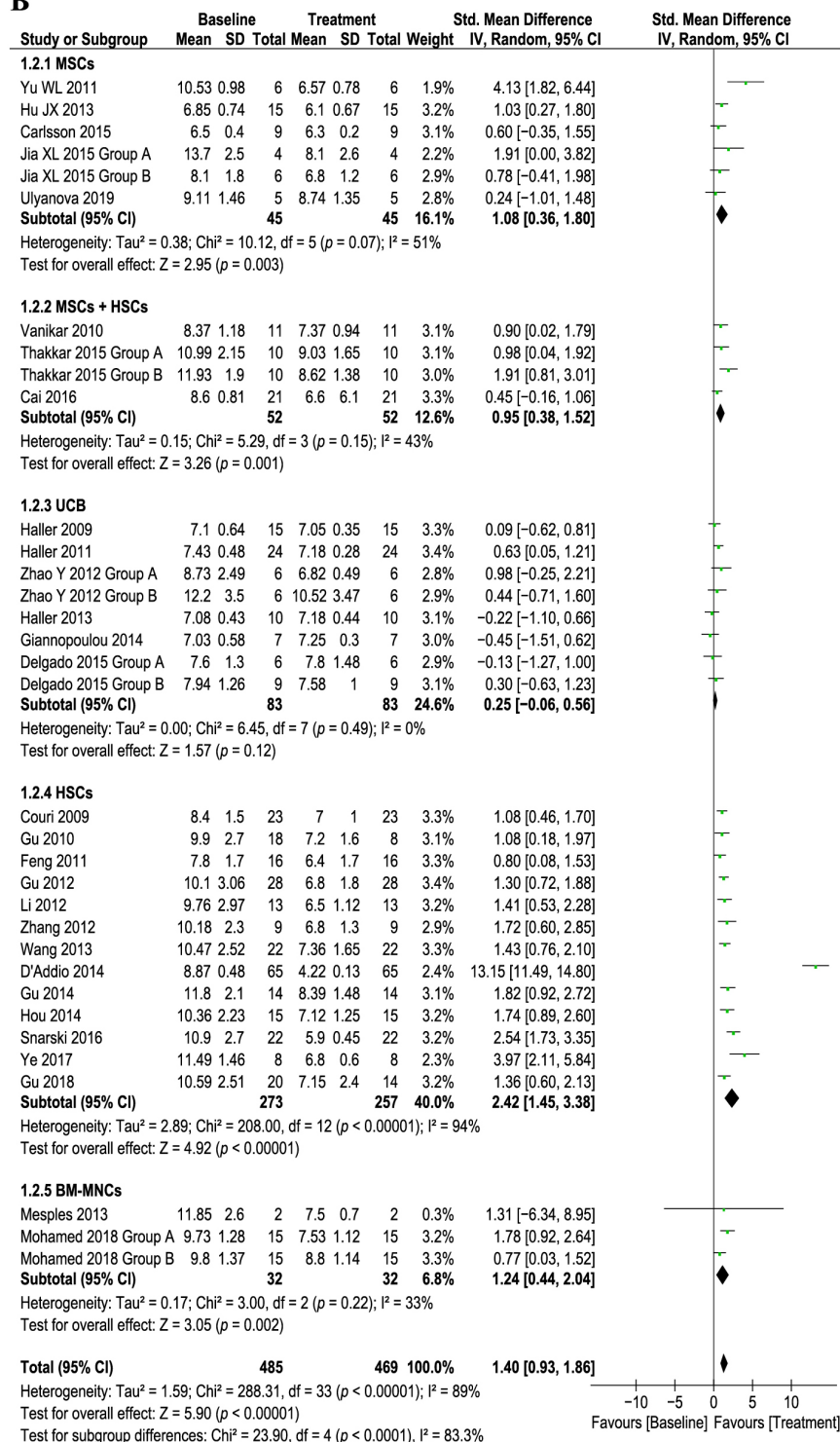


**Fig. 3** Forest plots showing the individual results of administrating different types of stem cells transplantation in T1DM: (A) daily insulin requirement (U/kg per day); (B) HbA1c (%); (C) C-peptide (ng/mL). (MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; UCB, umbilical cord blood; BM-MNCs, bone marrow mononuclear cells; HbA1c, glycosylated hemoglobin)

detail data of these studies and found that the mean disease durations before treatment in these patients were less than 1 year, especially most of them were less than 6 months. Thus, if newly diagnosed older patients with T1DM could undergo HSCs transplantation within 1 year, the better outcomes would be achieved. In addition, we also found that the higher GADA positive rate before

treatment showed significant association with the decrease of daily insulin requirement. The positive of GADA represented the definitely autoimmunity directed towards the islet  $\beta$  cells. The immunomodulatory of SCT might play a role on the glycemic control and the decreased insulin dosage.

Initially, the SCs therapeutic potential was considered

**B**

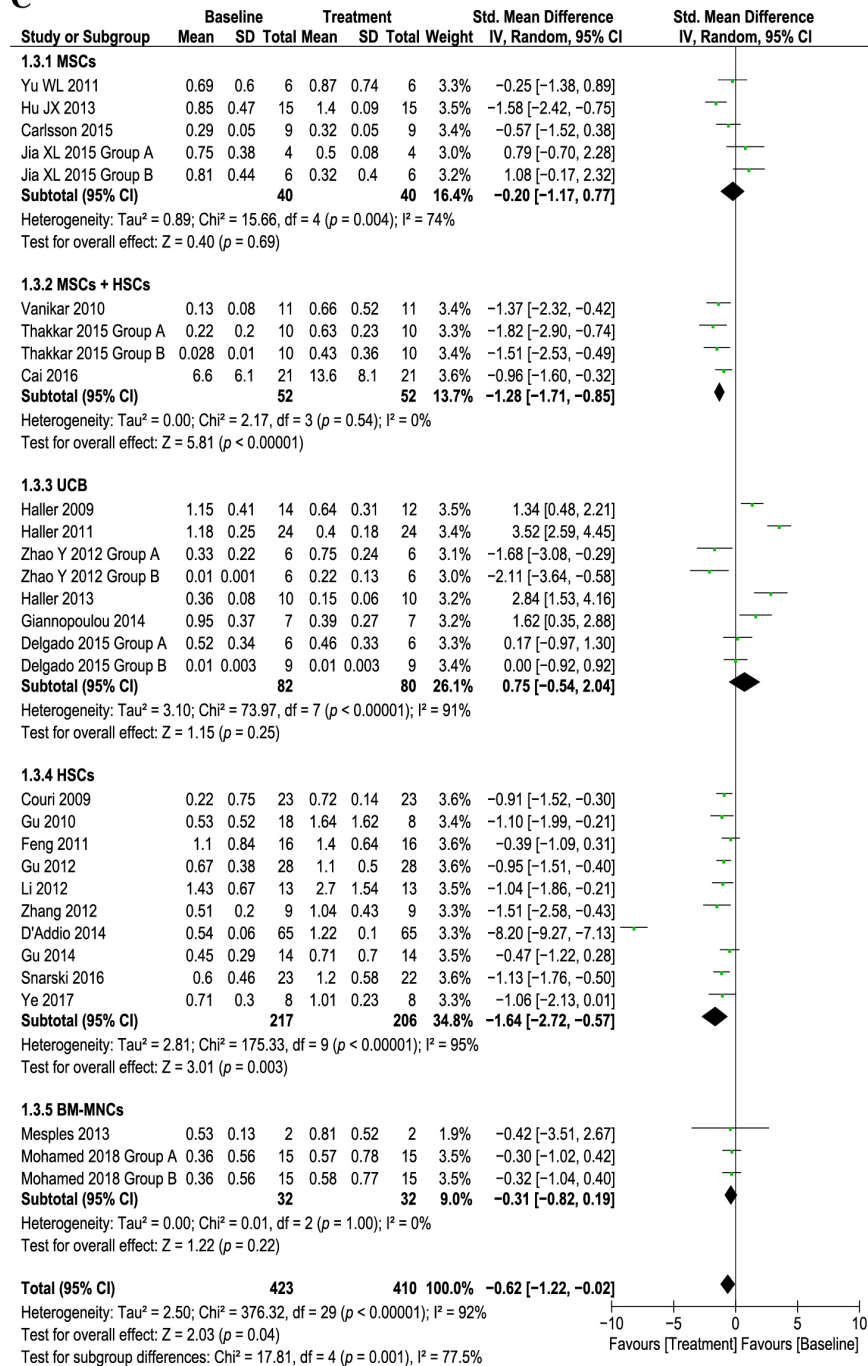
as the ability of differentiation into insulin-producing cells. However, this dogma has changed when new results had been published regarding to the immunomodulatory properties of SCs [46]. Vanikar *et al.* reported that the potential therapeutic effects of SCs was attributed to their intrinsic regenerative capacity and immunomodulatory properties, which could arrest autoimmune  $\beta$

cells destruction, protect residual  $\beta$  cells, promote endogenous regeneration, improve innate/alloimmune graft rejection, and restore  $\beta$ -cell-specific unresponsiveness without chronic immunosuppression and to reverse hyperglycemia [12].

While the UCB group showed no significant effect to decrease HbA1c levels or to improve C-peptide levels,



C



but even significantly increased daily insulin requirement after treatment. In addition to the small sample of the studies, some other factors might actually limit the capacity of UCB to preserve  $\beta$  cells function. First, an insufficient number of cells that carried regenerative or immunoregulatory capacity may have been transferred to patients with T1DM. Second, the ongoing autoimmune response in newly-onset T1DM may contain memory T cells, which are refractive to regulate by UCB [47], that facilitate the ongoing autoimmune destruction of endoge-

nous or *de novo*  $\beta$  cells. Parker MJ *et al.* suggested that a therapeutic approach involving transient immune depletion and subsequent induction of immune regulation is optimal [48]. Because of containing an abundant number of immature unprimed highly functional regulatory T cells (Tregs) which may facilitate bystander suppression of effector T cells, UCB still owns therapeutic potential on T1DM. Now the clinical trials are currently underway in patients with T1DM using expanded Tregs isolated from UCB (NCT02932826). We are looking forward to

**Table 3** The effect of stem cells therapy on the daily insulin requirement levels, HbA1c and C-peptide in T1DM

Variables	Type of stem cells	Summary estimates of mean difference 95% CI	<i>p</i> value	<i>I</i> <sup>2</sup> (%)
Daily insulin requirement (U/kg per day)	MSCs	0.50 [−0.18, 1.18]	0.15	20
	MSCs + HSCs	1.45 [1.01, 1.89]	<0.00001	0
	UCB	−1.96 [−3.65, −0.27]	0.02	93
	HSCs	1.51 [1.02, 2.00]	<0.00001	74
	BM-MNC	0.26 [−0.25, 0.77]	0.32	0
	Total	0.55 [−0.01, 1.10]	0.05	90
HbA1c (%)	MSCs	1.08 [0.36, 1.80]	0.003	51
	MSCs + HSCs	0.95 [0.38, 1.52]	0.001	43
	UCB	0.25 [−0.06, 0.56]	0.12	0
	HSCs	2.42 [1.45, 3.38]	<0.00001	94
	BM-MNC	1.24 [0.44, 2.04]	0.002	33
	Total	1.40 [0.93, 1.86]	<0.00001	89
C-peptide (ng/mL)	MSCs	−0.20 [−1.17, 0.77]	0.69	74
	MSCs + HSCs	−1.28 [−1.71, −0.85]	<0.00001	0
	UCB	0.75 [−0.54, 2.04]	0.25	91
	HSCs	−1.64 [−2.72, −0.57]	0.003	95
	BM-MNC	−0.31 [−0.82, 0.19]	0.22	0
	Total	−0.62 [−1.22, −0.02]	0.04	92

MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; UCB, umbilical cord blood; BM-MNCs, bone marrow mononuclear cells; HbA1c, glycosylated hemoglobin.

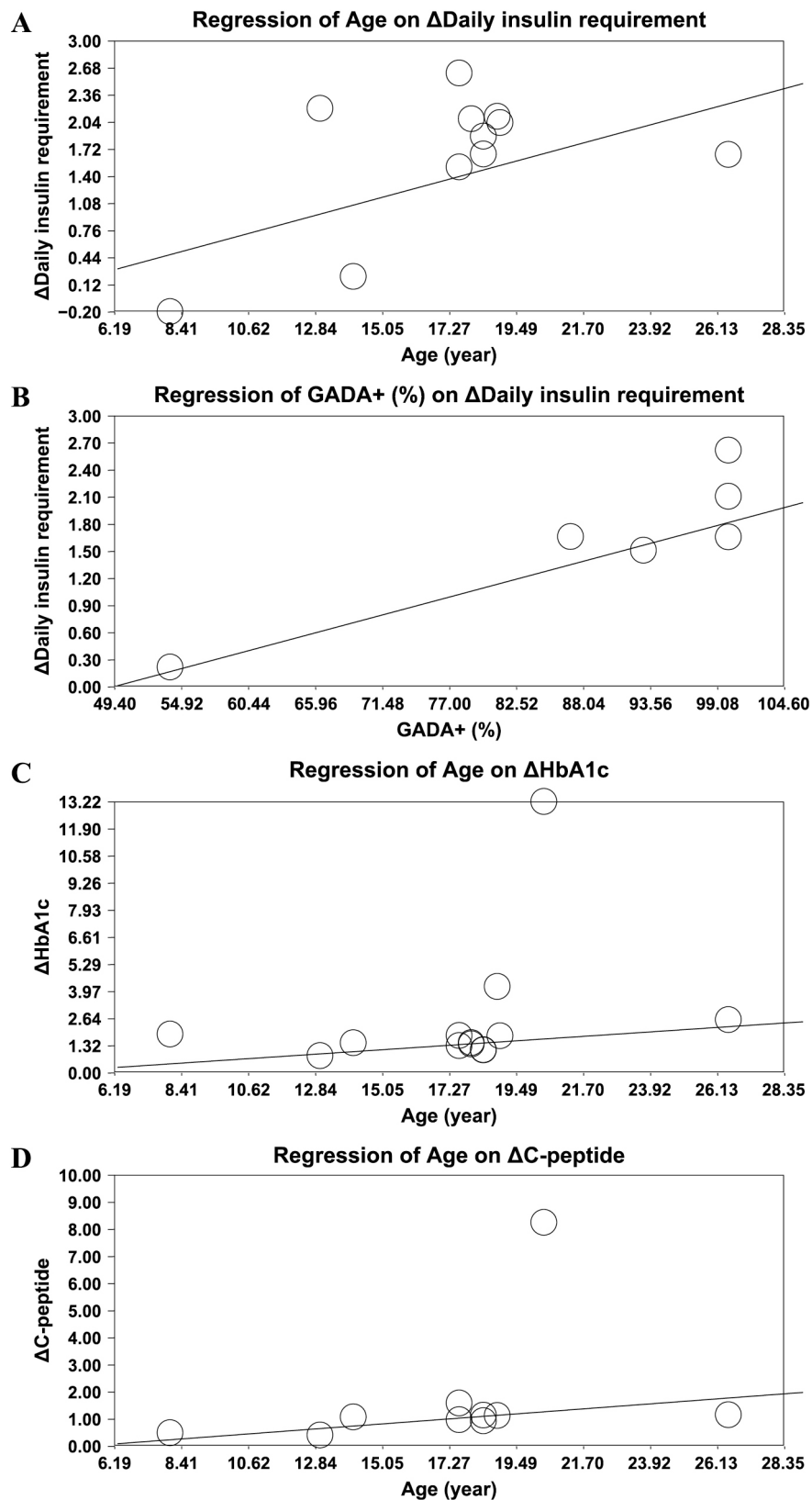
see the results to explore the therapeutic potential of UCB.

In addition, we analyzed the insulin independence length after SCT. The mean length of patients who achieved transient insulin independence after SCT was 15.6 months. As we all know, newly diagnosed T1DM patients may enter the honeymoon phase after initiation of insulin therapy. During this period, patients can maintain a good glycemic control with a little or no insulin treatment. This period usually lasts no longer than 1.5 years. After that, they will need more insulin to control their blood glucose. To eliminate the honeymoon period, we analyzed RR from the 4 RCT studies, the result suggested the SCT showed significant effect to improve insulin independence rate compared to control group. Among the 4 RCT studies, only one patient achieved 7-months insulin independence in the insulin group [42]. Thus, we preliminary draw the conclusion that SCT might prolong the insulin independence in T1DM. And more RCT studies with long times follow-up and large sample size analyses are needed to further investigation.

Although SCT appears to be effective, the safety is an important issue. The common adverse events contained alopecia, fever, vomiting, nausea, gastric tract symptoms, leucopenia, rash and diarrhea. Gu *et al.* reported that most of the early adverse events were caused by the mobilization and conditioning drugs used during HSCs transplantation, whereas later adverse events were unremarkable compared with patients using insulin therapy

[42]. D'Addio *et al.* found that, most of the adverse events due to the administration of a high-dose immunosuppressive regimen. This observation indicated the need for reducing the dosage of immunosuppressive or for eventually changing the immunosuppressive agents and for a stronger prophylaxis for infections to obtain a safer approach [31]. Our meta-analysis showed that the incidence rate of severe adverse events and the mortality rate were 3.9% and 3.4% respectively. Two patients died due to pseudomonas sepsis after autologous HSCs transplantation reported by two studies respectively. Thus, further studies and more clinical evidence are needed to ensure the safety of autologous HSCs transplantation before it can be more widely used in clinical.

In conclusion, our systematic review and meta-analysis suggested that MSCs + HSCs and HSCs transplantation have potential to significantly improve the  $\beta$  cells function of patients with T1DM. However, a complete cure of T1DM is yet to be achieved. Since the number of patients with T1DM is increasing, there needs more controlled and randomized trials with larger number of patients and long-term observations to draw more credible results of SCs therapy. In order to find the best approach, it is worthwhile exploring the precise mechanisms, dosage, timing and frequency to consummate the therapy.



**Fig. 4** Meta-regression analyses of the factors on the efficacy of HSCs transplantation.

(A) Meta-regression of age on  $\Delta$ daily insulin requirement (U/kg per day) ( $p = 0.00017$ );

(B) Meta-regression of GADA+ (%) on  $\Delta$ daily insulin requirement (U/kg per day) ( $p = 0.00041$ );

(C) Meta-regression of age on  $\Delta$ HbA1c (%) ( $p = 0.00077$ );

(D) Meta regression of age on  $\Delta$ C-peptide (ng/mL) ( $p = 0.00065$ ).

( $\Delta$ daily insulin requirement, decrease of daily insulin requirement after treatment; GADA+ (%), GADA positive rate before treatment;  $\Delta$ HbA1c, decrease of glycosylated hemoglobin after treatment;  $\Delta$ C-peptide, increase of C-peptide after treatment)

**Table 4** Results of meta-regression analysis between the outcomes and the factors may affect the efficacy of HSCs transplantation

Outcomes	Factors may affect the efficacy of HSCT	No. of Studies	<i>p</i> value
ΔDaily insulin requirement (U/kg per day)	Age (year)	11	0.00017
	Mean dose of transplanted cells ( $\times 10^6$ cells/kg)	6	>0.05
	Mean duration of T1DM (month)	11	>0.05
	GADA+ (%)	6	0.00041
ΔHbA1c (%)	Age (year)	13	0.00077
	Mean dose of transplanted cells ( $\times 10^6$ cells/kg)	7	>0.05
	Mean duration of T1DM (month)	13	>0.05
	GADA+ (%)	8	>0.05
ΔC-peptide (ng/mL)	Age (year)	10	0.00065
	Mean dose of transplanted cells ( $\times 10^6$ cells/kg)	6	>0.05
	Mean duration of T1DM (month)	10	>0.05
	GADA+ (%)	7	>0.05

No., number; Δdaily insulin requirement, decrease of daily insulin requirement after treatment; GADA+ (%), GADA positive rate before treatment; ΔHbA1c, decrease of HbA1c after treatment; ΔC-peptide, increase of C-peptide after treatment.

**Table 5** Transient insulin independence rate and adverse events assessment

	Studies	Events	Total	Rate	95% CI	<i>I</i> <sup>2</sup>
Transient insulin independence rate (100-PY)	27	138	447	9.6	5.8–13.5	72
Mean length of transient insulin independence (months)	10	—	—	15.6	12.3–18.9	95
Alopecia (%)	26	100	429	13.9	5.8–29.6	64
Fever (%)	28	83	465	12.5	6.9–21.6	69
Vomiting (%)	28	76	465	9.9	4.0–22.6	75
Nausea (%)	28	75	465	9.8	4.0–22.1	76
Gastric tract symptoms (%)	28	56	445	7.7	3.8–15.1	59
Leukopenia (%)	28	41	465	6.7	3.1–13.9	64
Rash (%)	28	29	465	5.5	2.7–10.7	56
Diarrhea (%)	28	24	465	5.3	3.0–9.0	27
Infection (%)	28	15	465	5.4	2.9–10.0	49
Allergic/Urticaria (%)	28	10	465	6.1	4.0–9.1	0
Oligospermia (%)	28	9	465	4.6	2.6–8.0	28
Anorexia (%)	28	8	465	5.0	3.0–8.3	19
Severe complications*	28	4	465	3.9	2.4–6.2	0
Mortality (%)	28	2	465	3.4	2.1–5.6	0

PY, person-year; \*Severe complications contains bilateral pneumonia and pseudomonas aeruginosa sepsis.

## Authors' Contributions

W.Q. was involved in conception and design, analysis and interpretation of data, drafting of the article. Z.S. worked on collection and interpretation of data. Q.Y., Z.XQ., C.H. and Y.T. were involved in the analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Z.M. was involved in conception and design, and critical revision

of the manuscript for important intellectual content. All the co-authors gave final approval of the version to be published.

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## Author Disclosure Statement

No competing financial interests exist.

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