

# Sequential Infusion of Mesenchymal Stem Cell for Graft-Versus-Host Disease Prevention in Haploidentical Hematopoietic Stem Cell Transplantation: An Open-Label, Multicenter, Randomized Controlled Clinical Trial

Han Yao, MD, PhD<sup>1,2,3</sup> ; Ruihao Huang, MD<sup>1,2,3</sup>; Haixia Fu, MD<sup>4</sup> ; Ren Lin, MD<sup>5</sup>; Yanqi Zhang, MD, PhD<sup>6</sup>; Yimei Feng, MD, PhD<sup>1,2,3</sup> ; Yu Wang, MD, PhD<sup>4</sup>; Ting Chen, MD, PhD<sup>1,2,3</sup>; Xiaoqi Wang, MD, PhD<sup>1,2,3</sup> ; Lidan Zhu, MD, PhD<sup>1,2,3</sup>; Jia Liu, MD, PhD<sup>1,2,3</sup>; Yuqing Liu, MD, PhD<sup>1,2,3</sup>; Lu Zhao, MD, PhD<sup>1,2,3</sup> ; Lu Wang, MD, PhD<sup>1,2,3</sup>; Peiyan Kong, MD, PhD<sup>1,2,3</sup>; Qin Wen, MD, PhD<sup>1,2,3</sup>; Cheng Zhang, MD, PhD<sup>1,2,3</sup> ; Li Gao, MD, PhD<sup>1,2,3</sup>; Lei Gao, MD, PhD<sup>1,2,3</sup> ; Qifa Liu, MD, PhD<sup>5</sup> ; Xiaohui Zhang, MD, PhD<sup>4</sup> ; Xiaojun Huang, MD, PhD<sup>4</sup> ; and Xi Zhang, MD, PhD<sup>1,2,3</sup>

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## ABSTRACT

**PURPOSE** The aim of this open-label, multicenter, randomized controlled trial was to determine the efficacy and safety of sequential umbilical cord–derived mesenchymal stem cell (UC-MSC) infusion for graft-versus-host disease (GVHD) prevention within 3 months of haploidentical hematopoietic stem cell transplantation (haplo-HSCT).

**METHODS** This open-label study evaluated UC-MSC infusion (administer  $1 \times 10^6/\text{kg}$  4 hours before the commencement of day 0, once weekly for the first month after transplantation, once every 2 weeks for the second month, and once during the third month, totaling eight doses). The primary end point was the 2-year cumulative incidence of severe chronic GVHD (cGVHD).

**RESULTS** In the primary analysis, 192 qualified participants between age 18 and 60 years with haplo-HSCT in three transplant centers in China were enrolled and randomly assigned to the MSC and control groups. In the primary analysis, the estimated 2-year cumulative incidence of severe cGVHD and all grades of cGVHD was lower in the MSC group than in the control group ( $P = .033$  and  $P = .022$ ). The cumulative incidence of grade 1 to 4, 2 to 4, and 3 to 4 acute GVHD (aGVHD) in patients in the MSC group significantly decreased (all  $P < .001$ ). The 3-year GVHD-free and relapse-free survival (GRFS) rate in the MSC group was 62.4%, which was significantly higher than that in the control group (32.0%, hazard ratio [HR], 0.34,  $P < .001$ ). MSC infusion did not influence the cumulative incidence of relapse ( $P = .34$ ) and nonrelapse mortality ( $P = .45$ ).

**CONCLUSION** Our findings suggest that sequential infusion of MSCs within 3 months after haplo-HSCT significantly reduced both the incidence and severity of cGVHD and aGVHD, manifesting as a better GRFS rate for patients.

## ACCOMPANYING CONTENT

- [Data Sharing Statement](#)
- [Data Supplement](#)
- [Protocol](#)

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## INTRODUCTION

In China, haploidentical hematopoietic stem cell transplantation (haplo-HSCT) has steadily gained traction as a therapeutic option for hematological malignancies. The high availability of donors, comparatively low costs, and ongoing optimization of transplantation techniques are the main drivers of this development.<sup>1,2</sup> However, haplo-HSCT-related difficulties continue to be a significant obstacle. Complications after transplantation, especially

graft-versus-host disease (GVHD) and recurrence, are still important in determining the prognosis and quality of life of patients. Although advancements in prophylaxis have reduced the incidence and severity of GVHD, the related hazards still exist, requiring additional studies and clinical trials to address the issues.<sup>3,4</sup>

Our center has been committed to the long-term exploration of underlying mechanisms and new combination approaches in cellular therapy to effectively prevent GVHD,

## CONTEXT

### Key Objective

To evaluate the efficacy and safety of sequential umbilical cord–derived mesenchymal stem cell (UC-MSC) infusions administered within 3 months of haploidentical hematopoietic stem cell transplantation for graft-versus-host disease (GVHD) prevention.

### Knowledge Generated

Sequential UC-MSC infusions significantly reduced the estimated 2-year cumulative incidence of severe chronic GVHD (cGVHD; 5.5% v 14.8%, hazard ratio [HR], 0.35,  $P = .033$ ), all-grade cGVHD (27.6% v 45.5%, HR, 0.57,  $P = .022$ ), and acute GVHD ( $P < .001$ ) compared with standard prophylaxis. Patients receiving UC-MSC infusions achieved a higher 3-year GVHD-free and relapse-free survival rate (62.4% v 32.0%, HR, 0.34,  $P < .001$ ) without increasing the cumulative incidence of relapse and nonrelapse mortality.

### Relevance (C. Craddock)

This randomized trial confirms the potential of post-transplant UC-MSC infusion to reduce the risk of GVHD after halo-identical transfusion and highlights the importance of future trials aimed at optimizing both dose and timing of UC-MSC infusion.\*

\*Relevance section written by JCO Associate Editor Charles Craddock, MD.

particularly through the application of umbilical cord–derived mesenchymal stem cell (UC-MSC) infusion in combination with haplo-HSCT.<sup>5–7</sup> MSCs are multipotent stromal cells that possess strong immunomodulatory properties, which make them capable of suppressing immune responses.<sup>8</sup> In line with this, our team explored the efficacy of repeated UC-MSC infusions administered 100 and 45 days after haplo-HSCT to prevent GVHD.<sup>9,10</sup> These studies produced promising results, although chronic GVHD (cGVHD) was still observed following infusion. This suggests that the timing of MSC infusion is crucial, with each time point offering distinct advantages for prevention.<sup>11</sup> Consequently, we questioned whether earlier administration could further improve the outcomes. Moreover, our study confirmed that infusions did not increase the risk of relapse. Building on these findings, we developed a sequential infusion protocol with earlier administration to enhance therapeutic effects and improve patient outcomes.

Given that relapse rates did not increase in the context of haplo-HSCT, we hypothesized that administering MSCs earlier could better control GVHD. To test this, we designed a clinical study focused on sequential MSC infusions starting from day 0 and continuing within the first 3 months after haplo-HSCT. This study represents the final validation phase of a three-stage clinical trial of MSC administration, conducted at our center. The objective was to determine whether earlier and more comprehensive MSC coverage from the start of transplantation can more

effectively prevent cGVHD without increasing the risk of relapse.

## METHODS

### Study Design and Participants

This trial was an open-label, multicenter, randomized clinical trial that evaluated the effectiveness of MSC infusions for the prophylaxis of acute GVHD (aGVHD) and cGVHD simultaneously in the strategy of cotransplanting UC-MSC within 3 months after haplo-HSCT. Patients were recruited between September 2019 and June 2023 after receiving approval from the ethics committees of the three university hospitals in China. Written informed consent was provided by the participants, their legal guardians, or next of kin. This study was registered in the Chinese Clinical Trial Registry (ChiCTR1900022292).

Patients were recruited from the transplantation centers of the Xinqiao Hospital of Army Medical University, Peking University People's Hospital, and Nanfang Hospital. Raw data were collected from the case report form electronic follow-up system of a clinical research participant. Patient follow-up included patient door (emergency) cases, hospitalized cases, telephone follow-up, outpatient follow-up registry, and disease course management system for transplant patients at Xinqiao Hospital. Eligible patients met the following criteria: (1) age between 18 and 60 years; (2) diagnosis of acute leukemia or failure to find an human leukocyte antigen (HLA)–

matched related or unrelated donor and having an HLA haploidentical suitable donor for HSCT; (3) a Karnofsky Performance Scale score<sup>12</sup> of more than 60 and a life expectancy of longer than 3 months; and (4) the absence of uncontrolled infections and severe liver, kidney, lung, and heart diseases.

## Procedures

The enrolled patients with an HLA-haploidentical relative for HSCT received the semustine + cytarabine + busulfan + cyclophosphamide + antithymocyte globulin modified conditioning regimen (semustine 250 mg/m<sup>2</sup> once on day -9; cytarabine 4 g/m<sup>2</sup> once daily on days -8 and -7; busulfan 0.8 mg/kg once every 6 hours days -6 to -4; cyclophosphamide 1.8 g/m<sup>2</sup> once daily on days -3 and -2; antithymocyte globulin 2.5 mg/kg once daily on days -5 to -2).<sup>13</sup> Donor selection and hematopoietic stem cell mobilization and collection were conducted based on the consensus of The Chinese Society of Hematology regarding indications, conditioning regimens, and donor selection for allogeneic hematopoietic stem cell transplantation.<sup>13</sup> Standard GVHD prophylaxis consisted of mycophenolate mofetil, cyclosporine A, and methotrexate (MTX). Human umbilical cords were collected from healthy, full-term cesarean births and processed within 24 hours with signed informed

consent from the third-party mother. UC-MSCs were then uniformly prepared from human UC at Chongqing iCELL Biotechnology Co Ltd (Chongqing, China). The enrolled patients were randomly assigned in a 1:1 ratio to either the MSC group (administer  $1 \times 10^6$ /kg 4 hours before the commencement of day 0, once weekly for the first month after transplantation, once every 2 weeks for the second month, and once during the third month, totaling eight doses) or the control group (receiving regular prophylaxis).

## End Points

The primary end point was the 2-year cumulative incidence of severe cGVHD. Secondary end points included the incidence and severity of aGVHD, rates of overall survival (OS) and GVHD-free and relapse-free survival (GRFS; survival without III to IV aGVHD, cGVHD requiring systematic treatment, leukemia relapse, or death<sup>14</sup>), leukemia relapse, nonrelapse mortality (NRM), and incidence and severity of adverse events (AEs) within the first 150 days after haplo-HSCT. Organ scoring and global assessment of cGVHD were conducted based on the 2014 National Institutes of Health consensus criteria,<sup>15</sup> whereas acute GVHD was assessed based on the Mount Sinai Acute GVHD International Consortium criteria.<sup>16</sup> AEs were graded according to the Common Terminology Criteria for Adverse Events version 5.0.<sup>17</sup> For the OS

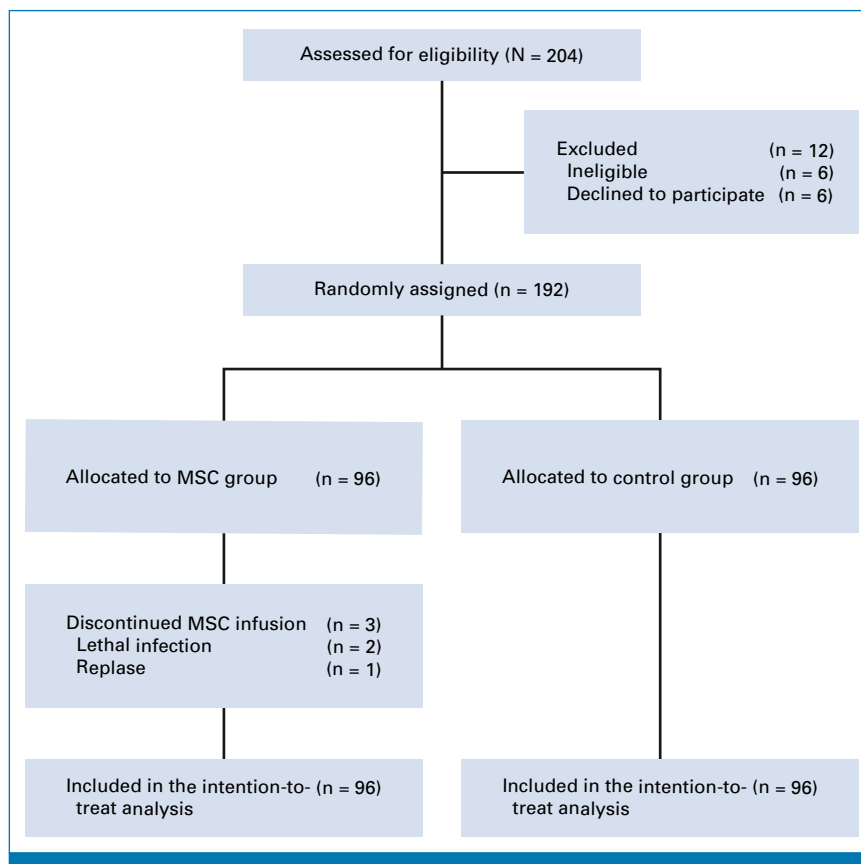


FIG 1. CONSORT diagram. MSC, mesenchymal stem cell.

analysis, death was counted as death of any reason after transplantation.

## Sample Size

Sample size estimates were based on the assumption of a log-rank test for the between-group comparison of the

primary end point and incidence of severe cGVHD. In a preliminary experiment, the cumulative incidence of severe cGVHD in the experimental and control groups was 5.5% and 14.6%, respectively. We assumed 20% cumulative incidence of competing events (relapse and non-relapse mortality), 2 years for enrollment and 5 years for follow-up. A sample size of 182 patients was calculated with a two-sided type II

**TABLE 1.** Baseline Clinical Characteristics

Clinical Characteristic	Control Group (n = 96)	MSC Group (n = 96)	P
Age, years (IQR)	33.0 (22.75-46.00)	37.0 (27.00-46.25)	.079
Refractory or relapse, No. (%)			
No	82 (85.42)	89 (92.71)	.165
Yes	14 (14.58)	7 (7.29)	
Sex, No. (%)			
Male	63 (65.62)	52 (54.17)	.141
Female	33 (34.38)	44 (45.83)	
Disease type, No. (%)			
AML/MDS-EB2	52 (54.17)	65 (67.71)	.126
ALL	41 (42.71)	30 (31.25)	
MPAL	3 (3.12)	1 (1.04)	
Disease risk index, No. (%)			
Low/Medium	7 (7.29)	6 (6.25)	>.999
High	89 (92.71)	90 (93.75)	
Disease status before HSCT, No. (%)			
CR	82 (85.42)	81 (84.38)	>.999
PR/NR	14 (14.58)	15 (15.62)	
MRD status, No. (%)			
Negative	66 (68.75)	74 (77.08)	.256
Positive	30 (31.25)	22 (22.92)	
Donor-recipient ABO match, No. (%)			
Same type	36 (37.50)	54 (56.25)	.056
Major mismatch	26 (27.08)	18 (18.75)	
Minor mismatch	25 (26.04)	15 (15.62)	
Major and minor mismatch	9 (9)	9 (9)	
Donor-recipient sex match, No. (%)			
Same gender	53 (55.21)	46 (47.92)	.441
Male to female	30 (31.25)	31 (32.29)	
Female to male	13 (13.54)	19 (19.79)	
HLA compatibility, No. (%)			
1-Locus mismatch	2 (2.08)	2 (2.08)	.217
2-Locus mismatch	8 (8.33)	17 (17.71)	
3-Locus mismatch	12 (12.50)	17 (17.71)	
4-Locus mismatch	16 (16.67)	15 (15.62)	
5-Locus mismatch	58 (60.42)	45 (46.88)	
Collateral relatives, No. (%)			
Yes	8 (8.33)	5 (5.21)	.566
Donor age, years (IQR)	40.0 (25.0-49.0)	34.0 (22.8-49.0)	.491
MNC, $\times 10^6$ /kg (IQR)	8.785 (7.505-10.585)	9.300 (7.90-10.73)	.174
CD34+ cells ( $\times 10^6$ /kg)	6.153 ( $\pm 2.166$ )	5.328 ( $\pm 2.348$ )	.012

Abbreviations: CR, complete remission; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MNC, mononuclear cells; MRD, minimal residual disease; NR, no response; PR, partial remission.

error of 0.05 and a statistical power of 90% for the cumulative incidence of cGVHD. Considering the expected rate of loss to follow-up (5%), 192 patients were included, with 96 in each arm. The sample size calculation was performed using PASS version 15 software (NCSS, Kaysville, UT).<sup>18</sup>

## Random Assignment and Statistical Analysis

Random assignment was performed by dedicated statisticians. A full randomization method was applied to participants who met the inclusion criteria and were strictly assigned according to the random sequence table. At each research center, eligible participants who provided consent were randomly assigned in a 1:1 ratio to the MSC or control group by statisticians who were not involved in recruitment, treatment, or outcome assessment.

The Mann-Whitney *U* test,  $\chi^2$  test, and Fisher's exact test were used to compare the baseline patients' characteristics and AEs between the MSC and control groups. The competing risk model (Fine and Gray model) was used to estimate the primary end point (2-year severe cGVHD cumulative incidence

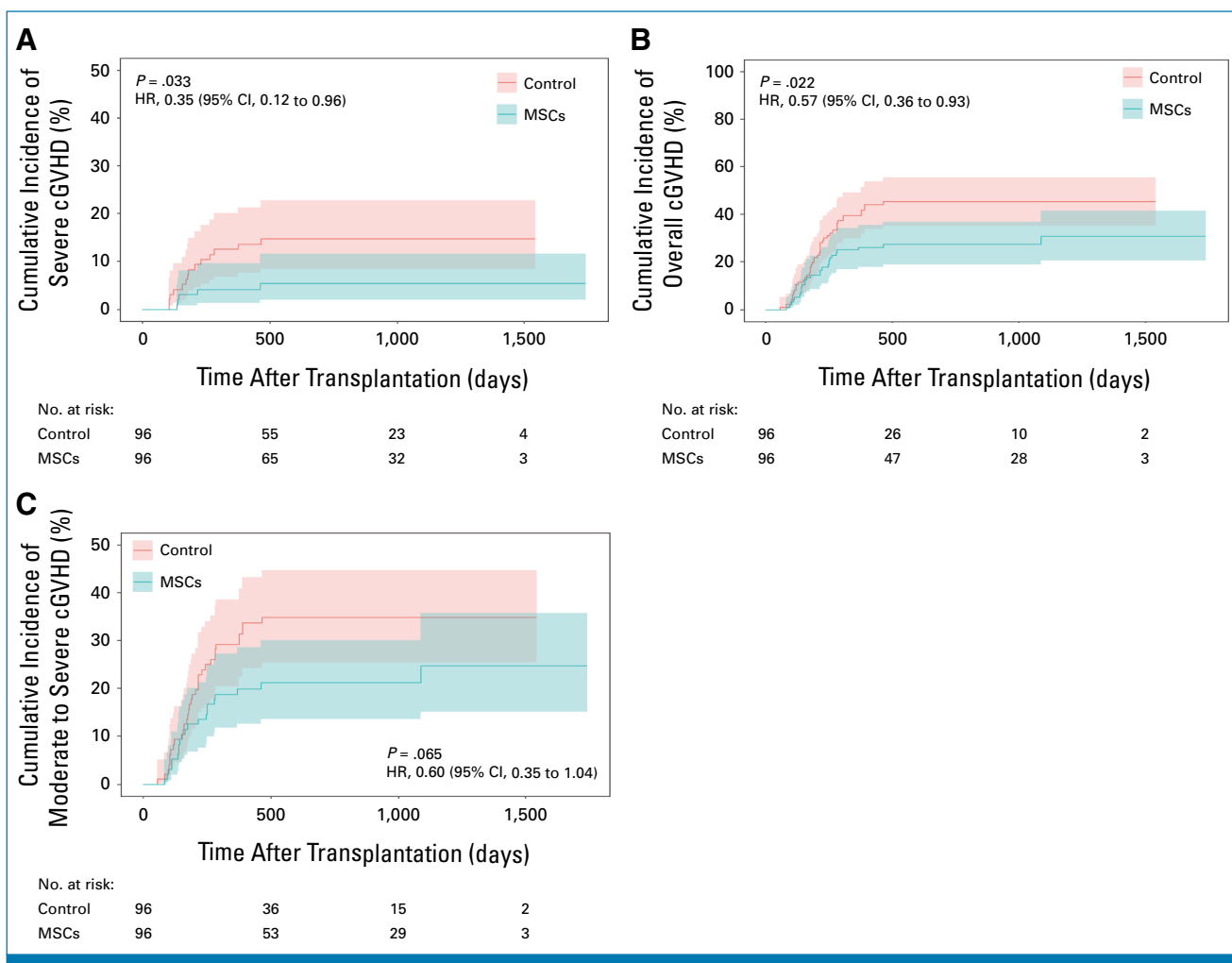
completed by death and relapse) and hazard ratios (HRs) with 95% CIs, and the incidence and severity of cGVHD, aGVHD (completed by non-relapse death), leukemia relapse (completed by nonrelapse death), and NRM (completed by relapse).

The rates of GRFS and OS were analyzed using Kaplan-Meier analysis and presented as percentages with 95% CIs and tested by log-rank test between the two groups.<sup>19</sup> All reported *P* values were two-sided. The *P* values and HRs for cGVHD, aGVHD, relapse, and NRM cumulative incidence were calculated using the Fine and Gray regression model. The HRs for GRFS and OS rate were analyzed using the Cox regression model. Statistical analyses were conducted using R (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria).

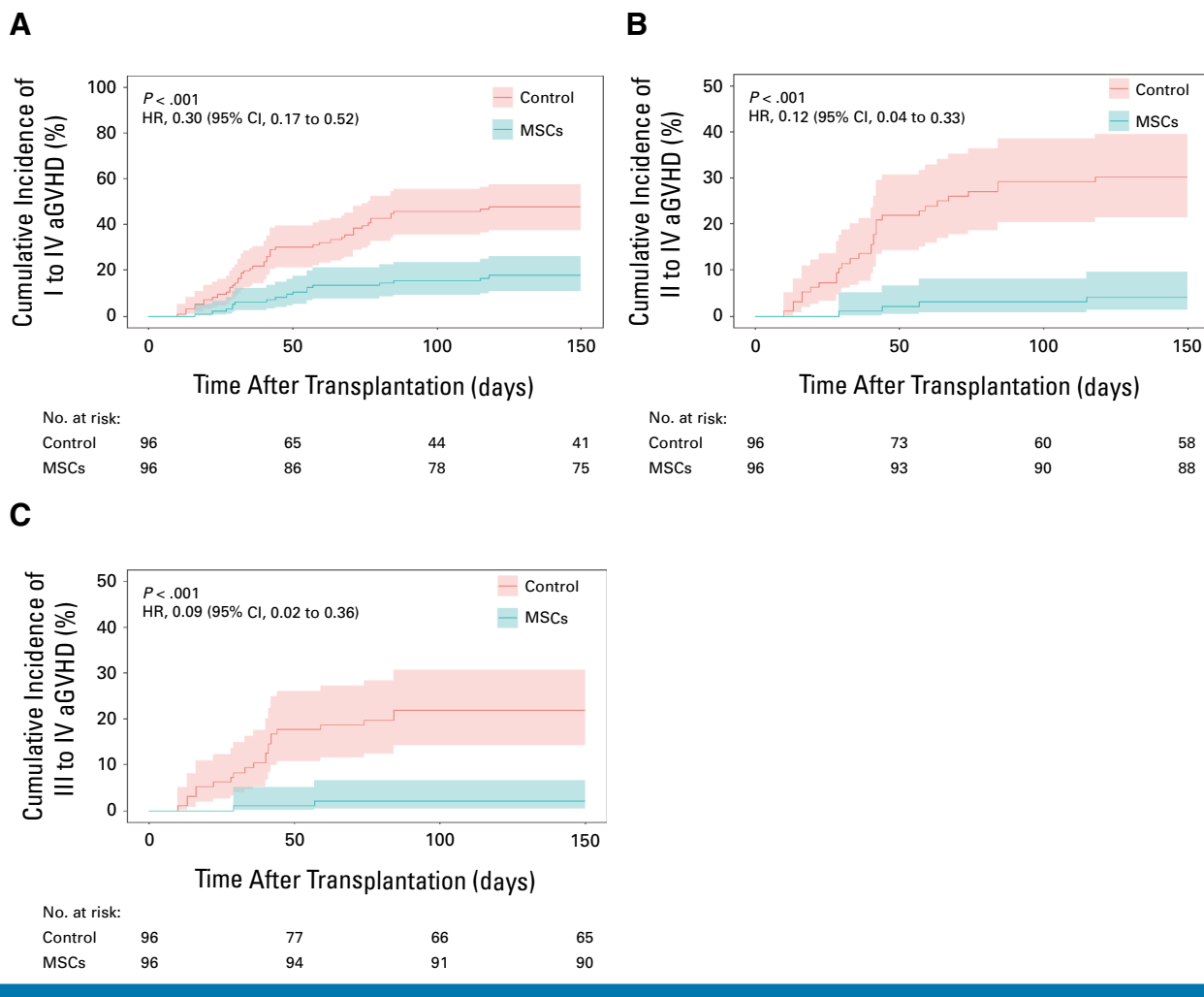
## RESULTS

### Baseline Characteristics of Participants

Between September 2019 and June 2023, 204 patients were screened at three transplant centers. Twelve patients failed to meet the inclusion criteria: six patients did not meet the



**FIG 2.** Cumulative incidence and severity of cGVHD. (A) Severe cGVHD. (B) Overall cGVHD. (C) Moderate to severe cGVHD. cGVHD, chronic graft-versus-host disease; HR, hazard ratio; MSC, mesenchymal stem cell.



**FIG 3.** Cumulative incidence of I to IV aGVHD, II to IV aGVHD and III to IV aGVHD. (A) I to IV aGVHD. (B) II to IV aGVHD. (C) III to IV aGVHD. aGVHD, acute graft-versus-host disease; GVHD, graft-versus-host disease; HR, hazard ratio; MSC, mesenchymal stem cell.

inclusion criteria, and six patients refused to participate in the study. All participants underwent haploidentical HSCT using hematopoietic stem cells donated by a direct family member (parent, child, sibling, cousin, aunt, or uncle). A total of 192 patients were randomly assigned to the MSC group ( $n = 96$ ) or the control group ( $n = 96$ ). The median follow-up time was 690 (6–1,319) days. The follow-up period will be June 2023. The details of the study population and controls are shown in Figure 1. Three patients failed to complete the infusions because of a lethal infection or relapse. The baseline patient characteristics are shown in Table 1 (hematological malignancies and transplants are shown in the Data Supplement [Table S1, online only]).

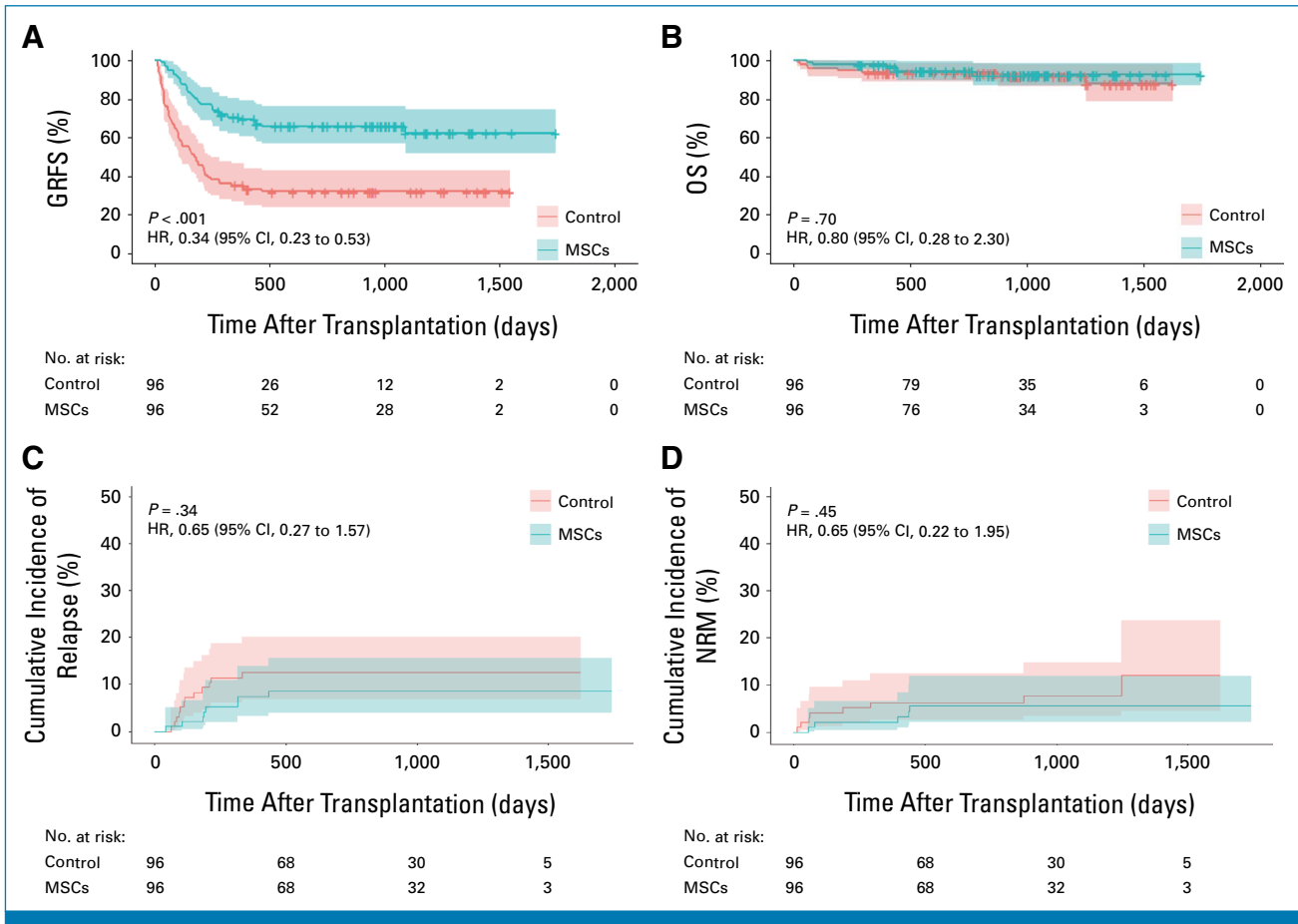
### Chronic GVHD

The estimated 2-year cumulative incidence of severe cGVHD was 5.5% (95% CI, 2.0 to 11.5) in the MSC group and 14.8% (95% CI, 8.5 to 22.7) in the control group, for an HR of 0.35 (95% CI, 0.12 to 0.96;  $P = .033$ ; Fig 2A). The estimated 2-year cumulative incidence of all-grade cGVHD was 27.6% (95% CI,

18.9 to 36.9) in the MSC group and 45.5% (95% CI, 35.1 to 55.3) in the control group, with an HR of 0.57 (95% CI, 0.36 to 0.93;  $P = .022$ ; Fig 2B). There is an improved tendency in moderate to severe cGVHD with an HR of 0.60 (95% CI, 0.35 to 1.04,  $P = .065$ ; Fig 2C). In the lesion site analysis, there were significant differences in lung cGVHD ( $P = .007$ ) and skin cGVHD ( $P = .034$ ) between the MSC group and control group, and there were no significant differences in joint and fascia cGVHD. MSC infusion significantly reduced the median and severe cGVHD in the skin ( $P = .029$ ), lungs ( $P = .030$ ), and eyes ( $P = .032$ ).

### Acute GVHD

An estimated cumulative incidence of 17.7% (95% CI, 10.8 to 26.0) of the patients developed I to IV aGVHD in the MSC group, whereas 47.9% (95% CI, 37.6 to 57.5) of the patients developed I to IV aGVHD in the control group, for an HR of 0.30 (95% CI, 0.17 to 0.52;  $P < .001$ ; Fig 3A). The incidence of grade 2 to 4 aGVHD in the patients in the MSC group was significantly lower, at 4.2% (95% CI, 1.4 to 9.6), compared with 30.2%



**FIG 4.** Survival analysis. (A) GRFS. (B) OS. (C) Cumulative incidence of relapse. (D) Cumulative incidence of NRM. GRFS, GVHD-free and relapse-free survival; GVHD, graft-versus-host disease; HR, hazard ratio; MSC, mesenchymal stem cell; NRM, non-relapse mortality; OS, overall survival.

(95% CI, 21.3 to 39.6) in the control group, for an HR of 0.12 (95% CI, 0.04 to 0.33;  $P < .001$ ; Fig 3B). The estimated incidence of grade 3 to 4 aGVHD in the MSC group was 2.1% (95% CI, 0.4 to 6.6) and 21.9% (95% CI, 14.2 to 30.6) in the control

group, with an HR of 0.09 (95% CI, 0.02, 0.36;  $P < .001$ ; Fig 3C). Lesion site analysis revealed significant differences in the liver ( $P = .010$ ), skin ( $P = .023$ ), upper small intestine ( $P = .024$ ), and lower small intestine ( $P = .001$ ).

**TABLE 2.** Adverse Events

Adverse Event	Control Group (n = 96), No. (%)		P	MSC Group (n = 96), No. (%)		P
	Any Grade	Any Grade		Maximum Grade 3/4	Maximum Grade 3/4	
Sepsis	5 (5.2)	5 (5.2)	1.0	2 (2.1)	2 (2.1)	1.0
HC	20 (20.8)	16 (16.7)	.579	12 (12.5)	3 (3)	.031
TMA	6 (6.3)	3 (3.1)	.497	—	—	
Hemorrhage	9 (9.4)	3 (3.1)	.136	0 (0)	0 (0)	1.0
EBV	45 (46.9)	43 (44.8)	1.0	—	—	
CMV	44 (45.8)	41 (42.7)	.771	13 (13.5)	11 (11.5)	.827
VOD	2 (2.1)	1 (1.0)	1.0	—	—	

NOTE. EBV reactivation was indicated by a virus load of  $>5 \times 10^3$  IU/mL (3 log10). CMV reactivation was indicated by a viral load of  $>10^3$  IU/mL (3 log10).

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HC, hemorrhagic cystitis; TMA, transplant-associated thrombotic microangiopathy; VOD, hepatic veno-occlusive disease.

## Survival

The 3-year GRFS rate was 62.4% (95% CI, 52.1 to 74.8) in the MSC group and 32.0% (95% CI, 23.8 to 42.9) in the control group, with an HR of 0.34 (95% CI, 0.23 to 0.53;  $P < .001$ ; Fig 4A). There was a potential improvement in the OS rate for the patients in the MSC group, although there was no significant difference between the two groups (HR, 0.80 [95% CI, 0.28 to 2.30];  $P = .70$ ; Fig 4B). There was no significant difference between the MSC and control groups in the cumulative incidence of leukemia relapse (HR, 0.65 [95% CI, 0.27 to 1.57];  $P = .34$ ; Fig 4C) and the cumulative incidence of NRM (HR, 0.65 [95% CI, 0.22 to 1.95];  $P = .45$ ; Fig 4D).

## AE Analysis

AEs occurring between days 0 and 150 following haplo-HSCT were documented, covering the period from the initial infusion to 50 days after the final infusion. No infusion-related side effects, such as allergic reactions, pain or discomfort, infection, phlebitis, or electrolyte disturbances, were observed in the MSC group. Two deaths occurred due to severe infections: one from sepsis and the other from fungal pneumonia. The most common side effects during the transplantation period were Epstein-Barr virus reactivation in 88 patients (45.8%) and cytomegalovirus (CMV) reactivation in 85 patients (44.3%). MSC infusion reduces the incidence of grade 3 to 4 hemorrhagic cystitis (HC) ( $P = .031$ ), whereas no significant differences were observed in the incidence of overall HC, CMV, hemorrhage, fungal infections, liver dysfunction, gastrointestinal infections, sepsis, mucositis, lung infections, kidney dysfunction, thrombotic microangiopathy, and hepatic veno-occlusive disease (Table 2, Data Supplement, Table S2).

## DISCUSSION

GVHD is a significant complication of haplo-HSCT with an incidence rate of 30%–70%.<sup>20</sup> The primary approach to prevent and treat GVHD involves the use of corticosteroids and immunosuppressants (such as antithymocyte globulin, cyclosporine, and tacrolimus). However, the long-term use of these drugs can lead to serious infections, relapse of hematological malignancies, and organ dysfunction, contributing to transplant-related mortality.<sup>21–23</sup> Therefore, the development of new, highly effective, and less toxic methods for GVHD prevention and treatment is of critical importance. MSCs have been extensively investigated for GVHD management.<sup>24</sup> However, the optimal MSC dosage, infusion regimen, and associated efficacy remain unclear, hindering broader clinical applications. Therefore, this study was designed on the basis of previous research to explore the most effective MSC treatment strategy.

Our study demonstrated that sequential infusion of MSCs within the first 3 months after haplo-HSCT

significantly reduced both the incidence and severity of chronic and acute GVHD, resulting in improved GRFS rates. Additionally, early MSC infusion applied to a broader patient population provided strong evidence supporting its use for comprehensive GVHD prevention. This approach may also help to address the clinical variability in MSC infusion protocols and inconsistency in therapeutic outcomes.

The positive outcomes of MSC infusion on day 0 in this study can be attributed to several key factors. First, MSCs exhibit a delayed therapeutic effect, and early administration on day 0 allows for the effective coverage of both acute and cGVHD. Second, sequential infusion not only addresses the window of acute GVHD onset but also modulates early immune cell activity during immune reconstitution, proactively regulating immune cell subsets.<sup>25,26</sup> Third, the reduction in the acute GVHD incidence contributes to a subsequent decrease in cGVHD, creating a synergistic effect. Moreover, in the context of haplo-HSCT, this strategy does not increase the risk of relapse, thereby enhancing the overall safety. Ultimately, this approach provides early, sustained, and broad MSC coverage while maintaining a favorable safety profile. About the MSC protection mechanisms, the anti-inflammatory properties of MSCs were well documented,<sup>27</sup> and their tissue repair capabilities help mitigate factors that drive GVHD while reducing the severity of inflammation through immunomodulation.<sup>28</sup> Empirically, both the immune regulatory function and the repair of endothelial damage are equally important, with neither being dominant. However, further studies are required to elucidate the underlying mechanisms.

Moreover, our study demonstrated that day 0 MSC infusions offered significant protective effects on GVHD-targeted organs. In acute GVHD, MSCs provide comprehensive protection across all affected organs. In cGVHD, infusions conferred notable protection, particularly in organs with moderate to severe involvement, such as the liver, eyes, and lungs. When addressing cGVHD, the goal extends beyond mere survival to include enhanced quality of life. MSCs have been shown to effectively improve GRFS, promote better patient outcomes, and facilitate reintegration into daily life.

In the clinical research phase, all haplo-HSCT patients received MSC protection. However, current infusion protocols have not significantly improved OS, likely because relapse remains the primary cause of mortality, despite advancements in GVHD treatment. Larger studies are required to confirm these potential survival benefits. Additionally, MSCs do not fully protect all cGVHD-affected organs, which may be due to the complex pathogenesis of cGVHD and small sample sizes for certain organ involvement. Future strategies may need to incorporate tailored combination prophylaxis alongside MSCs to better address specific patient needs.

The absence of a significant difference in OS suggests that MSCs may need to be combined with additional relapse prevention strategies to improve patient survival. Our center

is actively investigating the integration of MSCs with immune cell therapies to optimize the combination of cellular therapy and HSCT for improved patient outcomes.<sup>29</sup>

## AFFILIATIONS

<sup>1</sup>Medical Center of Hematology, Institute of Science Innovation for Blood Ecology and Intelligent Cells, Xinqiao Hospital of Army Medical University, Chongqing, China

<sup>2</sup>Chongqing Key Laboratory of Hematology and Microenvironment, Chongqing, China

<sup>3</sup>State Key Laboratory of Trauma and Chemical Poisoning, Army Medical University, Chongqing, China

<sup>4</sup>National Clinical Research Center for Hematologic Disease, Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Collaborative Innovation Center of Hematology, Peking University, Beijing, China

<sup>5</sup>Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, China

<sup>6</sup>Department of Health Statistics, College of Military Preventive Medicine, Army Medical University, Chongqing, China

## CORRESPONDING AUTHOR

Xi Zhang, MD, PhD; e-mail: zhangxxi@sina.com.

## EQUAL CONTRIBUTION

H.Y., R.H., H.F. and R.L. contributed equally to this work. Lei G., Q.L., Xiaohui Z., X.H., and Xi Z. contributed equally.

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## CLINICAL TRIAL INFORMATION

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI <https://doi.org/10.1200/JCO-24-02119>.

The principal investigator, Xi Zhang, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Lei Gao, Qifa Liu, Xiaohui Zhang, Xiaojun Huang, Xi Zhang

**Financial support:** Xi Zhang

**Administrative support:** Han Yao, Yanqi Zhang, Peiyan Kong, Cheng Zhang, Lei Gao, Xiaohui Zhang, Xi Zhang, Peiyan Kong, Cheng Zhang

**Provision of study materials or patients:** Ruihao Huang, Haixia Fu, Yimei Feng, Yu Wang, Ting Chen, Xiaoqi Wang, Lidan Zhu, Jia Liu, Yuqing Liu, Lu Wang, Peiyan Kong, Qin Wen, Cheng Zhang, Li Gao, Lei Gao, Qifa Liu, Xiaohui Zhang, Xiaojun Huang, Xi Zhang

**Collection and assembly of data:** Han Yao, Ruihao Huang, Haixia Fu, Ren Lin, Yanqi Zhang, Yimei Feng, Yu Wang, Ting Chen, Xiaoqi Wang, Lidan Zhu, Jia Liu, Yuqing Liu, Lu Zhao, Lu Wang, Peiyan Kong, Qin Wen, Cheng Zhang

**Data analysis and interpretation:** Han Yao, Ruihao Huang, Haixia Fu, Yanqi Zhang, Ting Chen, Lu Zhao, Peiyan Kong, Cheng Zhang, Li Gao, Lei Gao, Xiaohui Zhang, Xiaojun Huang, Xi Zhang

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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#### Xiaojun Huang

**Honoraria:** Johnson & Johnson, Sanofi

**Consulting or Advisory Role:** Sanofi, Johnson & Johnson

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