Long-term survivors demonstrate superior quality of life after haploidentical stem cell transplantation to matched sibling donor transplantation

Xiaoyu Zhang
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Jiao Wang
Tianjin Medical College: Tianjin Medical University
Yuqiu Liu
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Jie Liu
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Bei Wang
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Qiuhui Zhang
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Wei Guan
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Huijuan Zhang
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Li Xu
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Guiying Liu
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Ping Zhang
Fred Hutchinson Cancer Research Center
Yi He
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Sizhou Feng
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Mingzhe Han
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital
Changping Li
Tianjin Medical College: Tianjin Medical University
Erlie Jiang (hsct_huayuan@163.com)
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital

Wenjun Xie
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital

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Abstract

Background: It has been well-documented that haplo-identical hematopoietic stem cell transplantation (HID-HSCT) can provide outcomes comparable to conventional matched sibling donor (MSD) HSCT, however, little is known about the effects on quality of life (QoL) in long-term survivors. This study is to investigate the differences in longitudinal recovery of QoL between HID and MSD HSCT using a comprehensive assessment system.

Methods: This prospective study enrolled consecutive patients who had received allogenic-HSCT (allo-HSCT) between January 2018 and December 2019 in our center. All patients were informed to complete QoL questionnaires including the Mos 36-Item Short-Form Health Survey (SF-36) and the Functional Assessment of Cancer Therapy Bone Marrow Transplant (FACT-BMT, version 4), using an online applet, before transplantation and at scheduled time points after transplantation. The linear mixed-effects modal was used to analyze the variation trend of different dimensions of both SF-36 and FACT-BMT with different follow-up times.

Results: Of the 425 participants, recipients of HID and MSD who survived more than 1 year (n = 230) were included in the final analysis of QoL (median age [range]: 36, [15,66]). The 3-year overall survival (OS) of HID and MSD was 82.42% and 86.46%, respectively. QoL was assessed using both SF-36 and FACT-BMT and there was longitudinal recovery with clinical significance in the cohort. Compared to MSD-HSCT patients, HID-HSCT recipients demonstrated superior QoL recovery in some subscales describing physical and mental wellness. Specifically, the difference in physical performance is more remarkable using FACT-BMT whereas that in mental wellness is more significant using SF36. In the subsequent stratified analysis, patients with a history of aGVHD or CMV reactivation demonstrated inferior QoL.

Conclusions and relevance: Long-term survivors of HID HSCT achieved better QoL in some sub-scales compared to MSD HSCT. In addition, SF-36 and FACT-BMT demonstrated different performance thus combination of both improved capacity of the evaluation system.

Key Points

- Long-term survivors of HSCT recipients demonstrated longitudinal recovery in QoL which can be quantified with both SF-36 and FACT-BMT forms
- Recipients of HID-HSCT reported better recovery of QoL in both mental and physical dimensions.
- History of acute GVHD or CMV reactivation significantly was associated with inferior QoL.
- The SF-36 and FACT-BMT forms demonstrated different performance in the quantification of QoL recovery and combination of both may improve QoL evaluation system

Background

Allogenic hematopoietic stem cell transplantation (allo-HSCT) is a curative option for patients with hematological malignancies and some non-malignant hematological diseases. A high quality of life (QoL)

is crucial for the wellness of long-term survivors(1–3). The QoL is well acknowledged as multidimensional parameters including physical, emotional, social performance and well-being from patients' perceptions(2). QoL assessment helps healthcare providers to evaluate clinical interventions and is also an integral component in estimating medical outcome(4).

Numbers of haploidentical donor HSCTs (HID-HSCTs) are increasing rapidly due to decreasing family size and have become the largest source of allo-HSCT donors in China (5). Since haploidentical donors are immediately available to the majority of patients, HID-HSCT significantly extends treatment choice and demonstrates comparable clinical outcomes as compared to conventional HSCT(5–7). However, QoL represents a major concern in long-term survivors considering high incidence of complications following HID-HSCT (8, 9). A number of studies have evaluated QoL in HID-HSCT recipients with inconsistent findings(6, 10). While some reports studied QoL in the setting of HID-HSCT, control groups were heterogeneous which included HLA-matched sibling, matched unrelated, and unrelated umbilical cord blood donors(11). In addition, the majority of surveys were retrospective and QoL was not assessed with comprehensive questionnaires including HSCT-specific scales (12). To our knowledge, large-scale prospective study is lacking that focused on longitudinal changes in QoL in HID-HSCT recipients using multiple HSCT-specific questionnaires.

Our center has established a system for the assessment of QoL in HSCT recipients with the advantages of high specificity, high sensitivity, high acceptance and easy follow-up(13). In our previous study, we used the Mos 36-Item Short-Form Health Survey (SF-36) to describe the trajectory of QoL recovery and found significant improvement in QoL among one-year survivors (> 1 year after HSCT). In this prospective cohort study, we aim to establish a comprehensive QoL evaluation system for long-term survivors (> 1 year) making use of both SF36 and The Functional Assessment of Cancer Therapy Bone Marrow Transplant (FACT-BMT). General QoL was evaluated by SF36, a well-established QoL measurement that is often used in cancer populations(14). HSCT-specific QoL was evaluated with the FACT-BMT scale, a self-administered tool used to assess multidimensional domains of QoL in HSCT recipients(15, 16).

The primary end point of this study was to investigate the differences in QoL trajectory between HID-HSCT and MSD-HSCT during long-term follow-up. The secondary end point was to investigate the feasibility and practicability of the QoL assessment system with a combination of SF36 and FACT-BMT.

Methods

Study design and participants

This prospective study enrolled consecutive patients (n = 425) who had received HSCT between January 2018 and December 2019 at the HSCT Center, Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS&PUMC). Participants were informed of the objective of the study and asked to complete QoL questionnaires including the SF-36 and the FACT-BMT (version 4). In the present study, 44 patients were excluded due to declination to participate or inability to complete questionnaires independently. A total of 25 patients dropped off during follow-up. The total response rate

and follow-up rate reached 89.6% and 93.4% respectively. A number of 279 patients received MSD HSCT (*n* = 182) or HID HSCT (*n* = 97). Patients who survived 1 year after transplant (*n* = 230) were included for the analysis of QoL. A detailed study flow chart is shown in Fig. 1.

All participants signed written informed-consent forms and completed questionnaires online at their earliest convenience. All procedures were in accordance with the ethical standards of the institutional and national research committee (Ethics committee of Blood Disease Hospital, Chinese Academy of Medical Sciences + KT2013019001-EC-1) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institutional review board approved all study procedures and forms.

Data collection

Social-demographic variables were recorded including personal code, age, gender, clinical diagnoses, marital status, financial burden, insurance, employment status, and insurance payment. Clinical variables were abstracted from clinical records including primary disease, conditioning regimen, date of transplant, HSCT type, stem cell source, minimal residual disease (MRD) before HSCT, Eastern Cooperative Oncology Group performance score (ECOG score), history of acute and chronic GVHD, and infection. Acute graft versus host disease (aGVHD) and chronic graft versus host disease (cGVHD) were evaluated using international criteria(17, 18).

QoL assessment

This prospective study was designed for routine examination of QoL for recipients of MSD and HID-HSCT. All participants were asked to complete a questionnaire before transplantation and at scheduled time points after transplantation including 3 months, 6 months, 1 year, 1.5 years, 2 years, 3 years, and 5 years. All participants were asked to complete both SF-36 Form and FACT-BMT. SF36 From, a 36-item, generic questionnaire that assesses the functional status and well-being on eight multi-item subscales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The FACT-BMT used the subscales including physical well-being (PWB), functional well-being (FWB), social well-being (SWB), emotional well-being (EWB), BMT scale (BMTS), and total with BMT module (FACT-BMT). Patients completed the questionnaires on an online applet named *HSCT-QoL-CLOUD* which sends survey notifications to patients at scheduled timepoint. The results could be stored in the cloud and exported to the database.

Statistical analysis

All statistical analyses were performed using Stata SE 16.0 (Stata Corp, College Station, Texas). A 2-sided $P < 0.05$ was considered to indicate statistical significance. Baseline characteristics of the study population were analyzed by chi-square test for categorical variables and t-test or Wilcoxon rank-sum tests for continuous variables.

Kaplan-Meier and Laplace regression models were used to estimate and compare the median survival time (months) and 95% confidence intervals (CIs) according to different HSCT types. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% CIs for the incidence of death

according to HSCT type. Follow-up time (months) was calculated as the time from study entry to death or the final examination. The linear mixed-effects modal estimating the β-coefficients and 95% confidence intervals (CIs) was used to analyze the variation trend of different dimensions of both SF-36 and FACT-BMT with different follow-up times. The fixed effect included HSCT, follow-up time (month), and their interaction. Stratified analyses were performed to explore the association between HSCT and QoL according to incident aGVHD and cytomegalovirus (CMV) reactivation during the follow-up. All models were adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, and transplantation type, history of aGVHD and, cGVHD, and history of infection.

Results

Basic characteristics of HSCT recipients

This study included 279 participants (median age: 36, ranging from 15 to 66, 49.1% female) who received HID (*n* = 97) or MSD (*n* = 182) HSCT at our center. The basic characteristics were shown in Table 1. The majority of underlying diseases are hematological malignancies (93.1%) and all patients reached full chimerism post-HSCT. More than half of the patients (66.25%) were fully active before HSCT (ECOG score 0). Most patients (96.42%) accepted school education for more than 6 years and all patients were able to complete the QoL questionnaires independently. While 72.04% of patients were married, spouses are main caregivers for 54.8% of patients.

Table 1
Baseline characteristics and clinical outcomes of 279 patients underwent HSCT.

Characteristics	n (%) / median (interquartile range)
Age	36 (15, 66)
Gender	
Male / Female	141 (50.54) / 138 (49.46)
BMI	22.96 (12.58, 48.33)
<25 vs ≥ 25	192 (68.82) / 87 (31.18)
Education (years)	
<6, 6 ~ 12, > 12	10 (3.58) / 184 (65.95) / 85 (30.47)
Marital status	
Single, Married, Divorced/widowed	74 (26.52) / 201 (72.04) / 4 (1.43)
Main caregivers	
Spouse, Alternative	153 (54.84) / 126 (45.16)
Family income (rmb/year)	
<100000, ≥ 100000, Missing	114 (40.86) / 151 (54.12) / 14 (5.02)
Source of medical payment	
Insurance, Self-payment, Missing	175 (62.72) / 100 (35.84) /14 (5.02)
Diagnosis	
AML/ALL, MDS/MPN, AA, Lymphoma	196 (70.25) /64 (22.94)/ 17 (6.93)/ 2 (0.72)
ECOG Performance Score	
0 (fully active)/ >0	182 (65.23) / 97 (34.77)
HSCT type	
MSD / HID	182 (65.23) /97 (34.77)
Blood type	
Match / Mismatch	111 (39.78) /168 (60.22)

Values were expressed as n (%) or median (interquartile range).

Abbreviations: BMI, Body Mass Index; AML, acute myelogenous leukemia; ALL, acute lymphocte leukemia; MDS/MPN, myelodysplastic syndrome/ Myeloproliferative Neoplasm; AA, Aplastic Anemia; ECOG: Eastern Cooperative Oncology Group; HSCT: Hematopoietic Stem Cell Transplantation; MSD:Matched Sibling Donor; HID: Haplo-identical Donor; PB: Peripheral Blood; BM: Bone Marrow; CMV: Cytomegalovirus; aGVHD:acute Graft versus Host Disease; cGVHD: chronic Graft versus Host Disease.

Characteristics	n (%) / median (interquartile range)
Stem cell source	
PB / BM + PB	263 (94.27) /16 (5.73)
Neutrophil engraftment	276 (98.92)
Platelet engraftment	276 (98.92)
Infection	
Fungus/ CMV	31 (11.11) / 106 (37.99)
aGVHD	117 (41.94)
cGVHD	37 (13.26)
Values were expressed as n (%) or median (interquartile range).	
Abbreviations: BMI, Body Mass Index; AML, acute myelogenous leukemia; ALL, acute lymphocte leukemia; MDS/MPN, myelodysplastic syndrome/ Myeloproliferative Neoplasm; AA, Aplastic Anemia; ECOG: Eastern Cooperative Oncology Group; HSCT: Hematopoietic Stem Cell Transplantation; MSD:Matched Sibling Donor; HID: Haplo-identical Donor; PB: Peripheral Blood; BM: Bone Marrow; CMV: Cytomegalovirus; aGVHD:acute Graft versus Host Disease; cGVHD: chronic Graft versus Host Disease.	

HID-HSCT showed similar survival with higher incidence of aGVHD and CMV reactivation

We firstly compared the overall outcome of the HID-HSCT and MSD-HSCT recipients. After a median follow-up of 50 months (95% CI: 23.6–25.1 months), overall survival (OS) was comparable which was 82.42% and 86.46% at 3 years in all recipients of HID and MSD HSCT respectively (Fig. 2). Consistently, mortality rate in HID-HSCT was comparable to MSD-HSCT with HR (95% CI) at 0.77 (0.37–1.61) in a multi-adjusted COX model. Despite the similarity in survival, significantly higher proportion of HID-HSCT recipients had a history of acute GVHD (57.1% vs 34.0%, $p = 0.001$) and CMV reactivation (33.8% vs 21.6%, $p = 0.045$) which may affect the recovery of QoL.

Additional factors that may contribute to survival or QoL were subsequently analyzed. Unsurprisingly, HID-HSCT recipients were significantly younger than recipients of MSD-HSCT however the difference was very small (37.71 [11.438] vs 34.25 [11.703], mean [SD], p = 0.032,) which we didn't explore further. Of note, more than half of the HID patients were taken care of by their spouses (54.55%) whereas more patients in the MSD group were taken care of by alternative relatives. Other investigated factors were comparable between these two groups including gender, family income, body weight index (BMI), underlying diseases, performance status, school years, marital status, insurance sources, history of bacterial/fungal infections and history of chronic GVHD (Table 2).

Table 2
Difference of clinical characteristics between patients underwent MSD-HSCT and haploidentical HSCT (HID-HSCT) in one-year survivors (n = 230).

Characteristics	MSD-HSCT (N = 153)	HID-HSCT (N = 77)	*P*
Age	37.71 (11.438)	34.25 (11.703)	0.032[b]
Gender Male	77 (50.33)	38 (49.35)	1
BMI ≥ 25	46 (30.07)	25 (32.47)	0.763
Education (years)			0.666
< 6	5 (3.27)	4 (5.19)	
6 ~ 12	102 (66.67)	48 (62.34)	
> 12	46 (30.07)	25 (32.47)	
Marital status			0.083
Single	31 (20.26)	26 (33.77)	
Married	120 (78.43)	50 (64.94)	
Divorced/widowed	2 (1.31)	1 (1.29)	
Main caregivers			0.025[b]
Spouse	59 (38.56)	42 (54.55)	
Parent/offspring/Other/relatives	94 (61.44)	35 (45.45)	
Family income (rmb/year)			0.081
< 100000	69 (45.10)	24 (31.17)	
≥ 100000	79 (51.63)	48 (62.34)	
Source of medical payment			0.885
Insurance	96 (62.75)	49 (63.63)	
Self-payment	56 (36.60)	27 (35.06)	

Abbreviations: BMI, Body Mass Index; AML, acute myelogenous leukemia; ALL, acute lymphocyte leukemia; MDS/MPN, myelodysplastic syndrome/ Myeloproliferative Neoplasm; AA, Aplastic Anemia; ECOG: Eastern Cooperative Oncology Group; HSCT: Hematopoietic Stem Cell Transplantation; MSD: Matched Sibling Donor; HID: Haplo-identical Donor; PB: Peripheral Blood; BM: Bone Marrow; CMV: Cytomegalovirus; aGVHD: acute Graft versus Host Disease; cGVHD: chronic Graft versus Host Disease.

Values were expressed as n (%) or median (interquartile range).

[b] indicates the statistical significance for the factors.

Characteristics	MSD-HSCT (N = 153)	HID-HSCT (N = 77)	*P*
Diagnosis			0.092
AML/ALL	98 (64.05)	61 (79.22)	
MDS/MPN	42 (27.45)	14 (18.18)	
AA	11 (7.19)	2 (2.60)	
Lymphoma	2 (1.31)	0	
ECOG Performance Score			0.305
0 (fully active)	95 (62.09)	54 (70.13)	
> 0	58 (37.91)	23 (29.87)	
Blood type			0.777
Match	63 (41.18)	30 (38.96)	
Mismatch	90 (58.82)	47 (61.04)	
Neutrophil engraftment	14.96 (16.422)	15.11 (3.272)	0.940
Platelet engraftment	16.8 (14.295)	19 (8.785)	0.221
Infection			
Bacteria	74 (48.37)	28 (36.36)	0.084
Fungus	18 (11.76)	7 (10.87)	0.539
CMV	33 (21.57)	26 (33.77)	0.046[b]
aGVHD	52 (33.99)	44 (57.14)	0.001[b]
cGVHD	26 (16.99)	10 (12.99)	0.430

Abbreviations: BMI, Body Mass Index; AML, acute myelogenous leukemia; ALL, acute lymphocyte leukemia; MDS/MPN, myelodysplastic syndrome/ Myeloproliferative Neoplasm; AA, Aplastic Anemia; ECOG: Eastern Cooperative Oncology Group; HSCT: Hematopoietic Stem Cell Transplantation; MSD: Matched Sibling Donor; HID: Haplo-identical Donor; PB: Peripheral Blood; BM: Bone Marrow; CMV: Cytomegalovirus; aGVHD: acute Graft versus Host Disease; cGVHD: chronic Graft versus Host Disease.

Values were expressed as n (%) or median (interquartile range).

[b] indicates the statistical significance for the factors.

QoL recovered longitudinally using both SF-36 and FACT-BMT

We then investigated the longitudinal recovery of QoL in the whole cohort during the follow-up. Using the SF-36 form, scores on most scales increased gradually over time (Fig. 3, **and** Table 3), including physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), and role emotional (RE). Of note, statistically significant difference was observed in RP ($P < 0.001$), SF ($P < 0.001$) and PF ($P = 0.011$) indicating significant recovery mainly on physical function. However, we didn't observe significant improvement in mental health (MH) score over time (β= -0.07, 95% CI: -0.2 to 0.08). Consistently, most of the scales of FACT-BMT form also improved over time (Fig. 4 **and** Table 1). Similarly, physical well-being (PWB), the dimensions evaluating recovery of physical function, also reached clinically relevant significance. Thus, both forms demonstrated longitudinal improvement of QoL post-HSCT, especially in physical function related scales.

Table 3
Differences in longitudinal quality of life (QoL) assessed by SF36 and FACT-BMT Form between HID and MSD patients.

QoL	HSCT (HID vs. MSD)		Time	
	β (95% CI) [a]	P	β (95% CI) [a]	P
SF-36				
GH	5.46 (0.62, 10.29)	0.027[b]	0.03 (-0.15, 0.22)	0.722
PF	2.83 (-3.15, 8.82)	0.353	0.30 (0.07, 0.52)	0.011[b]
RP	4.06 (-1.83, 9.94)	0.177	0.82 (0.44, 1.20)	<0.001[b]
RE	4.83 (-4.41, 14.08)	0.306	0.33 (-0.10, 0.76)	0.129
SF	4.21 (-2.08, 10.51)	0.190	0.68 (0.41, 0.94)	< 0.001[b]
BP	4.06 (-0.79, 8.91)	0.101	0.09 (-0.09, 0.27)	0.336
VT	6.18 (1.37, 11.00)	0.012[b]	0.12 (-0.05, 0.29)	0.168
MH	4.53 (0.38, 8.68)	0.032[b]	-0.07 (-0.20, 0.08)	0.333
FACT-BMT				
PWB	1.49 (0.11, 2.87)	0.034[b]	0.09 (0.04, 0.14)	< 0.001[b]
SWB	1.29 (0.21, 2.38)	0.020[b]	-0.05 (-0.10, 0.01)	0.099
EWB	0.47 (-0.57, 1.50)	0.378	-0.01 (-0.04, 0.02)	0.482
FWB	1.89 (0.52, 3.26)	0.007[b]	0.02 (-0.06, 0.10)	0.560
FACT-G	5.34 (1.72, 8.76)	0.004[b]	0.05 (-0.11, 0.20)	0.545
TOI	2.80 (0.43, 5.18)	0.021[b]	0.09 (-0.01, 0.19)	0.095
FACT-BMT	4.64 (1.09, 8.19)	0.010[b]	0.03 (-0.12, 0.17)	0.727

[a] Model adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, transplantation type, history of aGVHD and cGVHD, and history of infection.

[b] indicates the statistical significance for the factors.

Abbreviations: GH, general health; PF, physical functioning; RP, role physical; RE, role emotional; SF, social functioning; BP, bodily pain; VT, vitality; MH, mental health; PWB, physical well-being; FWB, functional well-being; SWB, social well-being; EWB, emotional well-being, FACT-BMT, total with BMT module; TOI, FACT-BMT Trial Outcome Index (TOI).

Recipients of HID reported superior QoL

We next ask if there was difference between recipients of HID- and MSD-HSCT. Compared to MSD-HSCT recipients, HID-HSCT recipients exhibited accelerated recovery in physical dimensions using FACT-BMT form including global FACT score (FACT-G), physical well-being (PWB), social well-being (SWB), functional well-being (FWB) and FACT-BMT Trial Outcome Index (TOI). Using SF-36 form, the HID-HSCT recipients demonstrated superior advantage in GH, and mental dimensions including VT and MH (Table 1). In sum, HID-HSCT recipients demonstrated accelerated recovery of QoL in terms of physical and mental scales and the difference was more remarkable using FACT-BMT Form.

History of aGVHD and CMV reactivation compromised QoL recovery and attenuates the advantage of QoL in HID-HSCT

As more HID-HSCT recipients had a history of acute GVHD/CMV reactivation, we conducted stratified analysis to evaluate the effect of these complications on QoL recovery. In patients without a history of aGVHD, HID-HSCT recipients showed significantly greater recovery in both physical and mental scales especially for GH, SF, VT and MH items (Table 4). For patients with a history of aGVHD, HID-HSCT maintained the advantages albeit at smaller difference in VT and physical dimensions (GH and BP) while demonstrated inferior scores for SF without statistical significance (β= -3.19, 95% CI: -13.36 to 6.98). When FACT-BMT Form was used, HID-HSCT recipients with a history of aGVHD also showed significantly higher FWB subscale score (β = 2.51, 95% CI: 0.19 to 4.85) whereas lost the superiority for the rest of domains (PWB, SWB, FWB, FACT-G, TOI and FACT-BMT).

Table 4
Stratified analysis of QoL between HID and MSD patients in GVHD and no-GVHD groups.

QoL	No aGVHD				aGVHD			
	HSCT (HID vs. MSD)		Time		HSCT (HID vs. MSD)		Time	
	β (95% CI) [a]	P	β (95% CI) [a]	P	β (95% CI) [a]	P	β (95% CI) [a]	P
SF-36								
GH	6.90 (0.08, 13.72)	0.047[b]	0.06 (-0.16, 0.27)	0.608	8.88 (1.06,16.70)	0.026[b]	0.01 (-0.36, 0.38)	0.957
PF	1.67 (-6.36, 9.71)	0.684	0.28 (0.02, 0.54)	0.033[b]	4.00 (-7.33, 15.32)	0.489	0.35 (-0.10, 0.81)	0.127
RP	5.54 (-3.76, 14.84)	0.243	1.06 (0.57, 1.55)	0.000[b]	2.60(-7.14, 12.35)	0.601	0.40(-0.28, 1.08)	0.249
RE	7.91(-4.99, -0.09)	0.23	0.47(-0.09, 1.03)	0.10	13.90 (-0.57, 28.39)	0.06	0.31 (-0.48, 1.09)	0.449
SF	11.99 (2.90, 0.52)	0.010[b]	0.77 (0.52, 1.03)	0.000[b]	-3.19 (-13.36, 6.98)	0.538	0.35 (-0.14, 0.85)	0.162
BP	5.72 (-1.21, 12.64)	0.106	0.11(-0.10, 0.33)	0.308	7.74 (0.22, 15.26)	0.044[b]	0.12 (-0.21, 0.47)	0.480
VT	8.75 (1.67, 15.83)	0.015[b]	0.15(-0.03, 0.34)	0.104	7.66 (0.03, 15.29)	0.049[b]	0.09 (-0.22, 0.42)	0.565
MH	7.78 (2.08, 13.47)	0.007[b]	-0.09 (-0.24, 0.06)	0.217	5.47 (-1.51, 12.45)	0.124	0.10 (-0.17, 0.37)	0.456
FACT-BMT								
PWB	2.35 (0.40, 4.30)	0.018[b]	0.07 (0.01,0.14)	0.023[b]	1.67(-0.68, 4.01)	0.164	0.12 (0.05, 0.19)	0.001[b]

[a] Model adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, transplantation type, history of aGVHD and cGVHD, and history of infection.

[b] indicates the statistical significance for the factors.

Abbreviations: GH, general health; PF, physical functioning; RP, role physical; RE, role emotional; SF, social functioning; BP, bodily pain; VT, vitality; MH, mental health; PWB, physical well-being; FWB, functional well-being; SWB, social well-being; EWB, emotional well-being, FACT-BMT, total with BMT module; TOI, FACT-BMT Trial Outcome Index (TOI).

QoL	No aGVHD				aGVHD			
	HSCT (HID vs. MSD)		Time		HSCT (HID vs. MSD)		Time	
	β (95% CI) [a]	P	β (95% CI) [a]	P	β (95% CI) [a]	P	β (95% CI) [a]	P
SWB	1.46 (-0.17, 3.09)	0.000[b]	0.001 (-0.06, .06)	0.994	0.27(-1.37, 1.93)	0.742	-0.15 (-0.25, − .04)	0.007[b]
EWB	0.85 (-0.62, 2.32)	0.257	-0.02 (-0.06, 0.01)	0.220	0.58(-1.13, 2.30)	0.506	0.01 (-0.04, 0.06)	0.716
FWB	2.33 (0.49, 4.17)	0.013[b]	0.03 (-0.07, 0.14)	0.841	2.51 (0.19, 4.85)	0.034[b]	0.01 (-0.10, 0.12)	0.84
FACT-G	7.49 (2.52, 12.47)	0.003[b]	0.07(-0.14, 0.28)	0.507	4.34 (-1.59, 10.29)	0.151	-0.01 (-0.24, 0.21)	0.887
TOI	3.93(0.78, 7.08)	0.015[b]	0.03 (-0.09, 0.17)	0.554	2.79(-1.40, 6.98)	0.191	0.14(-0.00, 0.29)	0.058
FACT-BMT	6.65 (1.66, 11.64)	0.009[b]	0.01 (-0.19, 0.20)	0.944	3.27 (-2.74, 9.28)	0.286	0.01 (-0.21, 0.24)	0.917

[a] Model adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, transplantation type, history of aGVHD and cGVHD, and history of infection.

[b] indicates the statistical significance for the factors.

Abbreviations: GH, general health; PF, physical functioning; RP, role physical; RE, role emotional; SF, social functioning; BP, bodily pain; VT, vitality; MH, mental health; PWB, physical well-being; FWB, functional well-being; SWB, social well-being; EWB, emotional well-being, FACT-BMT, total with BMT module; TOI, FACT-BMT Trial Outcome Index (TOI).

For patients without a history of CMV reactivation, recipients of HID-HSCT had significantly better scores on the PWB, SWB, FWB, FACT-G, TOI, and FACT-BMT scales using FACT-BMT. However, all these advantages were lost when there was a history of CMV reactivation. When SF36 Form was used, HID-HSCT recipients without CMV reactivation history demonstrated a trend toward worse QoL recovery including PF, RE, SF and VT in the context of CMV reactivation which further confirmed the detrimental effect of CMV infection on QoL (Table 5). In sum, HID-HSCT recipients demonstrated accelerated recovery of QoL but the advantages were compromised by the incidence of aGVHD or CMV reactivation.

Table 5
Stratified analysis of QoL between HID and MSD patients in CMV and no-CMV reactivation groups.

	No CMV Reactivation				CMV Reactivation			
QoL	HSCT (HID vs. MSD)		Time		HSCT (HID vs. MSD)		Time	
	β (95% CI) [a]	P	β (95% CI) [a]	P	β (95% CI) [a]	P	β (95% CI) [a]	P
SF-36								
GH	6.46 (0.24, 12.69)	0.042[b]	0.13 (-0.12, 0.39)	0.305	4.54 (-5.01,14.11)	0.351	-0.03 (-0.31, 0.22)	0.804
PF	6.02 (-1.22, 13.28)	0.103	0.38 (0.09, 0.67)	0.009[b]	-7.22 (-20.77, 6.33)	0.297	0.26 (-0.14, 0.65)	0.200
RP	3.74 (-3.76, 11.25)	0.329	0.97 (0.40, 1.53)	0.001[b]	4.91(-9.04, 18.87)	0.49	0.37 (-0.12, 0.86)	0.135
RE	5.75 (-6.05, 17.55)	0.340	0.52 (-0.09, 1.13)	0.096	-1.18 (-19.07, 16.71)	0.897	-0.10 (-0.69, 0.48)	0.724
SF	6.83 (-1.30, 14.97)	0.099	0.92 (0.54, 1.29)	0.000[b]	-1.22 (-13.19, 10.75)	0.841	0.46 (0.08, 0.85)	0.018[b]
BP	4.12 (-1.75, 9.99)	0.169	0.18 (-0.05, 0.41)	0.129	0.37 (-10.31, 11.05)	0.946	0.10 (-0.24, 0.44)	0.565
VT	8.69 (2.60, 14.78)	0.005[b]	0.19 (-0.01, 0.39)	0.064	-2.12 (-10.76, 6.51)	0.63	0.08 (-0.20, 0.36)	0.582
MH	5.62 (0.25, 10.99)	0.040[b]	-0.04 (-0.20, 0.13)	0.639	1.04 (-6.88, 8.96)	0.797	-0.08 (-0.34, 0.17)	0.530
FACT-BMT								

[a] Model adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, transplantation type, history of aGVHD and cGVHD, and history of infection.

[b] indicates the statistical significance for the factors.

Abbreviations: GH, general health; PF, physical functioning; RP, role physical; RE, role emotional; SF, social functioning; BP, bodily pain; VT, vitality; MH, mental health; PWB, physical well-being; FWB, functional well-being; SWB, social well-being; EWB, emotional well-being, FACT-BMT, total with BMT module; TOI, FACT-BMT Trial Outcome Index (TOI).

	No CMV Reactivation			CMV Reactivation				
PWB	2.09 (0.33, 3.84)	0.020[b]	0.12 (0.06,0.19)	0.000[b]	-0.88 (-3.34, 1.57)	0.482	0.04 (-0.03, 0.11)	0.227
SWB	1.66 (0.23, 3.09)	0.023[b]	-0.05 (-0.13, 0.04)	0.314	2.04 (-0.07, 4.15)	0.058	-0.02 (-0.10, 0.05)	0.497
EWB	0.97 (-0.38, 2.31)	0.161	-0.01 (-0.05, 0.03)	0.644	-0.79(-2.67, 1.08)	0.406	-0.00 (-0.05, 0.04)	0.862
FWB	2.7 (1.01, 4.39)	0.002[b]	0.01 (-0.10, 0.12)	0.841	-0.33 (-3.36, 2.70)	0.83	0.05 (-0.06, 0.17)	0.357
FACT-G	7.78 (3.33, 12.23)	0.001[b]	0.04 (-0.19, 0.28)	0.706	-0.18 (-6.95, 6.59)	0.958	0.08 (-0.11, 0.27)	0.420
TOI	4.21 (1.29, 7.15)	0.005[b]	0.07 (-0.07, 0.22)	0.336	-1.38 (-5.68, 2.91)	0.529	0.10 (-0.02, 0.24)	0.108
FACT-BMT	6.93 (2.44, 11.42)	0.002[b]	0.01 (-0.22, 0.23)	0.957	-9.07 (-7.78, 5.96)	0.796	0.08 (-0.11, 0.28)	0.399

[a] Model adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, transplantation type, history of aGVHD and cGVHD, and history of infection.

[b] indicates the statistical significance for the factors.

Abbreviations: GH, general health; PF, physical functioning; RP, role physical; RE, role emotional; SF, social functioning; BP, bodily pain; VT, vitality; MH, mental health; PWB, physical well-being; FWB, functional well-being; SWB, social well-being; EWB, emotional well-being, FACT-BMT, total with BMT module; TOI, FACT-BMT Trial Outcome Index (TOI).

Combination of SF-36 and FACT-BMT is superior for the evaluation of QoL

As we have shown, either SF-36 or FACT-BMT is competent to describe the longitudinal QoL recovery in long-term survivors of HSCT. However, for the comparison of QoL between HID and MSD-HSCT cohorts, these two evaluation systems exhibited diverse point of focus. SF36 depicted the advantage of HID-HSCT in GH and mental subscales including VT and MH. Otherwise, FACT-BMT showed the accelerated recovery in physical dimensions including global FACT score (FACT-G), physical well-being (PWB), social well-being (SWB), functional well-being (FWB) and FACT-BMT Trial Outcome Index (TOI) in HID-HSCT recipients. The difference for GH and mental domain scores were greater using SF36 whereas superiority in the recovery for functional/physical domains was more profound when FACT-BMT was used. Furthermore, both forms

are able to show the effect of aGVHD and CMV reactivation on QoL recovery despite difference in performance.

Discussion And Conclusions

QoL is a major concern for long-term survivors of HSCT which significantly affect their wellbeing. HID-HSCT is increasingly used due to the shrinking family sizes whereas the apparently higher incidence of complications(19) such as GVHD warrants deeper investigation of the longitudinal recovery of QoL in this setting. However, few longitudinal studies assessed the QoL recovery between recipients of HID-HSCT and MSD-HSCT. In the present study, we combined SF36 and FACT-BMT to establish a comprehensive QoL assessment system in Chinese HSCT patients and found that QoL in physical/functional scales (spanning SF-36 and FACT-BMT) significantly improved with time. Notably, HID-HSCT demonstrated accelerated recovery in QoL including mental scales with SF-36 form and physical scales with FACT-BMT form.

We have previously showed significant recovery of QoL one-year after HSCT using the SF36 form (13). In this study, we aim to optimize treatment-specific tools in our QoL evaluation system by using a comprehensive scale (SF36) and a disease-specific scale (FACT-BMT), which has been adopted for quantifying patient-reported outcomes (20, 21). Combination of the two forms enhances the ability to detect patients' perception of health status and increase comparability in patients specifically associated with HSCT (21). In our study, the two questionnaires demonstrated good correlations in most domains in describing the trend of QoL recovery. Of note, SF36 and FACT-BMT exhibited differential performance in detecting differences in physical and mental dimensions respectively between the two study cohorts. Furthermore, the high response rate and low drop-off rate in the present study confirmed the feasibility to combine SF36 and FACT-BMT for the evaluation of QoL. The high compliance is also attributable to the application of applet which is superior to traditional hard mails by enabling timely notifications and immediate accessibility(20). Hence, combination of these two forms represent a feasible and powerful approach for the evaluation of QoL in recipients of HSCT.

As the largest source of allo-HSCTs in China since the last decade, HID-HSCT has clinical outcomes similar to that of MSD- or MUD-HSCT for patients with AML, ALL, MDS, and SAA(5, 6, 22, 23). HID-HSCT may also be superior for patient with high-risk leukemia or elderly patients with young offspring donors, attributable to an association with lower incidence of relapse(7). The present study confirmed comparable survival between HID- and MSD-HSCT groups despite higher incidence of aGVHD and CMV reactivation in the former. However, concern remains that HID-HSCT may achieve the survival rate at the cost of QoL in view of the higher incidences of post-HSCT complications. To date, limited studies have described the recovery of QoL in recipients of HID-HSCT whereby source of graft did not affect QoL (24, 25). Nevertheless, most studies were performed retrospectively with high heterogeneity in the control groups(10, 11). In this prospective study, we confirm that HID-HSCT has similar or superior recovery of QoL in long-term survivors as compared to the conventional MSD-HSCT. Notably, HID-HSCT patients reported favorable recovery of general health and emotional wellbeing. This is similar to the “post-traumatic growth” theory(26, 27)for example, recipients of allo-HSCT demonstrated better mental status compared to recipients of chemotherapy. In our study, patients receiving HID-HSCT lack matched sibling donors, or experienced more

or severer post-HSCT complications, which represents a traumatic stressor(28). This may partially contribute to the superior QoL recovery in recipients of HID-HSCT.

We furtherly performed stratified analysis to analyze the effect of post-HSCT complications on QoL recovery, as higher incidences of complications such as aGVHD and CMV reactivation in HID-HSCTs with clinical significance. History of GVHD represents a risk factor of inferior QoL post-HSCT(9, 29, 30). Incidence of aGVHD is associated with impaired recovery of physical / functional dimensions(31) which is consistent with our finding. Our results also indicated an inverse association between aGVHD and the recovery of mental health. CMV reactivation remains a common complication despite advances in preemptive interventions and poses significant risk of morbidity and mortality(32). Subsequent CMV infections incur longer hospitalization and profound economic burden(33, 34). To our knowledge, we are the first to demonstrate the detrimental role of CMV reactivation on QoL recovery post-HSCT. In addition to the impairment of longitudinal QoL recovery, the advantages of HID-HSCT on QoL also lost in the context of aGVHD or CMV reactivation. Thus, these complications exert long-term effect on recipients of HSCT in addition to the adverse effect on survival.

In sum, our study provides clear evidence that HID-HSCT can yield a considerate survival rate with ideal quality of life in long-term survivors thus extending the application of this transplant approach. Additionally, SF-36 and FACT-BMT have different performance in the quantification of QoL and combination of both improve the capacity of the evaluation system for QoL after HSCT.

Abbreviations

Allo-HSCT
Allogenic hematopoietic stem cell transplantation
QoL
quality of life
HID-HSCT
haploidentical donor HSCT
SF-36
Mos 36-Item Short-Form Health Survey
FACT-BMT
The Functional Assessment of Cancer Therapy Bone Marrow Transplant
MSD-HSCT
matched sibling donor HSCT
MRD
minimal residual disease
aGVHD
Acute graft versus host disease
cGVHD
Chronic graft versus host disease
PF

physical functioning
RP
role physical
BP
bodily pain
GH
general health
VT
vitality
SF
social functioning
RE
role emotional
MH
mental health
PWB
physical well-being
FWB
functional well-being
SWB
social well-being
EWB
emotional well-being
BMTS
BMT scale
FACT-BMT
total with BMT module
CMV
cytomegalovirus
BMI
body mass index
ECOG score
Eastern Cooperative Oncology Group performance score
OS
overall survival
AML
acute myelogenous leukemia
ALL
acute lymphocte leukemia
MDS/MPN
myelodysplastic syndrome/ Myeloproliferative Neoplasm

AA
Aplastic Anemia
PB
Peripheral Blood
BM
Bone Marrow

Declarations

Ethics approval and consent to participate: All participants signed written informed-consent forms and completed questionnaires online at their earliest convenience. All procedures were in accordance with the ethical standards of the institutional and national research committee (Ethics committee of Blood Disease Hospital, Chinese Academy of Medical Sciences + KT2013019001-EC-1) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institutional review board approved all study procedures and forms.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: W-J.X, E-L. J, and C-P. L designed the research; X-Y. Z and JW analyzed data and wrote the manuscript; Y-Q. L, J.L, B.W, Q-H. Z, W.G, H-J. Z, L.X, G-Y. L collected patient data and managed database. P.Z. contributed to data processing and critically edited the manuscript. Y.H, S-Z. F and M-Z.H contributed expertise, critically reviewed the manuscript and gave final approval. All authors gave final approval for the manuscript.

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Figures

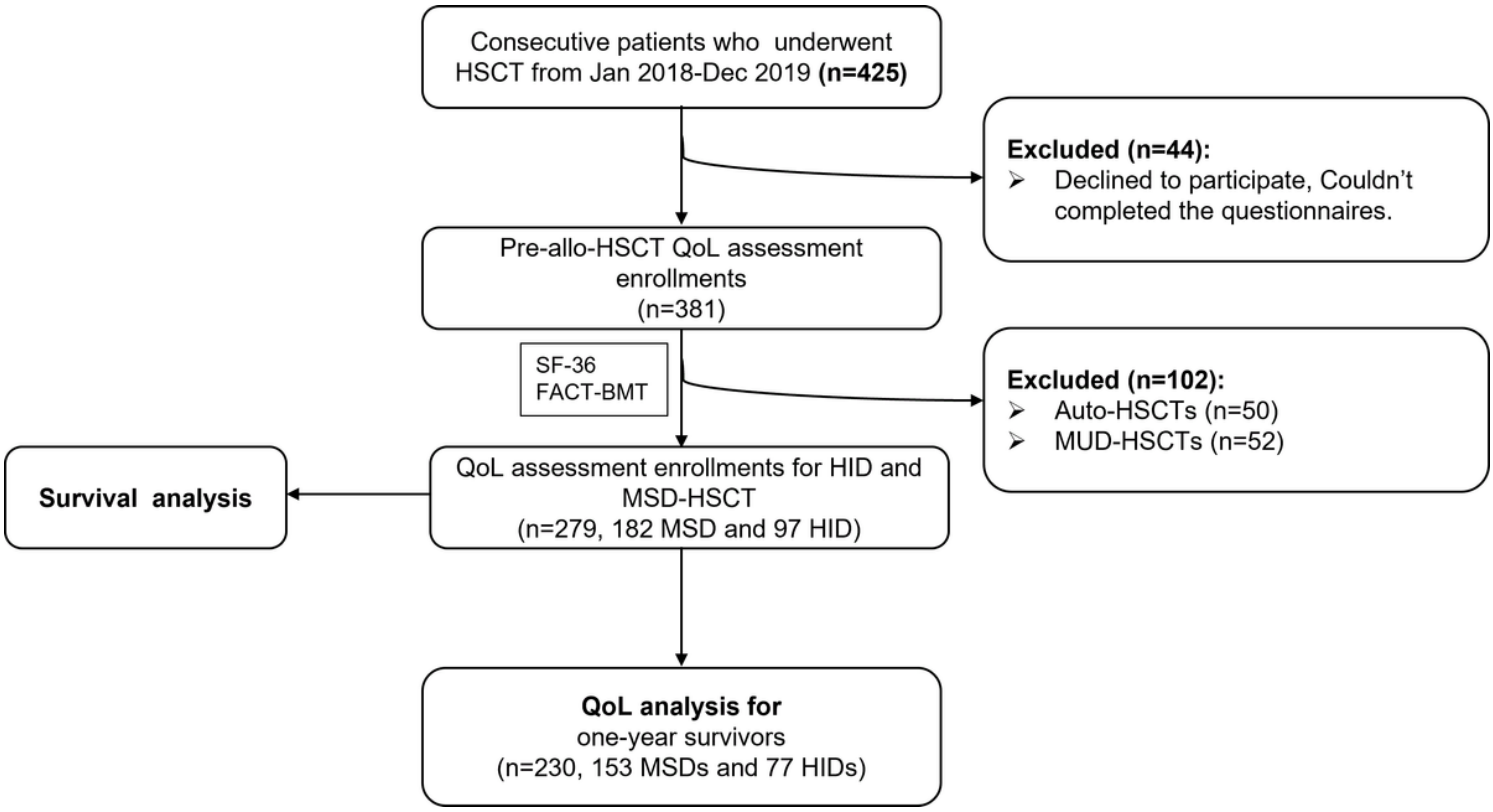

Figure 1

Flowchart of enrollment and analysis of participants.

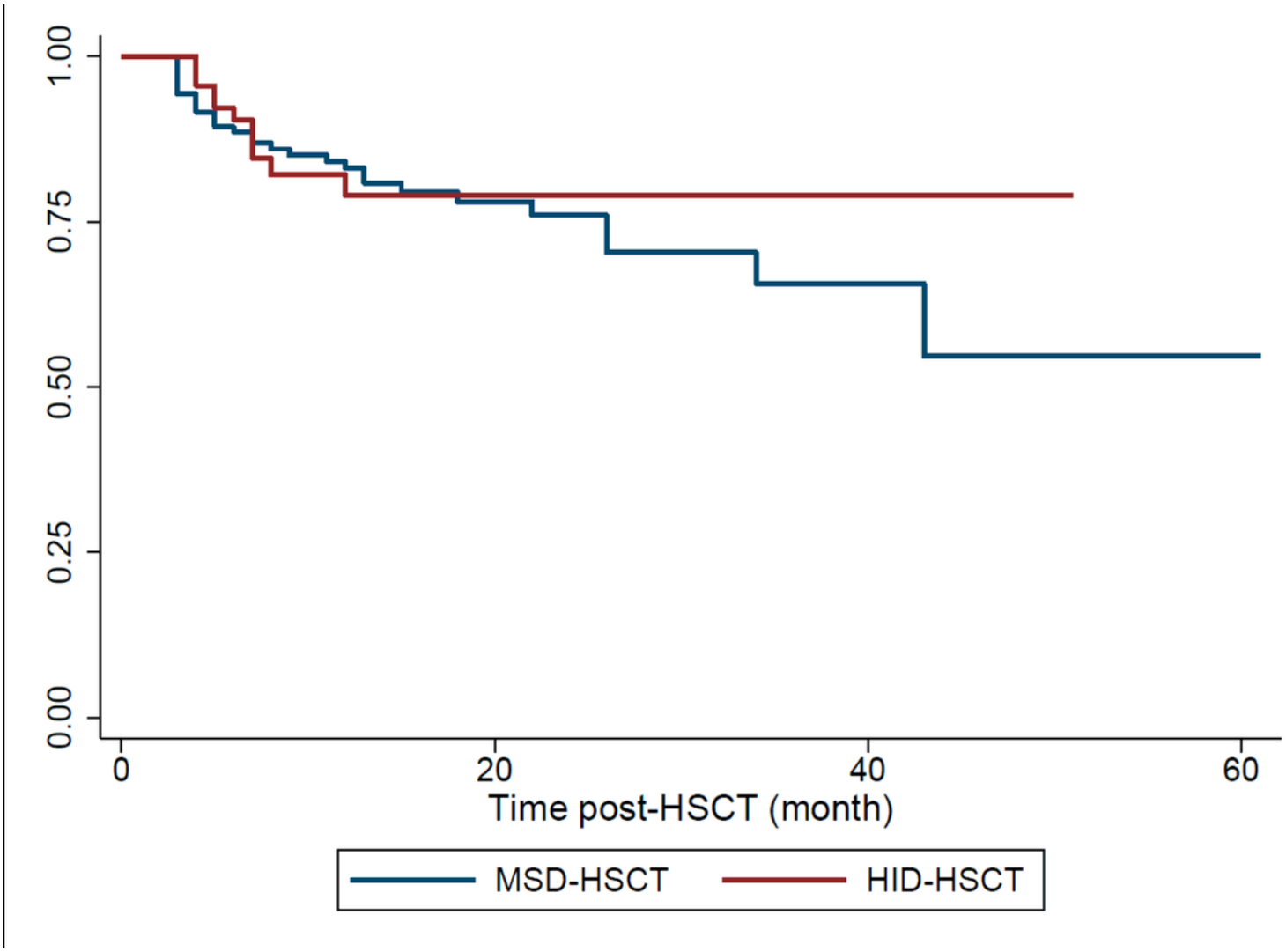

Figure 2

Survival analysis of MSD- and HID-HSCT recipients.

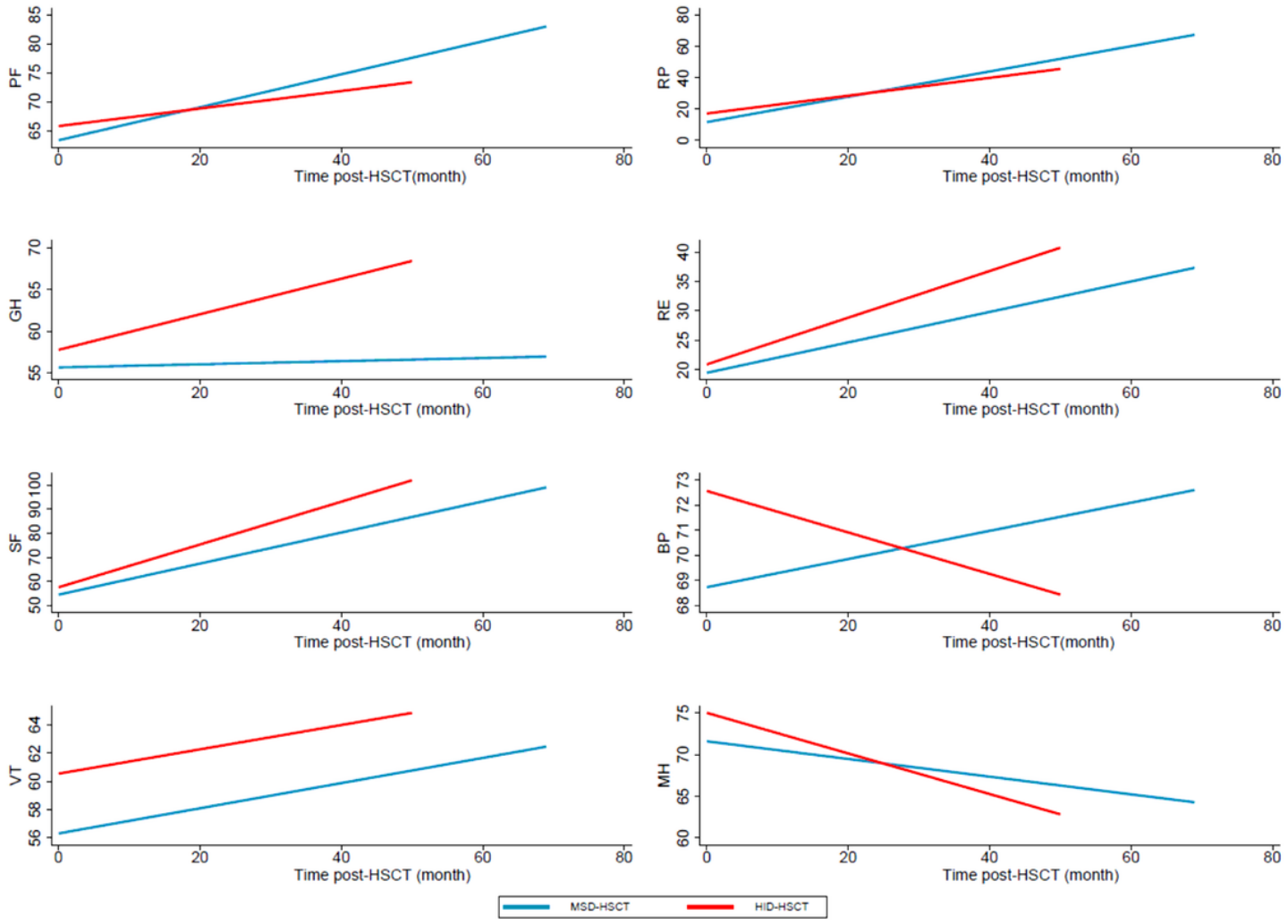

Figure 3

Cognitive trajectories in SF-36 dimensions between MSD- and HID-HSCT groups.

Notes: Trajectories represent β-coefficients from linear mixed-effect models adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, transplantation type, history of aGVHD and cGVHD, and history of infection. MSD-HSCT group as reference group.

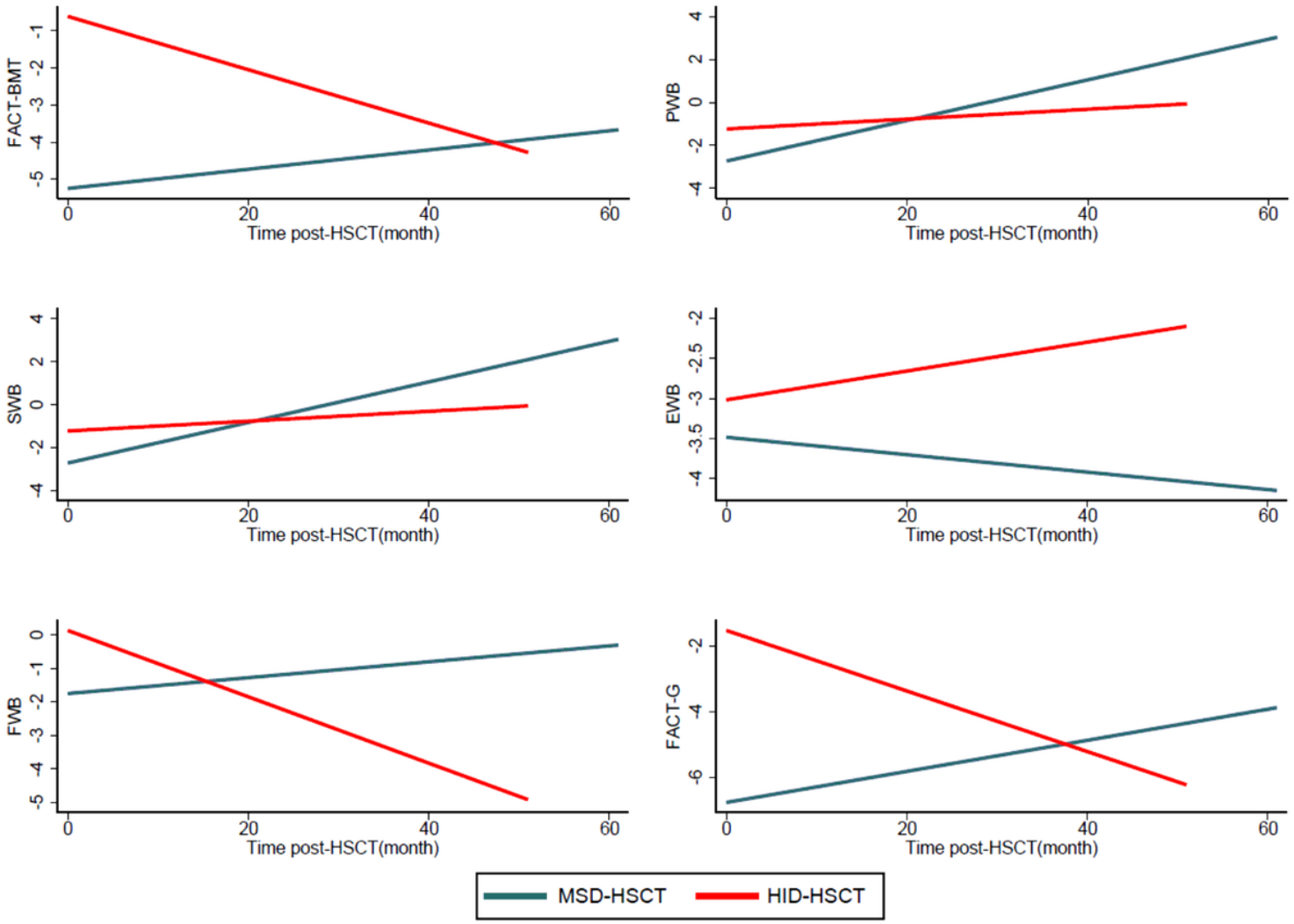

Figure 4

Cognitive trajectories in FACT-BMT dimensions between MSD- and HID-HSCT groups.

Notes: Trajectories represent β-coefficients from linear mixed-effect models adjusted for age, sex, education, body mass index (BMI), main caregivers, diagnosis, transplantation type, history of aGVHD and cGVHD, and history of infection. MSD-HSCT group as reference group.