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RESEARCH PAPER

Does recipient body mass index inform donor selection for allogeneic haematopoietic cell transplantation?

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Summary

It is not known whether obesity has a differential effect on allogeneic haematopoietic cell transplantation outcomes with alternative donor types. We report the results of a retrospective registry study examining the effect of obesity [body mass index (BMI) > 30] on outcomes with alternative donors (haploidentical related donor with two or more mismatches and receiving post-transplant cyclophosphamide [haplo] and cord blood (CBU)] *versus* matched unrelated donor (MUD). Adult patients receiving haematopoietic cell transplantation for haematologic malignancy (2013–2017) (N = 16 182) using MUD (n = 11 801), haplo (n = 2894) and CBU (n = 1487)

were included. The primary outcome was non-relapse mortality (NRM). The analysis demonstrated a significant, non-linear interaction between pretransplant BMI and the three donor groups for NRM: NRM risk was significantly higher with CBU compared to haplo at BMI 25–30 [hazard ratio (HR) 1.66–1.71, $p < 0.05$] and MUD transplants at a BMI of 25–45 (HR, 1.61–3.47, $p < 0.05$). The results demonstrated that NRM and survival outcomes are worse in overweight and obese transplant recipients (BMI ≥ 25) with one alternative donor type over MUD, although obesity does not appear to confer a uniform differential mortality risk with one donor type over the other. BMI may serve as a criterion for selecting a donor among the three (MUD, haplo and CBU) options, if matched sibling donor is not available.

KEYWORDS
allogeneic cell transplant, alternative donor types, cord blood units, haploidentical, non-relapse mortality, obesity

INTRODUCTION

Obesity is a worsening global public health problem.[1] In the United States, the age-adjusted prevalence of obesity in adults was approximately 42% in 2017–2018.[2,3] The impact of obesity on transplant outcomes has been the subject of much investigation.[4] Obesity is defined in several ways, but one commonly accepted definition is body mass index (BMI) of 30 kg/m^2 and above. It is often associated with other comorbid conditions, such as diabetes and cardiovascular diseases, and is generally associated with increased mortality. In the context of haematopoietic cell transplantation (HCT), obesity can be a barrier to a successful procedure. Published data suggest that obesity impacts non-relapse mortality (NRM), overall survival (OS) and disease-free survival (DFS) in both allogeneic HCT[5–8] and autologous HCT settings.[9–11] A Center for International Blood and Marrow Transplant Research (CIBMTR) observational study examined the transplant outcomes in over 4000 acute myeloid leukaemia patients undergoing myeloablative conditioning (MAC) and reported no significant effect of obesity (BMI >30 kg/m^2) on NRM and OS, although underweight (BMI <18 kg/m^2) recipients of related donor allogeneic HCT were found to have decreased OS compared to patients within the normal BMI (18–25 kg/m^2).[12] Another CIBMTR study examined the outcomes in children with severe aplastic anaemia and demonstrated worse OS among overweight (BMI >95th percentile adjusted for age) patients compared to children with a lower BMI (59% vs >70% at two years).[13] Among 3827 unrelated donor transplant recipients in the Japanese transplant registry, a higher BMI was associated with more acute graft-*versus*-host disease (GVHD) and infections, but with similar rates of relapse and OS.[14] HCT-Comorbidity Index (HCT-CI), a commonly used validated risk-assessment tool developed as a scoring system for patients undergoing allogeneic HCT,[15] includes obesity, defined as BMI over 35 kg/m^2, as an independent risk factor for NRM.

While there are significant data evaluating the impact of obesity on post-transplant outcomes, there is a paucity of contemporary data to confirm the differential effect of obesity on transplant outcomes with one donor type over the other. It is not clearly known if obesity affects transplant outcomes with one particular donor type more than or differently from an alternative donor type. A single-centre matched case–control study ($n = 322$) showed an association between obesity (weight over 120% of ideal body weight) and worse survival outcomes after HCT in patients with human leukocyte antigen (HLA)-matched donors, but not with mismatched donors.[6] However, this study had several caveats including small sample size of HLA-matched obese patients, short follow-up, and use of serologic HLA typing. Another single-centre study published in 1995 examined the impact of patient weight on NRM after marrow transplant ($n = 2238$) and showed no significant impact of obesity (weight over 145% of ideal body weight) on outcomes in any subgroup of patients.[16]

With the availability of alternative donor options including haploidentical related donor, and umbilical cord blood units (CBU)[17] in addition to unrelated donors for patients lacking HLA-identical siblings, understanding the

HIGHLIGHTS

1. Increasing body mass index ≥25 (overweight and obese) of allogeneic transplant patients adversely impacts mortality risk associated with umbilical cord blood and T-cell replete haploidentical related donor transplant compared with matched unrelated donor transplant.
2. Body mass index may serve as a criterion for donor selection. For patients with body mass index ≥ 25 with no human leucocyte antigen-matched sibling available, matched unrelated donor may be the preferred choice, followed by haploidentical related donor.

interaction between obesity and donor type may be relevant to pretransplant evaluation of, including donor selection for, obese patients. We, therefore, conducted a retrospective analysis from the observational database of the CIBMTR to examine the effect of obesity on outcomes after transplant with alternative donor types (of haploidentical related and umbilical cord blood units) *versus* matched unrelated donor (MUD). We hypothesized that obesity has a differential effect on transplant outcomes with one donor type over the other: the study hypothesis was that patients with alternative donor types have worse NRM and other survival outcomes with increasing BMI when compared to MUD.

PATIENTS AND METHODS

Data sources

The CIBMTR is a combined research programme of the Medical College of Wisconsin and the National Marrow Donor Program, which consists of a voluntary network of more than 450 transplantation centres worldwide that contribute detailed data on consecutive allogeneic and autologous transplantations to a centralized statistical centre. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information issued in the performance of such research is collected and maintained in the CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule.

Patients

Adult patients who received a first allogeneic HCT for any haematologic malignancy between 2013 and 2017, using the following donors: MUD, defined as 8/8-HLA match in *-A*, *-B*, *-C*, and *-DRB1*; haploidentical related donor (haplo), defined as related donor with two or more mismatches and CBU. Recipients of matched sibling donor and mismatched unrelated donor (defined as <8/8-HLA match) allogeneic HCT, haplo-HCT recipients not receiving post-transplant cyclophosphamide (ptCy), and patients undergoing an *ex vivo* T-cell-depleted and $CD34^+$-selected HCT were excluded. Patients with a BMI of less than 15 or more than 50 (n = 120) were also excluded.

Objective, end-points, and definitions

The study hypothesis was that patients' BMI has a differential effect on outcomes after HCT using one donor type over the other. The primary outcome studied was NRM, defined as time to death from any cause without disease relapse or progression. NRM was summarized as cumulative incidence estimate with disease relapse/progression as competing risk. The secondary outcomes studied were OS, DFS, and disease relapse. OS was defined as time to death from any cause. Patients who were alive were censored at the time of last contact. DFS was defined as time to disease relapse/progression or death from any cause. Patients who were alive were censored at the time of last follow-up. For relapse, NRM was a competing risk. Obesity was defined as a BMI of 30 or higher according to the consensus developed by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC).[18,19]

Statistical analysis

This is a retrospective comparative cohort study comparing outcomes after allogeneic HCT using three donor types for patients with haematologic malignancies. The objective of this analysis was to compare the NRM and other survival outcomes in the three donor groups. The primary end-point of the study was NRM, while relapse, DFS and OS were secondary end-points. Patient-, disease-, and transplant-related characteristics were compared among the three donor groups using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate analysis of outcomes by BMI group was performed for each of the three donor groups. Probabilities of NRM and relapse were calculated by a cumulative incidence function accounting for competing risks of relapse and death respectively. Survival probabilities of DFS and OS were calculated using the Kaplan–Meier estimator and compared using the log-rank test. Comparison of survival curves and cumulative incidence curves was done with the log-rank test and Grey's test respectively, along with point-wise comparisons at day +100, six months, one and two years post HCT. Multivariable analysis of NRM, relapse, DFS, and OS were performed using Cox proportional hazards regression models. All variables were assessed for proportional hazards using graphical and/or time-dependent approaches. Two sets of models were included, treating BMI either as a categorical variable based on traditional cut-offs, or treating BMI as a continuous variable (ranging from 20 through 45, in increments of 5) through the use of splines [e.g. BMI = 20 (±2.5)+, 25 (±2.5), etc.]. We used cubic basis splines (on BMI) defined with three equally spaced knots at 24, 33, and 41. Stepwise model building with a significance level of 0.05 was used to identify variables to be included in the multivariable models. However, interaction terms were kept in the model if their level of significance was less than 0.0025. Main effects of donor and BMI were added to the models after the model building steps were completed. Interactions between donor group and the BMI variable were assessed to examine whether the impact of BMI is consistent or differential across donor types, and if there is a significant interaction, the BMI effects were described in the three donor groups. In addition, three-way interactions between donor, conditioning intensity and BMI, and

two-way interactions between donor and conditioning intensity and BMI and conditioning intensity were examined. Secondary post hoc subgroup analyses were performed to compare outcomes between double cord blood unit (dCBU) transplant recipients and other donor groups, and haplo *versus* MUD recipients of peripheral blood (PB) stem cell graft source. A *p*-value of <0.05 was considered statistically significant. All analyses were performed using SAS v9.4 (SAS Inc., Cary, NC, USA).

RESULTS

Patient characteristics

Patient and transplant characteristics are shown in Table 1. The study cohort included a total of 16 182 patients receiving allogeneic HCT (MUD, *n* = 11 801; haplo, *n* = 2894; CBU, *n* = 1487). There were significant differences in the following baseline characteristics among the donor groups. African-Americans comprised 17% of the haplo and 13% of the CBU, compared to 2% of the MUD group. Myeloablative conditioning (MAC) was more frequently used in the MUD and CBU (51% and 49% respectively) than in the haplo group (39%), whereas non-myeloablative conditioning (NMA) was more common in the haplo (32%) *versus* the MUD (14%) and CBU (18%) groups. The graft source utilized was PB in a greater proportion of the MUD (86%) *versus* the haplo group (66%). The majority of CBU transplant patients received dCBU at transplant (82%). Graft-*versus*-host disease (GVHD) prophylaxis was tacrolimus-based in 80% and cyclosporin-based in 13% of MUD patients, while 43% of the CBU group received tacrolimus-based prophylaxis and 51% received cyclosporin-based prophylaxis. $CD34^+$ cell doses in the grafts were missing for a large number of haplo transplant recipients (41%) *versus* 8% of the MUD and 16% of the CBU groups. *In vivo* T-cell depletion using anti-thymocyte globulin was uncommon in the haplo group (2%), compared to the MUD (35%) and CBU (20%) groups. Table S1 shows the distribution of patients by BMI group (<30, 30–34.9 and ≥35) in the three donor groups. Only 15% (*n* = 63) of the obese CBU recipients received single CBU (Table S2). The median follow-up of survivors was 25, 36 and 36 months in the haplo, MUD and CBU groups respectively.

Results of the primary analysis

Multivariable analysis [after adjusting for age, Karnofsky Performance Score (KPS), race, HCT-CI, disease and disease risk, donor/recipient cytomegalovirus (CMV) serostatus, GVHD prophylaxis, conditioning intensity, *in vivo* T-cell depletion and using BMI as a continuous variable] showed a significant, but non-linear interaction between BMI and donor groups for NRM ($p < 0.0001$), DFS ($p = 0.0002$) and OS ($p < 0.0001$), but not for disease relapse (Tables S3–S6).

Non-Relapse mortality

NRM at two years after haplo, MUD and CBU transplants, regardless of BMI, was 19% [95% confidence interval (95 CI), 18%–21%], 19% (95 CI, 18%–20%) and 29% (95 CI, 27%–31%) respectively ($p < 0.001$) (Table S7). For patients with a BMI of 30–35, two-year NRM was 19% (95 CI, 16%–23%), 18% (95 CI, 17%–20%) and 29% (95 CI, 23%–35%) for the haplo, MUD and CBU group respectively ($p = 0.003$) (Table S8). For BMI >35, two-year NRM was 19% (95 CI, 15%–23%), 21% (95 CI, 19%–24%) and 30% (95 CI, 23%–38%) respectively ($p = 0.03$) (Table S9). Compared to MUD recipients, CBU transplant patients had a significantly increased risk of NRM at a BMI of 25 [hazard ratio (HR), 2.26, $p < 0.0001$]; a BMI of 30 (HR, 2.28, $p < 0.0001$); a BMI of 35 (HR, 1.61, $p = 0.02$); and a BMI of 45 (HR, 3.47, $p = 0.02$). Compared to haplo, CBU had an increased risk of NRM at a BMI of 25 (HR, 1.71, $p = 0.02$), and a BMI of 30 (HR, 1.66, $p = 0.04$). There was no statistically significant difference in NRM between haplo and MUD at any BMI (20–45) (Table 2, Figure 1A). Table S3 shows the additional variables significant for NRM in the multivariable analysis: patients 50 years and older, HCT-CI ≥ 3, KPS < 90, high Refined-Disease Risk Index, chronic myeloid leukaemia/myelodysplasia/myeloproliferative neoplasm, CMV-seropositive donor/recipient, calcineurin inhibitor plus mycophenolate mofetil-based GVHD prophylaxis and MAC regimen were associated with higher NRM risk.

Overall survival

Two-year OS probability was 57% (95 CI, 55%–59%), 58% (95 CI, 57%–59%) and 49% (95 CI, 46%–51%) for the haplo, MUD and CBU groups respectively ($p < 0.001$) regardless of BMI (Table S7). Compared to MUD, CB had a statistically increased mortality risk at a BMI of 25–35 (HR = 1.4–1.8) (Table 2). Compared to haplo, CB had an increased mortality risk at a BMI of 25 (HR = 1.45). Compared to MUD, haplo had an increased mortality risk at a BMI of 25–30 (HR = 1.3). There were no statistically significant differences at other BMIs (Table 2, Figure 1B).

Disease-Free survival

The probability of DFS at two years was 43% (95 CI, 41%–45%), 47% (95 CI, 46%–48%) and 42% (95 CI, 40%–45%) for haplo, MUD and CBU transplants respectively ($p < 0.001$), regardless of BMI (Table 2). Compared to MUD, CBU was associated with approximately 41% increased risk of treatment

TABLE 1 Characteristics of study population by donor type

Characteristic	Haploidentical	Matched unrelated	Cord blood	*p*-Value
No. of patients	2894	11 801	1487	
No. of centres	149	227	121	
Age, median (range)	55 (18–88)	58 (18–83)	50 (18–75)	<0.01[a]
Sex (%)				<0.01[b]
Male	1722 (60)	6832 (58)	778 (52)	
Race (%)				<0.01[b]
White	2004 (69)	10 496 (89)	1019 (69)	
Black or African American	479 (17)	253 (2)	192 (13)	
Asian	165 (6)	307 (3)	118 (8)	
Native Hawaiian/Pacific Islander	15 (1)	19 (0)	13 (1)	
American Indian or Alaska Native	10 (0)	38 (0)	11 (1)	
More than one race	12 (0)	27 (0)	14 (1)	
Ethnicity (%)				<0.01[b]
Hispanic or Latino	356 (12)	620 (5)	214 (14)	
Non-Hispanic or non-Latino	2211 (76)	10 133 (86)	1126 (76)	
Non-resident of the United States	269 (9)	802 (7)	112 (8)	
Karnofsky performance score < 90 (%)	1228 (42)	5047 (43)	511 (34)	<0.01[b]
HCT-CI without obesity (%)				0.01[b]
0	678 (23)	2504 (21)	352 (24)	
1	433 (15)	1590 (13)	226 (15)	
2	416 (14)	1838 (16)	222 (15)	
3	515 (18)	2237 (19)	277 (19)	
4	369 (13)	1517 (13)	177 (12)	
5+	478 (17)	2102 (18)	230 (15)	
BMI (%)				<0.01
Median (range)	28 (16–50)	27 (16–50)	26 (15–48)	
<18.5	45 (2)	177 (1)	31 (2)	
18.5–24.9	875 (30)	3732 (32)	534 (36)	
25–29.9	952 (33)	4183 (35)	506 (34)	
30–34.9	629 (22)	2273 (19)	263 (18)	
35+	393 (14)	1436 (12)	153 (10)	
Refined-Disease Risk Index (%)				<0.01[b]
Low	316 (11)	1078 (9)	134 (9)	
Intermediate	1464 (51)	6317 (54)	851 (57)	
High	752 (26)	3029 (26)	331 (22)	
Very high	141 (5)	416 (4)	50 (3)	
Disease (%)				<0.01[b]
AML	1197 (41)	5003 (42)	732 (49)	
ALL	433 (15)	1508 (13)	292 (20)	
CML	119 (4)	390 (3)	39 (3)	
Other leukaemias	108 (4)	399 (3)	39 (3)	
MDS	447 (15)	2358 (20)	178 (12)	
MPN	83 (3)	590 (5)	14 (1)	
NHL	319 (11)	1114 (9)	148 (10)	
HD	117 (4)	189 (2)	33 (2)	
MM	62 (2)	221 (2)	9 (1)	

TABLE 1 (Continued)

Characteristic	Haploidentical	Matched unrelated	Cord blood	*p*-Value
Non-MM PCD	9 (0)	29 (0)	3 (0)	
Prior autologous transplant (%)	303 (10)	973 (8)	102 (7)	<0.01[b]
Graft source (%)				<0.01[b]
Bone marrow	974 (34)	1606 (14)	0 (0)	
Peripheral blood	1920 (66)	10 195 (86)	0 (0)	
Umbilical cord blood	0 (0)	0 (0)	1487 (100)	
Number of cord blood units (%)				<0.01[b]
1	0 (0)	0 (0)	269 (18)	
2	0 (0)	0 (0)	1218 (82)	
NA	2894 (100)	11 801 (100)	0 (0)	
TBI used in conditioning regimen (%)	2100 (73)	2680 (23)	1245 (84)	<0.01[b]
Conditioning intensity (%)				<0.01[b]
MAC	1142 (39)	6054 (51)	724 (49)	
RIC	823 (28)	4102 (35)	489 (33)	
NMA	929 (32)	1645 (14)	274 (18)	
Donor/recipient sex match (%)				<0.01[b]
M–M	1092 (38)	5169 (44)	71 (5)	
M–F	679 (23)	3251 (28)	71 (5)	
F–M	630 (22)	1644 (14)	59 (4)	
F–F	493 (17)	1700 (14)	55 (4)	
Double cord — recipient M	0 (0)	0 (0)	642 (43)	
Double cord — recipient F	0 (0)	0 (0)	576 (39)	
Double cord — missing	0 (0)	0 (0)	13 (1)	
Missing	0 (0)	37 (0)	0 (0)	
Donor/recipient CMV serostatus (%)				<0.01[b]
+/+	1300 (45)	3289 (28)	53 (4)	
+/–	241 (8)	1287 (11)	32 (2)	
–/+	721 (25)	3889 (33)	64 (4)	
–/–	615 (21)	3277 (28)	38 (3)	
Double cord — recipient +	0 (0)	0 (0)	854 (57)	
Double cord — recipient –	0 (0)	0 (0)	353 (24)	
Double cord — recipient CMV unknown	0 (0)	0 (0)	12 (1)	
Missing	17 (1)	59 (0)	81 (5)	
$CD34^+$ dose, $\times 10^6$/kg (BM only) (%)				<0.01[b]
Median (25th–75th quartile)	2.67 (1.75, 3.88)	2.65 (1.75, 3.91)		
0–1.9	194 (7)	453 (4)		
2–3.9	258 (9)	612 (5)		
4–7.9	123 (4)	304 (3)		
≥8	17 (1)	37 (0)		
NA (PBSC graft)	1920 (66)	10 195 (86)		
Missing	382 (13)	200 (2)		
$CD34^+$ dose, $\times 10^6$/kg (PBSC) (%)				<0.01[b]
Median (25th–75th quartile)	5.12 (4.33, 7.68)	6.39 (4.88, 8.64)		
0–1.9	77 (3)	449 (4)		
2–3.9	156 (5)	958 (8)		
4–7.9	645 (22)	5057 (43)		
≥8	250 (9)	2951 (25)		

(Continues)

TABLE 1 (Continued)

Characteristic	Haploidentical	Matched unrelated	Cord blood	*p*-Value
NA (BM graft)	974 (34)	1606 (14)		
Missing	792 (27)	780 (7)		
$CD34^+$ dose, $\times 10^5$/kg (CBU) (%)				
Single				
Median (IQR)			2.31 (1.33, 4.34)	
0–1.9			84 (6)	
2–3.9			58 (4)	
4–7.9			30 (2)	
≥8			21 (1)	
Missing			76 (5)	
Double				
Median (IQR)			2.24 (1.45, 3.51)	
0–1.9			456 (31)	
2–3.9			378 (25)	
4–7.9			152 (10)	
≥8			63 (4)	
Missing			169 (11)	
GVHD prophylaxis (%)				<0.01[b]
TAC + MMF ± others	0	1381 (12)	508 (34)	
TAC + MTX ± others (not MMF)	0	6841 (58)	26 (2)	
TAC ± others (not MMF, MTX)	0	1214 (10)	109 (7)	
CSA + MMF ± others (not TAC)	0	650 (6)	736 (50)	
CSA + MTX ± others (not MMF,TAC)	0	853 (7)	6 (<1)	
CSA ± others (not TAC, MMF, MTX)	0	91 (<1)	11 (<1)	
Other GVHD prophylaxisc	0	125 (1)	79 (5)	
Posttransplant cyclophosphamide ± others	2844 (100)	579 (5)	7 (1)	
ATG/alemtuzumab (%)				<0.01[b]
ATG + alemtuzumab	54 (2)	4086 (35)	279 (19)	
ATG alone	0 (0)	1 (0)	0 (0)	
Alemtuzumab alone	2812 (97)	7052 (60)	1202 (81)	
Missing	28 (1)	662 (6)	6 (0)	
Year of transplant (%)				<0.01[b]
2013	104 (4)	1146 (10)	231 (16)	
2014	369 (13)	2558 (22)	375 (25)	
2015	615 (21)	2585 (22)	343 (23)	
2016	835 (29)	2744 (23)	302 (20)	
2017	971 (34)	2768 (23)	236 (16)	

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ATG, anti-thymocyte globulin; BM, bone marrow; BMI, body mass index; CBU, cord blood unit; CML, chronic myeloid leukaemia; CMV, cytomegalovirus; CSA, cyclosporine; GVHD, graft-*versus*-host disease; HCT-CI, haematopoietic cell transplantation-comorbidity index; HD, Hodgkin lymphoma; IQR, interquartile range; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MM, multiple myeloma; MMF, mycophenolate mofetil; MPN, myeloproliferative neoplasm; MTX, methotrexate; *N*, number; NA, not applicable; NHL, non-Hodgkin lymphoma; NMA, nonmyeloablative conditioning PBSC, peripheral blood stem cells; PCD, plasma cell disorders; RIC, reduced-intensity conditioning; TAC, tacrolimus.

Hypothesis testing: [a]Kruskal-Wallis test; [b]Pearson chi-square test.

[c]Other GVHD prophylaxis: MMF or MTX + siro: $n = 84$; missing: $n = 120$.

failure at a BMI of 25 (HR, 1.41, $p = 0.005$) and a BMI of 30 (HR, 1.42, $p = 0.006$) (Table 2, Figure 1C). There were no significant differences at other BMIs, nor between the other donor groups.

Relapse

The cumulative incidence of disease relapse at two years was 38% (95 CI, 37%–40%), 34% (95 CI, 33%–35%) and 29% (95

TABLE 2 Multivariable analysis: Interaction between BMI as a continuous variable and donor type[a]

Label	Hazard ratio	95% Hazard ratio confidence limits		Adjusted *p*-value[b]
NRM	1.000			***<0.0001***
Haplo vs MUD at BMI = 20	1.250	0.882	1.770	0.4923
Haplo vs MUD at BMI = 25	1.318	1.015	1.710	0.1557
Haplo vs MUD at BMI = 30	1.375	1.065	1.775	0.0724
Haplo vs MUD at BMI = 35	1.224	0.920	1.628	0.4632
Haplo vs MUD at BMI = 40	1.082	0.723	1.618	0.7314
Haplo vs MUD at BMI = 45	1.279	0.638	2.567	0.7314
CBU vs Haplo at BMI = 20	1.152	0.711	1.868	0.5652
CBU vs Haplo at BMI = 25	1.712	1.175	2.494	***0.0250***
CBU vs Haplo at BMI = 30	1.657	1.135	2.418	***0.0375***
CBU vs Haplo at BMI = 35	1.319	0.862	2.020	0.3711
CBU vs Haplo at BMI = 40	1.514	0.836	2.742	0.3711
CBU vs Haplo at BMI = 45	2.709	0.971	7.561	0.1852
CBU vs MUD at BMI = 20	1.440	0.991	2.092	0.0882
CBU vs MUD at BMI = 25	2.256	1.699	2.995	***<0.0001***
CBU vs MUD at BMI = 30	2.278	1.705	3.043	***<0.0001***
CBU vs MUD at BMI = 35	1.615	1.155	2.258	***0.0166***
CBU vs MUD at BMI = 40	1.638	1.010	2.656	0.0882
CBU vs MUD at BMI = 45	3.466	1.470	8.175	***0.0166***
OS	1.000			***0.0002***
Haplo vs MUD at BMI = 20	1.231	0.985	1.538	0.1857
Haplo vs MUD at BMI = 25	1.267	1.069	1.503	***0.0334***
Haplo vs MUD at BMI = 30	1.263	1.068	1.494	***0.0334***
Haplo vs MUD at BMI = 35	1.215	1.008	1.465	0.1397
Haplo vs MUD at BMI = 40	1.133	0.869	1.477	0.5802
Haplo vs MUD at BMI = 45	1.154	0.735	1.812	0.5802
CBU vs Haplo at BMI = 20	0.856	0.611	1.201	0.6337
CBU vs Haplo at BMI = 25	1.446	1.105	1.891	***0.0350***
CBU vs Haplo at BMI = 30	1.389	1.056	1.828	0.0762
CBU vs Haplo at BMI = 35	1.176	0.864	1.600	0.6337
CBU vs Haplo at BMI = 40	1.357	0.891	2.067	0.4364
CBU vs Haplo at BMI = 45	1.512	0.662	3.450	0.6337
CBU vs MUD at BMI = 20	1.054	0.800	1.389	0.7090
CBU vs MUD at BMI = 25	1.832	1.478	2.271	***<0.0001***
CBU vs MUD at BMI = 30	1.755	1.403	2.195	***<0.0001***
CBU vs MUD at BMI = 35	1.429	1.105	1.847	***0.0235***
CBU vs MUD at BMI = 40	1.537	1.075	2.197	0.0537
CBU vs MUD at BMI = 45	1.744	0.826	3.683	0.2630
DFS	1.000			***0.0002***
Haplo vs MUD at BMI = 20	1.130	0.933	1.369	0.5003
Haplo vs MUD at BMI = 25	1.191	1.029	1.377	0.0927
Haplo vs MUD at BMI = 30	1.172	1.015	1.353	0.1238
Haplo vs MUD at BMI = 35	1.144	0.974	1.343	0.3134
Haplo vs MUD at BMI = 40	1.065	0.846	1.341	0.8300
Haplo vs MUD at BMI = 45	1.022	0.680	1.536	0.9184
CBU vs Haplo at BMI = 20	0.832	0.613	1.129	0.6028

(Continues)

TABLE 2 (Continued)

Label	Hazard ratio	95% Hazard ratio confidence limits		Adjusted *p*-value[b]
CBU vs Haplo at BMI = 25	1.187	0.927	1.519	0.5361
CBU vs Haplo at BMI = 30	1.211	0.942	1.557	0.4742
CBU vs Haplo at BMI = 35	1.023	0.772	1.356	0.8748
CBU vs Haplo at BMI = 40	1.115	0.754	1.649	0.7980
CBU vs Haplo at BMI = 45	1.343	0.623	2.894	0.7980
CBU vs MUD at BMI = 20	0.940	0.727	1.215	0.6835
CBU vs MUD at BMI = 25	1.413	1.150	1.735	***0.0054***
CBU vs MUD at BMI = 30	1.419	1.147	1.755	***0.0057***
CBU vs MUD at BMI = 35	1.170	0.919	1.490	0.5420
CBU vs MUD at BMI = 40	1.188	0.844	1.671	0.6835
CBU vs MUD at BMI = 45	1.372	0.681	2.764	0.6835

BMI, body mass index; CBU, cord blood unit; DFS, disease-free survival; haplo, haploidentical related donor transplant; MUD, matched unrelated donor transplant; NRM, non-relapse mortality; OS, overall survival.

[a]Adjusting for age, Karnofsky Performance Score , haematopoietic cell transplantation-comorbidity Index, disease and disease risk, donor/recipient cytomegalovirus sero-status, graft-*versus*-host disease prophylaxis, conditioning intensity, *in vivo* T-cell depletion.

[b]*p*-Values were adjusted to control for multiplicity using the method of Westfall[24,25] and are statistically significant at the 0.05 level for all comparisons.

CI, 27%–31%) for the haplo, MUD and CBU groups respectively ($p < 0.001$), regardless of BMI (Table S7). While there was no interaction found between BMI and donor source for relapse, a significant interaction was observed between BMI and conditioning intensity for relapse ($p < 0.0001$) (Table S10, Figure S1). Reduced-intensity conditioning (RIC) had a significantly higher risk of relapse (*versus* MAC) at a BMI of 25 (HR, 1.14, $p = 0.04$) and 40 (HR, 1.38, $p = 0.03$), and NMA had a higher risk of relapse *versus* MAC at a BMI of 25 to 40 (HR ranging from 1.22–1.71, $p < 0.05$) and *versus* RIC at a BMI of 25, 30 and 35 (HR ranging from 1.18–1.35, $p < 0.05$).

Secondary analyses

A post hoc subgroup analysis was conducted after excluding patients receiving a single CBU to identify if the outcomes with dCBU were differently influenced by recipient BMI, adjusting for the centre effect for each outcome. This multivariable analysis demonstrated a significant interaction between BMI and donor group for NRM ($p = 0.0005$), OS ($p = 0.0007$) and DFS ($p = 0.002$): the outcomes after dCBU (*versus* haplo and *versus* MUD) were no longer significantly different at any BMI, and haplo recipients had a significantly higher risk of NRM (*versus* MUD) at a BMI of 25–30 (HR, 1.35–1.49, $p < 0.05$), and had a significantly worse OS at a BMI of 20–35 (HR, 1.26–1.34, $p < 0.05$) (Table S11). In addition, we performed a subgroup analysis comparing the outcomes between patients receiving PB stem cell graft for MUD *versus* haplo transplants and demonstrated no interaction between BMI and donor type for NRM and OS. For *all* BMIs tested, HR for death (in multivariable analysis) for NRM [1.05–1.50] and OS [1.02–1.27]) was numerically higher for the haplo group (contrasting with HR values for haplo *versus* MUD in the primary analysis: 1.08–1.37 for NRM and 1.13–1.27 for OS) but did not meet statistical significance (Table S12).

DISCUSSION

In this large registry-based retrospective analysis of adult recipients of allogeneic HCT using one of the three donor types (haplo, MUD and CBU) for treatment of haematologic malignancies, we have demonstrated that obesity in transplant recipients, as defined by BMI at the time of transplant, has a differential effect on mortality among recipients of CBU and haplo transplants, although level of significance was met only for certain BMI ranges. Moreover, it appears that obesity does not have a consistent or uniform effect on mortality risk with CBU and haplo (*versus* MUD). We observed a non-linear pattern ('saddle-shaped' or 'N-shaped') of hazard for NRM with haplo (*versus* MUD) and CBU (*versus* haplo and *versus* MUD): in general, with increasing BMI, we observed a trend for increasing mortality risk at a BMI of 25–30, followed by a plateauing or declining trend with higher BMI, and then a further increase in risk towards the end of the BMI spectrum of the study. The secondary subgroup analysis displayed no statistically significant difference in survival outcomes between dCBU *versus* haplo and dCBU *versus* MUD groups at any BMI, even though the hazards of death with dCBU were numerically similar that for to the overall CBU group in the primary analysis. For non-obese patients (BMI = 20–25), there was no significant difference in outcomes between any two donor types in any of the analyses.

It is important to clarify that the study did not attempt to identify the impact of BMI on outcomes after allogeneic HCT using a particular donor, but hypothesized the presence of an interaction between pretransplant BMI and donor type for NRM and other survival outcomes. Since the study did not compare outcomes in HCT recipients with different BMI within a donor group, we cannot comment on the effect of BMI on mortality risk after MUD transplant or alternative donors of haplo or CBU individually.

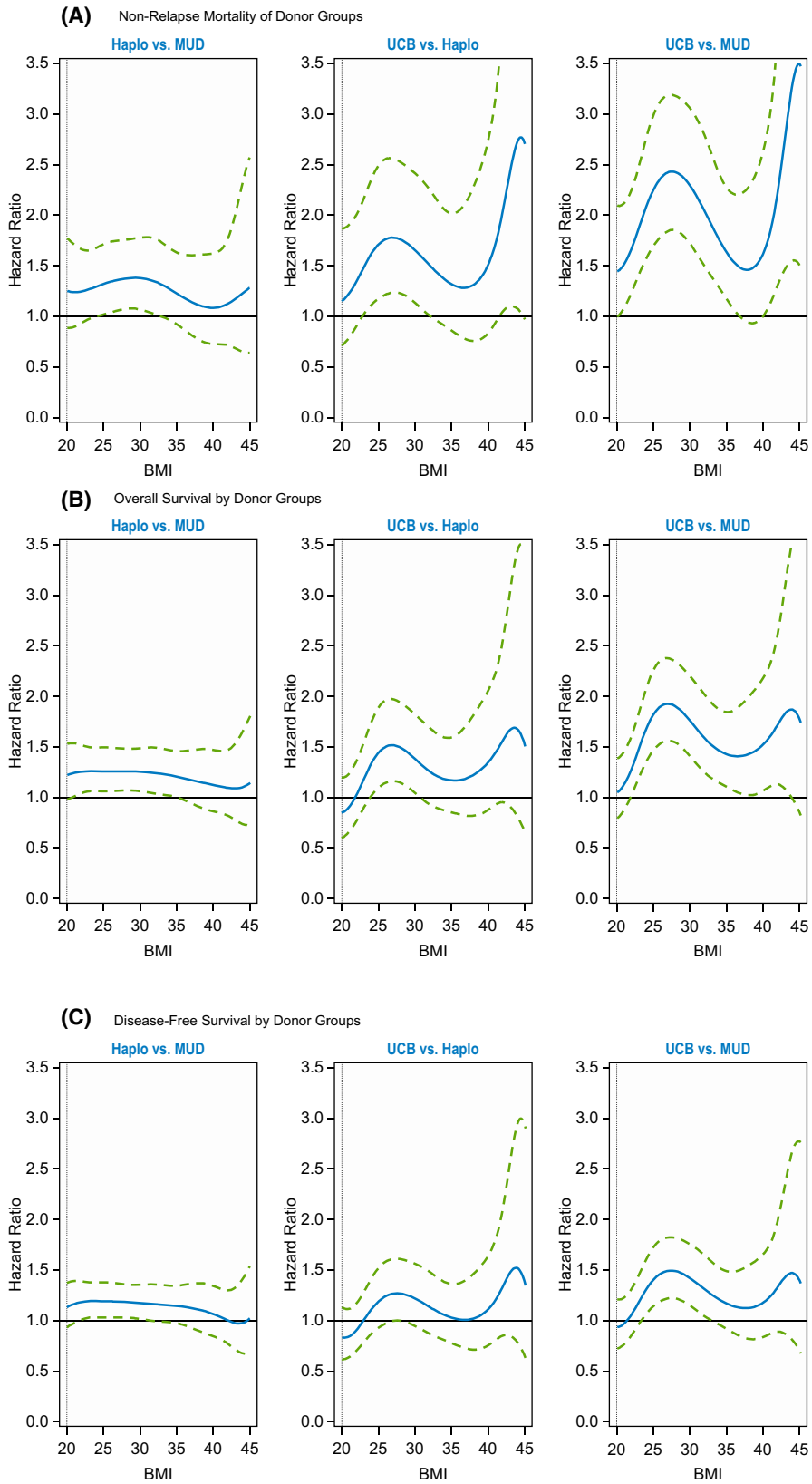

FIGURE 1 Interaction between body mass index of the allogeneic transplant recipient and donor type (matched unrelated donor, umbilical cord blood, and haploidentical related donor) for transplant outcomes. (A) Non-relapse mortality of donor groups. (B) Overall survival by donor groups. (C) Disease-free survival by donor groups [Colour figure can be viewed at wileyonlinelibrary.com]

This is the first contemporary study to examine the presence of a differential effect of obesity on transplant outcomes after alternative donor type compared to MUD. It was anticipated that the differential effect of obesity on outcomes after one of the alternative donors, if present, will provide new insight into the donor selection process for obese patients. The results suggest that BMI, in fact, has a differential effect on outcomes after alternative donor transplant. We observed significantly, but not uniformly, worse NRM and survival outcomes in overweight and obese transplant recipients with one alternative donor type over MUD. The analysis, therefore, suggests that for obese patients, or overweight patients (BMI = 25–29.9) for that matter, with no HLA-matched sibling available, MUD may be the preferred choice.

The secondary analysis showed no significantly worse NRM in dCBU patients, when compared to MUD and haplo recipients. We do acknowledge that improved outcomes with dCBU have been demonstrated in prior studies.[20,21] These results might suggest that the significantly higher mortality in the CBU cohort was due to the inclusion of single units in the CBU group, and may be partially explained by the low $CD34^+$/total nucleated cell (TNC) dose received by adult transplant recipients with higher BMI. However, the fact that the mortality risk was still the same for dCBU as in the primary analysis, as evidenced by the HR values, suggests that the removal of single CBU for the cohort may have resulted in a loss of power to demonstrate statistical significance. The delayed neutrophil recovery in the CBU subgroups with a BMI of 30–35 and >35 (28-day recovery in 78% and 69% patients respectively, compared to 92% and 88% respectively, in haplo and 97% in MUD group; Tables S8 and S9) may also be suggestive of the effect of low $CD34^+$/TNC dose in obese CBU recipients.

The study has a few limitations, including its retrospective nature, the potential for unrecognized biases and residual confounding despite a carefully conducted multivariable analysis adjusting for several variables. The registry does not capture the reason for using haplo *versus* CBU as donor. Some institutions/physicians possibly preferred an alternative donor type, over other options including MUD. It is also possible that BMI itself factored into donor selection, which could also have confounded the results. The only possible way to circumvent these biases is to conduct a prospective randomized clinical trial. Another limitation is that conditioning dose adjustments for higher BMIs used by transplant centres could not be ascertained from the registry database. The study results cannot inform whether the outcomes were worse in haplo and cord blood recipients with higher BMIs due to lower $CD34^+$ cell dose in the respective grafts. $CD34^+$ cell doses infused during transplant were not available for the majority of haplo patients. In addition, the post hoc subgroup analyses demonstrating that dCBU patients had numerically equivalent risks of NRM as the overall CBU cohort (based on HR values, though not meeting the significance threshold), and haplo recipients of PB stem cell grafts had worse NRM and OS compared to MUD patients receiving a PB graft (numerically higher HRs, though not statistically significant) suggest that differences in $CD34^+$ cell doses are likely not the primary reason for differences observed in the outcomes. The decrease in sample size for the subgroup analyses may have resulted in loss of statistical significance.

Conditioning regimen dosing in the study may have been based on actual body weight or adjusted ideal body weight[22] and as a result, the outcomes may have been confounded by chemotherapy dose adjustments made for obese patients. In addition, obesity may have affected the choice of conditioning intensity in that obese patients may have been more likely to receive reduced-intensity or non-myeloablative conditioning, thereby affecting relapse risk. Another caveat is using BMI as a surrogate for obesity, which is not the most accurate measure. Calculating BMI to assess body fat indirectly,[23] while convenient, has flaws — a key limitation being that BMI cannot differentiate between bone density, muscle mass, and body fat. Furthermore, BMI may not necessarily reflect age-related changes of increase in body fat, with a decrease in muscle mass. The sensitivity and specificity of BMI are low.[23] In addition, the correlation between BMI and body fat percentage is non-linear and is different in men and women. The study did not examine the effect of obesity on the incidence and severity of GVHD and infections with the three donor types, and that can be construed as a limitation of the study. Children and adolescents (<18 years) were not included in this study, and so the results are not applicable to this patient population.

It is difficult to provide a simple explanation for the 'saddle-' or 'N-shaped' survival curves with varying degrees of slopes displaying BMI–donor type interactions. We speculate that more careful patient selection may be the reason for the characteristic mortality trend in patients with a BMI above 35, despite having similar HCT-CI scores, but with BMI approaching the upper limit of the spectrum (45–50), the presence of comorbidities accompanying morbid obesity may have resulted in higher mortality risk. It is worth noting that mismatched unrelated donors (MMUD) were not included in the study given the traditionally inferior survival in MMUD transplant recipients with conventional GVHD prophylaxis and the small number of patients with ptCy-based GVHD prophylaxis after MMUD transplant. Matched siblings are, by far, the preferred donors, and if one is not available, then the donor is usually selected from the available unrelated and alternative donor options. So, in order to reduce the bias in the study, it was logical to use MUD instead of matched sibling donors as a control group for analysis with the two alternative donor groups. The great majority of MUD patients received calcineurin inhibitor-based GVHD prophylaxis, and therefore, we cannot comment on the effect of obesity on MUD recipients with ptCy-based prophylaxis. We also evaluated the effect of race on outcomes after transplants using the three donor types: race was forced into the multivariable models, and was not found to be a significant covariate (Table S13).

In summary, this registry study showed differential effect of obesity on survival outcomes after allogeneic HCT among haplo and CBU recipients, as compared to MUD

transplant recipients. It is apt to state that increased BMI does confer a greater mortality risk, albeit in a non-uniform manner, after allogeneic HCT with an alternative donor over MUD. In the absence of prospective clinical trial data, the study results support including patients' BMI in the donor selection process in patients without matched sibling donor and, if the available options are matched, unrelated, haploidentical related and umbilical cord blood. The choice of donor for obese patients is less clear if it is between MUD and haplo.

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AUTHOR CONTRIBUTION

Mouhamed Yazan Abou-Ismail, Gayathri Ravi, Leland Metheny III, Marcos de Lima, Raphael Fraser and Saurabh Chhabra designed the study, Mariam Allbee-Johnson acquired the data, Raphael Fraser, Kwang Woo Ahn, Mariam Allbee-Johnson, Mouhamed Yazan Abou-Ismail, Leland Metheny III, Gayathri Ravi, Marcos de Lima and Saurabh Chhabra analysed and interpreted the data, and Mouhamed Yazan Abou-Ismail and Saurabh Chhabra drafted the manuscript. Saurabh Chhabra, Mohamed L. Sorror, Bipin N. Savani, and Edward A. Stadtmauer critically reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

CONFLICTS OF INTEREST

Leland Metheny III reports grants or contracts from Pfizer, consulting fees from Gamida Cell, payment or honoraria from Incyte, Takeda and, Tiaho, and participation on a Data Safety Monitoring Board or Advisory Board from Gamida Cell. Marcos de Lima reports grants from Pfizer, grants from Celgene, personal fees from Kadmon, personal fees from Pfizer, personal fees from Incyte, and personal fees from BMS, outside the submitted work. Akshay Sharma reports grants or contracts from CRISPR therapeutics, consulting fees from Spotlight Therapeutics and Medexus, Inc., payment or honoraria from Vindico Medical Education, and clinical trial site PI, and support paid to the institution from Novartis, CRISPR Therapeutics, and Vertex Pharmaceuticals. Taiga Nishihori reports research support for clinical trials to the institution from Novartis and research support (drug supply) for clinical trials to the institution from Karyopharm, both outside of the current work. Saurabh Chhabra reports payment or honoraria from GSK, and research support for clinical trials to the institution from Amgen, Janssen and Sanofi.

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