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ORIGINAL ARTICLE

# Baseline body mass index among children and adults undergoing allogeneic hematopoietic cell transplantation: clinical characteristics and outcomes

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Obesity is an important public health problem that may influence the outcomes of hematopoietic cell transplantation (HCT). We studied 898 children and adults receiving first-time allogeneic hematopoietic SCTs between 2004 and 2012. Pretransplant body mass index (BMI) was classified as underweight, normal weight, overweight or obese using the WHO classification or age-adjusted BMI percentiles for children. The study population was predominantly Caucasian, and the median age was 51 years (5 months–73 years). The cumulative 3-year incidence of nonrelapse mortality (NRM) in underweight, normal weight, overweight and obese patients was 20%, 19%, 20% and 33%, respectively. Major causes of NRM were acute and chronic GVHD. The corresponding incidence of relapse was 30%, 41%, 37% and 30%, respectively. Three-year OS was 59%, 48%, 47% and 43%, respectively. Multivariate analysis showed that obesity was associated with higher NRM (hazard ratio (HR) 1.43, $P=0.04$) and lower relapse (HR 0.65, $P=0.002$). Pretransplant plasma levels of ST2 and TNFR1 biomarkers were significantly higher in obese compared with normal weight patients ($P=0.04$ and $P=0.05$, respectively). The increase in NRM observed in obese patients was partially offset by a lower incidence of relapse with no difference in OS.

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## INTRODUCTION

Overweight or obesity is a complex, multifactorial chronic disease that arises from social, behavioral, economic, cultural, physiological and genetic factors.[1] The prevalence of overweight and obesity has increased substantially since the 1960s, resulting in a broad range of health problems and economic consequences.[2–5] An estimated 1.4 billion adults (ages 20 and older) worldwide are overweight or obese, with an additional 170 million overweight or obese children and adolescents, one quarter of whom are under the age of five.[6,7] Evidence-based research has demonstrated the relationship between obesity and high blood pressure, elevated cholesterol, type 2 diabetes, stroke, congestive heart failure, coronary heart disease, osteoarthritis, sleep apnea and respiratory problems, as well as various cancers.[2] As such, overweight and obesity place individuals at very high risk for morbidity and mortality.[8]

In the allogeneic hematopoietic cell transplantation (HCT) setting, pretransplant comorbidities have shown prognostic associations with acute GVHD and subsequent mortality.[9] The HCT comorbidity index (HCT-CI) is a tool that assigns a pretransplant score for various organ dysfunctions, including pulmonary, hepatic, cardiac and renal comorbidities.[10,11] Obesity is also included as one of the comorbidities and a score is assigned based on BMI $>35$ kg/m$^2$ in adults or BMI for age of the 95th percentile or higher in children. Although the role of obesity as an independent risk factor on allogeneic transplant outcomes, such as GVHD, relapse, nonrelapse mortality (NRM) and OS, has been previously explored by several groups, inconsistencies have been reported depending on the study population.[12–24] Recently, plasma biomarkers predictive of GVHD and NRM have been identified.[25–27] However, none of these studies examined biomarkers according to BMI categories.

In the present study, we measured pretransplant BMI of pediatric and adult patients undergoing allogeneic HCT. On the basis of the greater risk for morbidity and mortality in overweight and obesity, we hypothesized that allogeneic HCT recipients with increased pretransplant BMI would have high risk of GVHD and NRM, resulting in inferior OS, compared with normal weight patients. The study design included a retrospective cohort analysis of allogeneic HCT patients and their outcomes stratified by BMI at a single institution over a 9-year study period. Plasma biomarkers were also measured in patient samples prospectively and compared across BMI categories relative to normal weight patients.

## MATERIALS AND METHODS

### Literature review

We used PubMed/MEDLINE and Google Scholar to identify previously published peer-reviewed articles on the risk of BMI in outcomes after allogeneic HCT. The search was restricted to studies published in the English language between January 1994 and May 2014. We applied the

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following MeSH terms in the search: ('obesity,' OR 'overweight' OR 'body mass index') AND ('stem cell transplant' OR 'bone marrow transplant'). The initial search yielded 23 manuscripts. Ten were excluded immediately, because they contained either autologous[9] or syngeneic[1] transplants. Two co-authors (MG and SWC) read the full text of the 13 remaining papers. Supplementary Table S1 summarizes key outcomes from each of the studies.

### Definition of BMI

BMI was calculated as weight (kg) divided by height (m) squared.[28] The index was used either as a categorical variable to evaluate hazard ratios (HRs) and 95% confidence intervals (CIs). For adult patients (age $\geqslant$ 18 years), the categories were defined according to the WHO:[29] underweight (BMI $<$ 18.5 kg/m$^2$), normal weight (BMI 18.5–24.9 kg/m$^2$), overweight (BMI 25.0–29.9 kg/m$^2$) and obese (BMI $\geqslant$ 30.0 kg/m$^2$). For children and adolescents (ages $<$ 18 years), age-adjusted BMI were compared with the CDC BMI for age group charts to obtain percentile rankings. Categories were defined as previously described:[30] underweight (BMI $<$ 5th percentile), normal weight (BMI 5th—84.9th percentile), overweight (BMI 85th—94.9th percentile) and obese (BMI $\geqslant$ 95th percentile).

### Study design

A retrospective cohort study was conducted of 988 consecutive allogeneic HCT performed between 1 January 2004 and 31 December 2012. The study was approved by the University of Michigan Institutional Review Board (IRB). Only first-time allogeneic HCT were included; 41 patients with prior allogeneic transplants were therefore excluded. Fifty-six patients who received umbilical cord blood transplants were excluded *a priori* to reduce potential confounding. The total study population was 898 patients. Height and weight information, documented within 2 weeks before the transplant procedure (day 0), was retrieved from the University of Michigan's electronic health record (EHR). The BMI was computed for each individual, as described above. Outcomes of the study included OS and the cumulative incidences of acute and chronic GVHD, NRM and relapse.

### Demographics and transplant characteristics

Demographics, including age at transplant, gender, race, ethnicity, disease at transplant and number of prior autologous transplants were collected for each patient and recorded in the integrated University of Michigan Blood and Marrow Transplantation (BMT) Clinical Research Database and Repository. Transplant data, including donor stem cell source, donor type (related or unrelated), donor gender, HLA matching, CMV status of donor and recipient at transplant, ABO and Rh blood types of donor and recipient, conditioning regimen, CD34$^+$ cell dose infused for transplant, GVHD prophylaxis regimen, acute and chronic GVHD, time to engraftment and comorbidity scores (low, intermediate or high) according to the HCT-CI[11] were also collected and recorded. Granulocyte colony-stimulating factor was started on day 6 to promote neutrophil engraftment, which was defined as the first of three consecutive days with ANC $\geqslant$ 500/mm$^3$.

### Electronic Medical Record Search Engine (EMERSE): chart review

Data abstraction of the above transplant variables was supported by the use of the University of Michigan EMERSE, as previously described.[31] A script was also devised to extract the latest available pretransplant weight and height for the study population. These values were inspected (MG and SWC) to ensure that they were measured within 14 days of the transplant procedure.

### Plasma biomarkers

Pretransplant blood samples were collected prospectively from allogeneic HCT patients between January 2004 and May 2010, with informed consents and in agreement with the Declaration of Helsinki. Samples were collected in heparin-containing Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and underwent Ficoll (Amersham, Piscataway, NJ, USA) gradient centrifugation to separate the plasma. Plasma concentrations of suppression of tumorigenicity 2 (ST2), TNF receptor 1 (TNFR1) and IL 2 receptor alpha (IL2Rα) were measured in duplicate using ELISAs according to the manufacturer's protocol (R & D Systems, Minneapolis, MN, USA), as previously described.[25–27,32] Absorbances were read using a SpectraMax M2e plate reader (Molecular Devices, Sunnyvale, CA, USA). The integrated BMT Clinical Research Database and Repository that contained demographic and transplant characteristics, as well as the clinical outcomes (GVHD, NRM, relapse and survival), was linked to plasma biomarker samples that were collected and stored in accordance with IRB-approved protocols.

### Statistical analysis

Demographics of all first-time allogeneic HCT patients who received BM or PBSC grafts were summarized. Counts and percentages were determined for categorical variables. Medians and ranges were determined for continuous variables. Cumulative incidences with competing risks were determined using the methods of Fine and Gray[33] and compared using the test described by Gray.[34] OS was compared using the Kaplan–Meier method.[35] Differences in characteristics between patient groups were assessed with the Kruskal–Wallis test for continuous variables and the $\chi^2$ test of association for categorical values. Differences in the distribution of baseline plasma biomarker levels among categories of BMI were assessed with the Kruskal–Wallis test. Multivariate analysis incorporating possible confounders (age, malignant vs nonmalignant diagnosis, related vs unrelated donor, HLA match vs mismatch, BM vs PBSC transplant, full vs reduced intensity conditioning and transplant 2004 – 2008 vs 2009 – 2012) while examining the association of BMI with acute and chronic GVHD, NRM and relapse were assessed with competing risks regression[33] and with OS using Cox regression. Data were analyzed using R version 2.15.02 (GNU General Public License). Statistical significance was defined as a $P$-value $<$ 0.05.

## RESULTS

### Patient and transplant characteristics of the study population

The median age of the study population was 51 years (range 5 months–73 years, interquartile range [IQR] 31–58 years), comprised predominantly of adults ($\geqslant$18 years, 89%), males (60%) and Caucasians (92%). Thirty-four percent of the population was categorized as obese, 32% as overweight, 32% as normal weight and 2% as underweight, with a median BMI of 26.9 kg/m$^2$ (Table 1). The combined prevalence of pretransplant overweight and obesity increased from 58% in 2004 to 69% in 2012, an average increase of ~1.2% per year. The frequency of intermediate or high comorbidity index (HCT-CI) was greatest in overweight and obese patients (Table 1).

Ninety-four percent of patients had hematological malignancies. Patients received HLA-matched related (47%), mismatched related (3%), matched unrelated (38%) or mismatched unrelated transplants (12%). HCT was performed using cells from peripheral blood (PB, 85%) or BM (15%). Sixty-one percent of patients were conditioned with myeloablative regimens (of these, 20% included TBI $\geqslant$ 1200 cGy) and 39% with reduced intensity regimens, according to the ASBMT working definitions.[36] Six percent were conditioned with regimens that involved antihuman T cell Ab (ATG/thymoglobulin or alemtuzumab). CD34$^+$ cells were infused at a median concentration of $5.5\times10^6$ cells/kg (range $1.1\times10^6$–$1.75\times10^7$ cells/kg, IQR $4.6\times10^6$–$6.9\times10^6$). Engraftment occurred on median day 12 (range 5–28, IQR 11–13). Fifty-five percent of transplants were performed between 2004 and 2008 and 45% between 2009 and 2012 (detailed characteristics are presented in Table 1).

### NRM

The cumulative incidence of 3-year NRM in our population was 24%, and according to BMI categories (underweight, normal weight, overweight and obese) was 20%, 19%, 20% and 33%, respectively (Figure 1a). Across BMI categories, obese patients were at greater risk of NRM at 3 years compared with normal weight patients (HR 1.43, 95% CI 1.02–2.01, $P$ = 0.04, Table 2). Other variables significantly associated with increased NRM in the multivariate analysis were unrelated donor ($P$ $<$ 0.001), PBSC as transplant source ($P$ = 0.002) and HLA mismatch ($P$ = 0.004) (Table 2). The major causes of NRM were acute GVHD (40%) and chronic GVHD (45%) (Table 3).

**Table 1.** Demographic and transplant characteristics of patients receiving HCT from 2004 to 2012 by BMI category

| | *UW* | *NW* | *OW* | *OB* |
|---|---|---|---|---|
| Total ($n = 898$) | 20 (2.2) | 290 (32.3) | 287 (32.0) | 301 (33.5) |
| *Age (years)* | | | | |
| Pediatric ( < 18 years) | 8 (0.9) | 61 (6.8) | 15 (1.7) | 17 (1.9) |
| Adult | 12 (1.3) | 229 (25.5) | 272 (30.3) | 284 (31.6) |
| *Gender* | | | | |
| Male | 10 (1.1) | 132 (14.7) | 197 (21.9) | 201 (22.4) |
| Female | 10 (1.1) | 158 (17.6) | 90 (10.0) | 100 (11.1) |
| *Race/ethnicity* | | | | |
| White (non-Hispanic) | 20 (2.2) | 251 (28.0) | 268 (29.8) | 282 (31.4) |
| All other | — | 39 (4.3) | 19 (2.1) | 19 (2.1) |
| *Disease* | | | | |
| Malignant | 16 (1.8) | 257 (28.6) | 279 (31.1) | 293 (32.6) |
| Non-Hodgkin lymphoma | 3 (0.3) | 40 (4.5) | 52 (5.8) | 49 (5.5) |
| AML | 6 (0.7) | 89 (9.9) | 108 (12.0) | 114 (12.7) |
| ALL | 2 (0.2) | 40 (4.5) | 31 (3.5) | 45 (5.0) |
| Myelodysplastic syndrome | — | 17 (1.9) | 33 (3.7) | 29 (3.2) |
| Multiple myeloma | 2 (0.2) | 18 (2.0) | 19 (2.1) | 18 (2.0) |
| CLL | 1 (0.1) | 16 (1.8) | 14 (1.6) | 14 (1.6) |
| CML | 1 (0.1) | 11 (1.2) | 6 (0.7) | 6 (0.7) |
| Myelofibrosis | — | 8 (0.9) | 6 (0.7) | 7 (0.8) |
| Myeloproliferative disorder | 1 (0.1) | 7 (0.8) | 6 (0.7) | 3 (0.3) |
| Hodgkin lymphoma | — | 8 (0.9) | 2 (0.2) | 6 (0.7) |
| Biphenotypic leukemia | — | 3 (0.3) | 1 (0.1) | 2 (0.2) |
| Histiocytic sarcoma | — | — | 1 (0.1) | — |
| Nonmalignant | 4 (0.4) | 33 (3.7) | 8 (0.9) | 8 (0.9) |
| SAA | 2 (0.2) | 14 (1.6) | 4 (0.4) | 4 (0.4) |
| Sickle cell disease | — | 8 (0.9) | — | — |
| Thalassemia | 1 (0.1) | 2 (0.2) | 1 (0.1) | — |
| Familial erythrophagocytic lymphohistiocytosis | — | 2 (0.2) | — | — |
| Paroxysmal nocturnal hemoglobinuria | — | 1 (0.1) | 1 (0.1) | — |
| SCID | — | 2 (0.2) | — | — |
| Severe congenital neutropenia | — | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| X-linked lymphoproliferative syndrome | — | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| IPEX | — | — | — | 1 (0.1) |
| Dyskeratosis congenita | — | 1 (0.1) | — | 1 (0.1) |
| Osteopetrosis | 1 (0.1) | — | — | — |
| Congenital dyserythropoietic anemia | — | 1 (0.1) | — | — |
| *Transplant type/source* | | | | |
| Overall | | | | |
| Peripheral blood (PB) | 12 (1.3) | 217 (24.2) | 259 (28.8) | 275 (30.6) |
| BM | 8 (0.9) | 73 (8.1) | 28 (3.1) | 26 (2.9) |
| *HLA matching and relatedness* | | | | |
| Matched related | 11 (1.2) | 148 (16.5) | 130 (14.5) | 129 (14.4) |
| Mismatched related | — | 8 (0.9) | 10 (1.1) | 11 (1.2) |
| Matched unrelated | 7 (0.8) | 102 (11.4) | 107 (11.9) | 128 (14.2) |
| Mismatched unrelated | 2 (0.2) | 32 (3.6) | 40 (4.5) | 33 (3.7) |
| *Conditioning intensity* | | | | |
| Myeloablative | 9 (1.0) | 182 (20.3) | 176 (19.6) | 184 (20.5) |
| TBI $\geqslant$ 1200 cGy | | | | |
| Yes | 3 (0.3) | 47 (5.2) | 30 (3.3) | 37 (4.1) |
| No | 6 (0.7) | 135 (15.0) | 146 (16.3) | 147 (16.4) |
| Reduced intensity | 11 (1.2) | 108 (12.0) | 111 (12.4) | 117 (13.0) |
| *HCT-CI* | | | | |
| Low | 4 (57) | 41 (35) | 35 (28) | 33 (23) |
| Intermediate | 1 (14) | 35 (30) | 38 (30) | 43 (29) |
| High | 2 (29) | 41 (35) | 53 (42) | 71 (48) |
| *Conditioning Intensity* | | | | |
| Myeloablative | 9 (1.0) | 182 (20.3) | 176 (19.6) | 184 (20.5) |
| TBI $\geqslant$ 1200 cGy | | | | |
| Yes | 3 (0.3) | 47 (5.2) | 30 (3.3) | 37 (4.1) |
| No | 6 (0.7) | 135 (15.0) | 146 (16.3) | 147 (16.4) |
| Reduced Intensity | 11 (1.2) | 108 (12.0) | 111 (12.4) | 117 (13.0) |

**Table 1.** (Continued)

| | *UW* | *NW* | *OW* | *OB* |
|---|---|---|---|---|
| *GVHD prophylaxis* | | | | |
| Calcineurin inhibitor+MTX | 10 (1.1) | 203 (22.6) | 162 (18.0) | 188 (20.9) |
| Calcineurin inhibitor+mycophenolate mofetil | 9 (1.0) | 80 (8.9) | 117 (13.0) | 106 (11.8) |
| Calcineurin inhibitor alone | 1 (0.1) | 2 (0.2) | 1 (0.1) | — |
| Other | — | 5 (0.6) | 7 (0.8) | 7 (0.8) |
| *Year of transplant* | | | | |
| 2004–2008 | 13 (1.4) | 168 (18.7) | 160 (17.8) | 151 (16.8) |
| 2009–2013 | 7 (0.8) | 122 (13.6) | 127 (14.1) | 150 (16.7) |

Abbreviations: BMI = body mass index; HCT = hematopoietic cell transplantation; HCT-CI = HCT comorbidity index; IPEX = immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; NW = normal weight; OB = obese, OW = overweight; UW = underweight. HCT-CI Available for underweight ($n = 7$), normal weight ($n = 117$), overweight ($n = 126$) and obese ($n = 147$). Data are shown as count (%) or median (range, interquartile range).

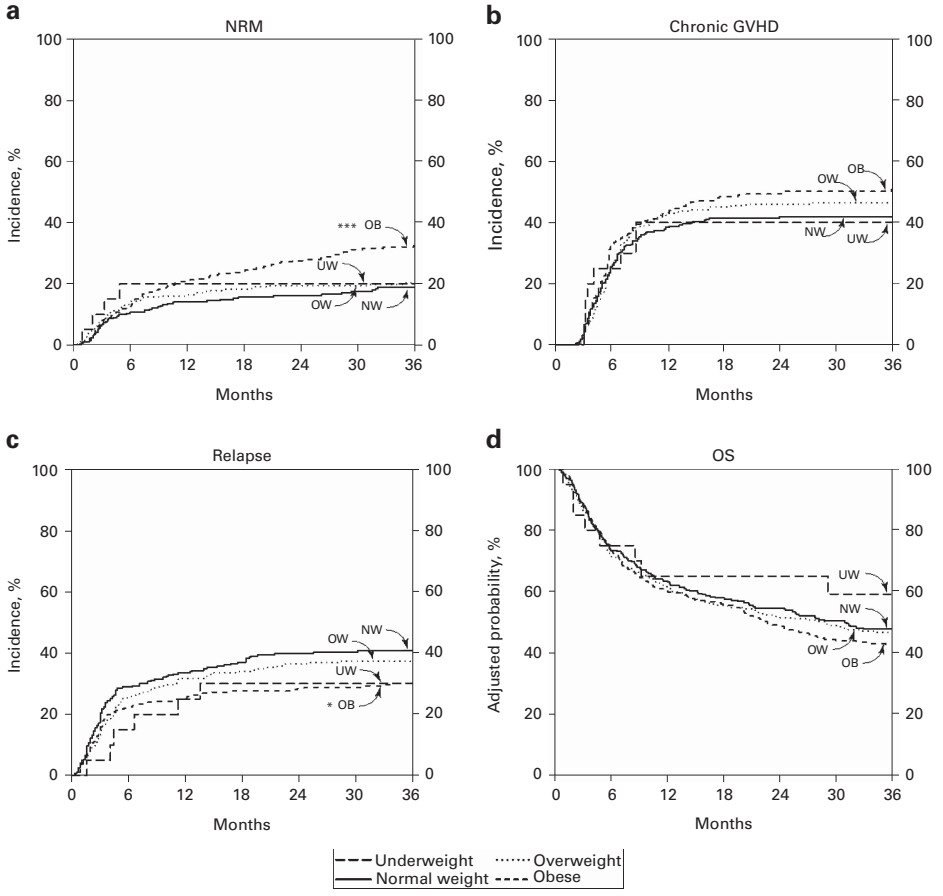


**Figure 1.** Transplant outcomes by BMI category. Cumulative incidence of NRM, $P < 0.001$*** (**a**), chronic GVHD, $P = 0.07$ (**b**), relapse, $P = 0.02$* (**c**) and adjusted probability of OS, $P = 0.13$ (**d**). $N = 20$ underweight (UW), 290 normal weight (NW), 287 overweight (OW) and 301 obese (OB). *P*-values represent outcomes of obese relative to normal weight patients.

GVHD

The cumulative incidence of grade 2–4 acute GVHD in the study population at day 100 was 37%. According to BMI categories (underweight, normal weight, overweight and obese), the incidences were 40%, 33%, 37% and 41%, respectively. In adjusted models, categorical BMI (Table 2) was not significantly associated with acute GVHD. Variables significantly associated with acute GVHD in the multivariate analysis were unrelated donor ($P < 0.001$), PBSC as transplant source ($P = 0.04$), HLA mismatch ($P < 0.001$) and transplant before 2009 ($P = 0.02$) (Table 2).

The cumulative incidence of chronic GVHD at 3 years was 46%, which was greatest in obese patients (50%), followed by overweight, normal weight and underweight (46%, 42% and 40%, respectively) (Figure 1b). After controlling for potential confounders, however, BMI as a categorical variable was not associated with risk of chronic GVHD. There were no other variables that significantly predicted the risk of chronic GVHD (Table 2).

**Table 2.** Clinical outcomes by BMI category

| | *UW* | *NW* | *OW* | *OB* |
|---|---|---|---|---|
| Total | 20 | 290 (34.5) | 287 (32.0) | 301 (33.5) |
| Follow-up time (months) | 29.4 (0.8–113.7, 7.6–64.4) | 18.9 (0.5–117.7, 5.7–50.0) | 17.8 (0.3–117.6, 5.4–49.9) | 17.8 (0.6–115.5, 5.9–43.4) |
| Hospital length of stay (days) | 29 (18–68, 24–35) | 24 (12–175, 21–29) | 23 (0–154, 20–27) | 23 (0–98, 21–26) |
| *Acute GVHD*[a] | | | | |
| Yes | 9 (1.0) | 159 (17.7) | 174 (19.4) | 178 (19.8) |
| 1 | — | 42 (4.7) | 50 (5.6) | 36 (4.0) |
| 2 | 4 (0.4) | 69 (7.7) | 64 (7.1) | 76 (8.5) |
| 3 | 4 (0.4) | 24 (2.7) | 25 (2.8) | 32 (3.6) |
| 4 | 1 (0.1) | 24 (2.7) | 35 (3.9) | 34 (3.8) |
| No | 11 (1.2) | 131 (14.6) | 113 (12.6) | 123 (13.7) |
| *Chronic GVHD* | | | | |
| Yes | 9 (1.0) | 135 (15.0) | 148 (16.5) | 166 (18.5) |
| No | 11 (1.2) | 155 (17.3) | 139 (15.5) | 135 (15.0) |
| *Relapse* | | | | |
| Yes | 6 (0.7) | 116 (12.9) | 107 (11.9) | 91 (10.1) |
| No | 14 (1.6) | 174 (19.4) | 180 (20.0) | 210 (23.4) |
| *Survival* | | | | |
| Alive | 10 (1.1) | 133 (14.8) | 122 (13.6) | 116 (12.9) |
| Dead | 10 (1.1) | 157 (17.5) | 165 (18.4) | 185 (20.6) |
| *Causes of death* | | | | |
| Relapse | 4 (40.0) | 99 (63.1) | 91 (55.2) | 76 (41.1) |
| Acute GVHD | 2 (20.0) | 26 (16.6) | 36 (21.8) | 35 (18.9) |
| Chronic GVHD | 2 (20.0) | 20 (12.7) | 27 (16.4) | 57 (30.1) |
| Graft rejection or failure | — | 2 (1.3) | 3 (1.8) | 2 (1.1) |
| Idiopathic pneumonia syndrome | — | — | 1 (0.6) | 7 (3.8) |
| Infection[b] | 1 (10.0) | 2 (1.3) | 3 (1.8) | 2 (1.1) |
| Hepatic veno-occlusive disorder | — | 1 (0.6) | 1 (0.6) | 3 (1.6) |
| Engraftment syndrome | — | — | 1 (0.6) | 1 (0.5) |
| Cardiac event | — | 1 (0.6) | 1 (0.6) | — |
| PTLD | — | 1 (0.6) | — | — |
| Pulmonary hypertension | — | 1 (0.6) | — | — |
| Small bowel obstruction | — | — | — | 1 (0.5) |
| Accidental trauma | — | — | — | 1 (0.5) |
| Other[c] or unknown | 1 (10.0) | 4 (2.5) | 1 (0.6) | — |

Abbreviations: BMI = body mass index; IQR = interquartile range; NW = normal weight; OB = obese; OW = overweight; PTLD = post-transplant lymphoproliferative disorder; UW = underweight. Data are shown as count (%) or median (range, IQR). [a]Acute GVHD onset day ⩽ 100 post transplant and not post relapse, max grade shown. [b]Among deaths from infection, one UW patient died from *Pneumocystis jirovecii* pneumonia, one NW patient from human herpes virus 6 meningoencephalitis, one NW, two OW and one OB patients from culture-negative sepsis, one OW patient from pneumonia of unknown etiology and one OB patient from a bacterial infection at another hospital. [c]One UW patient died from esophageal cancer; three NW patients died from lung cancer.

### Relapse

The cumulative incidence of relapse in the study population at 3 years was 36%. On the basis of BMI groups (underweight, normal weight, overweight and obese), the incidences were 30%, 41%, 37% and 30%, respectively (Figure 1c). In the adjusted models, obese patients experienced significantly decreased relapse when compared with normal weight patients (HR 0.65, 95% CI 0.49–0.86, $P = 0.002$, Table 2). Other variables associated with relapse in the multivariate analysis included malignant disease ($P = 0.002$), related donor ($P < 0.001$) and transplant date before 2009 ($P = 0.02$) (Table 2).

### OS

The 3-year OS of our study population was 46%, with the poorest survival outcome of 43% in obese patients compared with 59%, 48% and 47% in the other BMI categories (underweight, normal weight, and overweight, respectively) (Figure 1d). However, in adjusted models, categorical BMI revealed no significant association with survival. Variables found to be associated with decreased OS included patient age ($P = 0.003$), unrelated donor ($P = 0.02$), PBSC as transplant source ($P = 0.003$), HLA mismatch ($P = 0.03$) and transplant date before 2009 ($P = 0.01$) (Table 2).

### Baseline levels of plasma biomarkers

Pretransplant plasma levels of proinflammatory biomarkers ST2, TNFR1 and IL2Rα were measured by ELISA in a subset of patients. The median ST2 concentration in obese patients (257 pg/mL, IQR 0–1045 pg/mL) was significantly higher than in normal weight patients (131 pg/mL, IQR 0–628, $P = 0.04$, Table 4). Likewise, the median TNFR1 concentration was elevated in obese patients (2644 pg/mL, IQR 1922–3395) compared with normal weight patients (2129 pg/mL, IQR 1486–3232, $P = 0.05$, Table 5). The concentration of IL2Rα was not significantly different among BMI categories (data not shown).

## DISCUSSION

Obesity is a major public health problem worldwide.[7,29,37] The prevalence of obesity is rapidly rising, leading to serious social, health and economic challenges.[1,2,38] In this study, we set out to

**Table 3.** Results of multivariate regression analysis by BMI category

| | N | *HR (95% CI)* | P-*value* |
|---|---|---|---|
| *aGVHD* | | | |
| BMI | | | |
| Normal | 290 | 1.00 | — |
| UW | 20 | 1.11 (0.56–2.21) | 0.76 |
| OW | 287 | 1.03 (0.78–1.35) | 0.85 |
| OB | 301 | 1.15 (0.89–1.50) | 0.29 |
| Other covariates | — | — | — |
| Continuous age | 898 | 1.00 (0.99–1.00) | 0.37 |
| Malignancy | | | |
| Nonmalignant | 53 | 1.00 | — |
| Malignant | 845 | 1.73 (0.82–3.68) | 0.15 |
| Relatedness | | | |
| Related | 447 | 1.00 | — |
| Unrelated | 451 | 1.88 (1.50–2.35) | < 0.001 |
| Transplant type | | | |
| PB | 763 | 1.00 | — |
| BM | 135 | 0.66 (0.44–0.99) | 0.04 |
| HLA match | | | |
| Matched | 762 | 1.00 | — |
| Mismatched | 136 | 1.69 (1.30–2.17) | < 0.001 |
| Conditioning intensity | | | |
| Myeloablative | 551 | 1.00 | — |
| Reduced | 347 | 1.19 (0.94–1.49) | 0.14 |
| Year of transplant | | | |
| 2004–2008 | 492 | 1.00 | — |
| 2008–2013 | 406 | 0.76 (0.61–0.95) | 0.02 |
| *cGVHD* | | | |
| BMI | | | |
| Normal | 290 | 1.00 | — |
| UW | 20 | 0.99 (0.46–2.12) | 0.98 |
| OW | 287 | 1.07 (0.83–1.38) | 0.60 |
| OB | 301 | 1.21 (0.94–1.55) | 0.14 |
| Other covariates | | | |
| Continuous age | 898 | 1.00 (0.99–1.01) | 0.69 |
| Malignancy | | | |
| Nonmalignant | 53 | 1.00 | — |
| Malignant | 845 | 1.29 (0.72–2.31) | 0.38 |
| Relatedness | | | |
| Related | 447 | 1.00 | — |
| Unrelated | 451 | 1.13 (0.92–1.39) | 0.23 |
| Transplant type | | | |
| PB | 763 | 1.00 | — |
| BM | 135 | 0.91 (0.61–1.36) | 0.65 |
| HLA match | | | |
| Matched | 762 | 1.00 | — |
| Mismatched | 136 | 0.95 (0.73–1.25) | 0.73 |
| Conditioning intensity | | | |
| Myeloablative | 551 | 1.00 | — |
| Reduced | 347 | 1.02 (0.82––1.27) | 0.82 |
| Year of transplant | | | |
| 2004–2008 | 492 | 1.00 | — |
| 2008–2013 | 406 | 0.96 (0.79–1.17) | 0.70 |
| *NRM* | | | |
| BMI | | | |
| Normal | 290 | 1.00 | — |
| UW | 20 | 1.74 (0.76–4.01) | 0.19 |
| OW | 287 | 0.95 (0.65–1.37) | 0.77 |
| OB | 301 | 1.43 (1.02–2.01) | 0.04 |
| Other covariates | | | |
| Continuous age | 898 | 1.01 (1.00–1.02) | 0.18 |
| Malignancy | | | |
| Nonmalignant | 53 | 1.00 | — |
| Malignant | 845 | 0.37 (0.10–1.33) | 0.13 |
| Relatedness | | | |
| Related | 447 | 1.00 | — |
| Unrelated | 451 | 2.20 (1.65–2.94) | < 0.001 |
| Transplant type | | | |
| PB | 763 | 1.00 | — |
| BM | 135 | 0.23 (0.09–0.58) | 0.002 |
| HLA match | | | |
| Matched | 762 | 1.00 | — |
| Mismatched | 136 | 1.59 (1.16–2.22) | 0.004 |
| Conditioning intensity | | | |
| Myeloablative | 551 | 1.00 | — |
| Reduced | 347 | 1.02 (0.76–1.35) | 0.91 |
| Year of transplant | | | |
| 2004–2008 | 492 | 1.00 | — |
| 2008–2013 | 406 | 0.79 (0.60–1.05) | 0.10 |
| *Relapse* | | | |
| BMI | | | |
| Normal | 290 | 1.00 | — |
| UW | 20 | 0.70 (0.32–1.50) | 0.36 |
| OW | 287 | 0.79 (0.61–1.03) | 0.08 |
| OB | 301 | 0.65 (0.49–0.86) | 0.002 |
| Other covariates | | | |
| Continuous age | 898 | 1.00 (1.00–1.01) | 0.36 |
| Malignancy | | | |
| Nonmalignant | 53 | 1.00 | — |
| Malignant | 845 | 26.50 (3.49– 201.02) | 0.002 |
| Relatedness | | | |
| Related | 447 | 1.00 | — |
| Unrelated | 451 | 0.61 (0.48–0.77) | < 0.001 |
| Transplant type | | | |
| PB | 763 | 1.00 | — |
| BM | 135 | 1.09 (0.72–1.66) | 0.68 |
| HLA match | | | |
| Matched | 762 | 1.00 | — |
| Mismatched | 136 | 0.83 (0.60–1.18) | 0.29 |
| Conditioning intensity | | | |
| Myeloablative | 551 | 1.00 | — |
| Reduced | 347 | 0.90 (0.69–1.16) | 0.42 |
| Year of transplant | | | |
| 2004–2008 | 492 | 1.00 | — |
| 2008–2013 | 406 | 0.76 (0.60–0.95) | 0.02 |
| *OS* | | | |
| BMI | | | |
| Normal | 290 | 1.00 | — |
| UW | 20 | 1.02 (0.54–1.95) | 0.95 |
| OW | 287 | 0.85 (0.68–1.07) | 0.17 |
| OB | 301 | 0.93 (0.75–1.16) | 0.55 |
| Other covariates | | | |
| Continuous age | 898 | 1.01 (1.00–1.02) | 0.003 |
| Malignancy | | | |
| Non–malignant | 53 | 1.00 | — |
| Malignant | 845 | 2.05 (0.92, 4.58) | 0.08 |
| Relatedness | | | |
| Related | 447 | 1.00 | — |
| Unrelated | 451 | 1.24 (1.03–1.49) | 0.02 |
| Transplant type | | | |
| PB | 763 | 1.00 | — |
| BM | 135 | 0.56 (0.38–0.82) | 0.003 |
| HLA match | | | |
| Matched | 762 | 1.00 | — |
| Mismatched | 136 | 1.41 (1.12–1.79) | 0.003 |
| Conditioning intensity | | | |
| Myeloablative | 551 | 1.00 | — |
| Reduced | 347 | 0.89 (0.74–1.09) | 0.24 |
| Year of transplant | | | |
| 2004–2008 | 492 | 1.00 | — |
| 2008–2013 | 406 | 0.78 (0.65–0.94) | 0.01 |

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; NRM = nonrelapse mortality; OB = obese; OW = overweight; PB = peripheral blood; UW = underweight.

**Table 4.** Baseline levels of plasma biomarker ST2 by BMI category

| *BMI category* | N | *Median concentration (IQR), pg/mL* | P-*value* |
|---|---|---|---|
| Normal | 115 | 131 (0–628) | — |
| UW | 7 | 256 (82–659) | 0.51 |
| OW | 115 | 208 (0–845) | 0.22 |
| OB | 110 | 257 (0–1045) | 0.04 |

Abbreviations: BMI = body mass index; IQR = interquartile range; OB = obese; OW = overweight.

**Table 5.** Baseline levels of plasma biomarker TNFR1 by BMI category

| *BMI category* | N | *Median concentration (IQR), pg/mL* | P-*value* |
|---|---|---|---|
| Normal | 88 | 2129 (1486–3232) | — |
| UW | 7 | 1596 (1467–2971) | 0.57 |
| OW | 81 | 2266 (1708–3725) | 0.32 |
| OB | 99 | 2644 (1922–3395) | 0.05 |

Abbreviations: BMI = body mass index; IQR = interquartile range; OB = obese; OW = overweight; UW = underweight.

investigate the impact of obesity on outcomes following allogeneic HCT, including GVHD, NRM, relapse and OS. We found that our population was comprised of 34% obese patients, which was higher than expected based on the geographic locale of our institution; in 2011, Michigan ranked 10th in USA among states with the highest prevalence of obesity at 31.1% in adults age 20 years and older.[39] The 34% of obese patients in our study was striking, particularly because it was threefold higher compared with the worldwide obesity estimate of 11%.[7] This important finding highlights the growing number of patients with concomitant obesity who are being treated for life-threatening hematological malignancies and undergoing high-risk allogeneic HCT.

Among allogeneic HCT recipients, the impact of obesity on outcomes remains controversial.[12–24] Here in, BMI examined either as a categorical predictor did not significantly change the overall results and interpretations. After adjusting for other covariates, our findings provided evidence that obese patients experienced significantly increased NRM and decreased relapse, with no difference in OS compared with normal weight patients. Although our study population was comprised predominantly of adults, these observations are concordant with a recent registry-based analysis of 3687 pediatric patients (age 2–18 years).[12]

Obesity in solid organ transplantation has been shown to be associated with worse outcomes, including delayed graft function, graft failure, surgical site infection, cardiovascular disease, prolonged hospital course and increased healthcare costs.[40] Interestingly, our data show that obesity was associated with significantly decreased risk of relapse, in agreement with two large registry data studies.[12,20] By contrast, a single-center study of 325 children reported a higher incidence of relapse in obese patients,[14] highlighting the challenges of comparing results across studies with heterogeneous populations. It is important to consider that BMI does not distinguish excess body fat from lean mass.[41] In addition, the pharmacokinetics and distribution of drugs in different tissues may vary across the range of BMI and thereby impact outcomes.[42] Alternatively, decreased relapse may not have been a direct result of excessive fat stores or obesity. For instance, the mechanisms underlying the increased frequency of chronic GVHD in obese patients may have offered protection against relapsed disease (GVL effect).[43] It is also possible that our institutional practice of chemotherapy dose modifications according to adjusted ideal body weight compared with actual weight may have impacted the risk of NRM and relapse. The potential effects of these adjustments on outcomes are not well understood. Further investigation is warranted to confirm the findings reported herein.

Obesity is strongly associated with metabolic abnormalities and likely to be mediated in part by a chronic inflammatory state induced by secretion of cytokines in the adipocytes, such as TGF-β, TNF-α, IL-6 and angiotensinogen.[44] We have previously shown that ST2, TNFR1 and IL2Rα can predict GVHD and NRM after allogeneic HCT.[25–27] We were therefore interested to know whether these biomarkers differed across a range of BMI. We found that obese patients had higher plasma levels of ST2 and TNFR1 at the time of transplant. ST2, a decoy receptor for IL-33 secreted by epithelial cells, endothelial cells and fibroblasts in response to proinflammatory stimuli, biases T cells toward a $T_H1$ phenotype and its high levels are associated with acute GVHD, resistance to GVHD treatment and NRM.[27] TNFR1, a receptor and surrogate marker for TNFα, which is shed from the cell surface following ligand binding, is a significant predictor of GVHD and NRM.[25] Elevated ST2 levels have previously been reported in serum and adipose tissue of obese humans,[45] adipose tissue of diet-induced obese mice[45] and in the serum of rats fed a high-fat diet.[46] TNFR1 is also present at an increased level in obese individuals[47] and can be lowered with exercise and weight loss.[48] Our recapitulation of these findings in an HCT cohort may provide a basis for future studies of the molecular mechanisms linking obesity with transplant outcomes.

To our knowledge, this is the first study in HCT to measure baseline biomarkers and correlate them across BMI categories. Clearly, further investigation of these biomarkers is needed. Target-specific biomarkers that can help inform about risks and outcomes in the HCT setting may assist in risk stratification for risk-adapted clinical trials. For instance, depending on the patient's pre-HCT disease characteristics, BMI, HCT-CI and/or biomarkers levels, the transplant team may begin to stratify patients according to low risk vs high risk. The pathogenesis of GVHD involves a complex network of proinflammatory cytokines.[25] Therefore, in the present study, it was not surprising that in obese individuals higher baseline levels of TNFR1 and ST2 were associated with increased risk of developing GVHD. Thus, future discovery of biomarkers in the early pre-HCT setting is warranted to better develop risk-adapted treatment strategies. Importantly, they may provide insight into the delicate balance between relapse and GVHD and NRM.

The current study was conducted over nearly a decade in 898 children and adults undergoing first-time allogeneic HCT, predominantly due to hematological malignancies. Strengths of the study included a large, heterogeneous population with an array of sociodemographic data, including patient age, underlying disease, stem cell source and conditioning regimen and the prospective evaluation of plasma biomarkers before transplant, allowing us to form generalized conclusions. At the same time, we recognize this heterogeneous patient population is also a limitation, precluding us from detecting associations that may have reached significance if potential confounders, such as age (pediatric vs adult) or type of transplant (full vs reduced intensity conditioning), were restricted. Nonetheless, we attempted to control for this by performing multivariate analyses with other covariates and with BMI modeled as both a categorical and continuous (data not shown) variable. Our results were largely unchanged by both these approaches. Furthermore, we performed a subgroup analysis of children $< 18$ years of age and patients with ALL, AML and myelodysplastic syndrome. Although the sample sizes were very small, we found no differences in outcomes (GVHD, NRM, relapse and survival) between the overall study population and these subgroups (Supplementary Table S2). Clearly, future studies are needed with larger populations to

address these effects along with considerations of race and ethnicity. Our patient population was primarily Caucasian with very few Asians, Hispanics and Blacks, and we recognize that findings may differ across these populations. In addition, other confounding factors, such as smoking and alcohol use, that may impact the association of body weight with mortality were not included in our analyses.

In conclusion, the current results showed increased NRM but decreased relapse in obese patients undergoing allogeneic HCT. To our knowledge, this study is the first to report significantly elevated pretransplant levels of ST2 and TNFR1 among obese patients relative to normal weight patients. Our data argue for a well-designed prospective study that incorporates correlative laboratory analyses,[25–27] which may improve our understanding of the impact of BMI on transplant outcomes.[11] Although obesity is an important risk factor for development of other comorbid complications, such as hypertension, dyslipidemia, cardiovascular diseases and diabetes mellitus, we recognize that the presence of these disturbances may vary widely among obese individuals. Nonetheless, obesity-related comorbidities should be routinely assessed and treated by appropriate specialists working closely with the transplant team. Accordingly, explaining these risks could inform post-HCT expectations.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## AUTHOR CONTRIBUTIONS

MG collected and analyzed the data and drafted and approved the manuscript; YL analyzed the data and approved the manuscript; LC collected and analyzed the data and approved the manuscript; SP conducted scientific analyses and approved the manuscript; DAH collected the data and approved the manuscript; DGF collected and analyzed the data and approved the manuscript; CAB cared for patients and approved the manuscript; PRR designed the study, cared for patients and approved the manuscript; TMB designed the study, analyzed the data and approved the manuscript; SWC designed the study, cared for patients, collected and analyzed the data and drafted and approved the manuscript.

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