



Impact of Body Mass Index on Outcomes of Hematopoietic Stem Cell Transplantation in Adults

Kristine Doney^{1,2,*}, Kerry McMillen³, Laura Buono³, H. Joachim Deeg^{1,2}, Ted Gooley^{1,2}

¹ Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

² University of Washington Medical Center, Seattle, Washington

³ Seattle Cancer Care Alliance, Seattle, Washington

Article history:

Received 22 May 2018

Accepted 3 October 2018

Key Words:

Body mass index
Transplantation

A B S T R A C T

This retrospective analysis of 2503 adult (age ≥ 20 years) allogeneic hematopoietic cell transplantation (HCT) recipients assessed the effect of body mass index (BMI) on transplantation outcomes. The median patient age was 51.7 years. Patients with both nonmalignant and malignant diagnoses were included. Patients received either a myeloablative (52%) or a reduced-intensity (48%) conditioning regimen. Donors were either related (42%) or unrelated (58%). Cord blood recipients were excluded. Granulocyte colony-stimulating factor-mobilized peripheral blood cells were the stem cell source in 86% of transplantations. Graft-versus-host disease prophylaxis included at least 2 immunosuppressive agents, 1 of which was a calcineurin inhibitor. Patient groups were categorized as underweight, normal weight, overweight, obese, or very obese based on BMI. Endpoints included day +100 mortality, overall mortality, nonrelapse mortality (NRM), and relapse. Changes in nutritional status, based on laboratory parameters, were also examined. Underweight patients had significantly lower early and overall survival and greater NRM. Very obese patients had increased NRM, which was associated with the intensity of conditioning regimen. With long-term follow-up, increasing NRM was associated with both underweight and obese patients compared with normal-weight individuals. Changes in serum protein and albumin levels did not correlate with BMI. Although enteral nutrition is now recommended for some undernourished patients, the efficacy of enteral or parenteral nutrition has not been well studied. For obese patients, there are no guidelines regarding weight loss before transplantation, and acute weight loss in the pretransplantation period may be detrimental.

© 2018 American Society for Blood and Marrow Transplantation.

INTRODUCTION

In 1995, the authors published a retrospective analysis of 2238 pediatric and adult patients who underwent allogeneic hematopoietic cell transplantation (HCT) between 1985 and 1992 that assessed the effect of patient weight before transplantation on nonrelapse mortality (NRM) [1]. Since that time, several single and multicenter analyses have assessed the effect of additional measures of body habitus, including body mass index (BMI), body surface area (BSA), and weight loss during transplantation, on transplantation outcomes. These studies, summarized in a recent review, had varying results and sometimes reached disparate conclusions [2]. Comparing the results of these studies is difficult because of the diversity of patient populations studied, differing duration of follow-up, small patient numbers, and diagnosis- or conditioning regimen-restricted patient groups. Our initial study showed that

patients who were at $<85\%$ of their ideal body weight (IBW) pretransplantation had significantly decreased survival during the first 150 days after transplantation compared with patients at 95% to 145% of IBW. Overweight patients did not have a significantly higher risk of death. Given the increasing incidence of obesity in the United States, the advances in HCT since 1995, and the increased complexity of patients undergoing HCT, we reevaluated the impact of body habitus on transplantation outcomes in our patient population.

METHODS

Patients

Adult patients (age ≥ 20 years) who underwent a first allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance between January 1, 2001, and December 31, 2015 were included in this analysis. Indications for transplantation included both malignant and nonmalignant disorders. Patients received either a high-intensity myeloablative conditioning (MAC) regimen or a reduced-intensity conditioning (RIC) regimen. Unfractionated bone marrow or granulocyte colony-stimulating factor-mobilized peripheral blood from a related or an unrelated donor served as the stem cell source. Both HLA-matched (10/10) and HLA-mismatched donor transplants were included. Cord blood transplants were excluded. Patient weight was not used to exclude a patient from HCT.

The study group comprised 2503 patients who had their weight and height recorded pretransplantation to calculate BMI. Protocols and consent

Financial disclosure: See Acknowledgments on page 619.

* Correspondence and reprint requests: Kristine Doney, MD, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D5-280, PO Box 19024, Seattle, WA 98109-1024.

E-mail address: kdoney@fhcrc.org (K. Doney).

forms were approved by the FHCRC Institutional Review Board, and informed consent was obtained from all patients and donors. Patients were analyzed by weight groups as defined by the World Health Organization: underweight, BMI <18.5 kg/m²; normal weight, BMI 18.5 to 24.9 kg/m²; overweight, BMI 25 to 29.9 kg/m²; and obese, BMI >30 kg/m² [3]. Patients with a BMI >30 kg/m² were then subcategorized as obese (BMI 30.0 to 34.9) and very obese (BMI ≥35.0). Data were obtained from the FHCRC patient database and archived patient charts. Patient and donor characteristics by weight groups are summarized in Table 1.

Transplantation Regimens

Conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, and outcome data are summarized in Table 2. Conditioning regimens were classified as MAC or RIC, as defined by the Center for International Blood and

Marrow Transplant Research (CIBMTR) [4]. A slight majority of patients (53%) received an MAC regimen, with busulfan/cyclophosphamide the most frequent chemotherapy-only regimen and cyclophosphamide plus 12 Gy total body irradiation (TBI) the most frequent radiation-containing regimen. Sixty-nine percent of the 1189 patients treated with RIC regimens received 200 to 450 cGy TBI in combination with fludarabine. Chemotherapy dosing was based on BSA or actual body weight. For patients at >120% of IBW, BSA was calculated using adjusted weight, defined as $IBW + .25(\text{actual weight} - IBW)$. GVHD prophylaxis most often included a calcineurin inhibitor in combination with either methotrexate or mycophenolate mofetil. A small group of patients (n = 109) received sirolimus in combination with a calcineurin inhibitor. Comparable numbers of patients received either matched related donor or matched unrelated donor stem cells. Granulocyte colony-stimulating factor-mobilized peripheral blood was the stem cell source in 86% of patients.

Table 1
Patient Characteristics

| Characteristic | Underweight (BMI <18.5) | Normal Weight (BMI 18.5–24.9) | Overweight (BMI 25.0–29.9) | Obese (BMI 30.0–34.9) | Very Obese (BMI ≥35.0) |
|--|----------------------------|----------------------------------|-------------------------------|--------------------------|---------------------------|
| Number of patients (%) | 30 (1.2) | 860 (34.3) | 949 (37.9) | 413 (16.5) | 251 (10.0) |
| Patient age, yr, median (range) | 47.8 (22.5–69.7) | 50.5 (20–78.9) | 53.5 (20–79.5) | 52.4 (21–75) | 48.9 (20.8–77.1) |
| Donor/recipient sex, n (%) | | | | | |
| Male/male | 5 (17)* | 249 (29) | 357 (38) | 154 (37) | 75 (30) |
| Male/female | 9 (30) | 232 (27) | 137 (14) | 78 (19) | 73 (29) |
| Female/female | 14 (47) | 215 (25) | 157 (16) | 75 (18) | 53 (21) |
| Female/male | 2 | 164 (19) | 298 (31) | 106 (26) | 50 (20) |
| Race/ethnicity, n (%) | | | | | |
| White | 22 (73) | 697 (81) | 789 (83) | 359 (87) | 204 (81) |
| Hispanic | 0 | 24 | 41 | 13 | 11 |
| African American/African black | 1 | 3 | 8 | 11 | 8 |
| Asian | 5 (18) | 67 | 35 | 5 | 1 |
| Native American/Alaskan/ Hawaiian/ Pacific Islander | 0 | 12 | 9 | 5 | 9 |
| Other, multiple, or unknown | 2 | 57 | 67 | 20 | 18 |
| Diagnosis, n (%) | | | | | |
| Aplastic anemia | 0 | 13 | 26 | 6 | 4 |
| MDS, low risk | 1 | 37 | 52 | 24 | 14 |
| MDS, high risk | 5 (17) | 84 (10) | 97 (10) | 38 | 16 |
| MPN | 5 (17) | 83 (10) | 93 (10) | 31 | 15 |
| AML, low risk | 2 | 194 (23) | 190 (20) | 95 (23) | 52 (21) |
| AML, high risk | 4 (13) | 165 (19) | 160 (17) | 69 (17) | 46 (18) |
| ALL, low risk | 2 | 51 | 73 | 34 | 19 |
| ALL, high risk | 0 | 45 | 25 | 21 | 18 |
| CML, chronic phase | 0 | 34 | 39 | 21 | 18 |
| CML, other | 1 | 30 | 33 | 13 | 8 |
| Lymphoma, remission [†] | 0 | 22 | 14 | 4 | 4 |
| Lymphoma, relapse [†] | 2 | 22 | 40 | 15 | 10 |
| Myeloma | 1 | 5 | 5 | 2 | 1 |
| Other | 3 (10) | 28 | 18 | 10 | 10 |
| Chronic lymphocytic leukemia | 1 | 29 | 59 | 20 | 12 |
| Blank or unknown status | 3 (10) | 18 | 25 | 10 | 4 |
| Comorbidity Index | | | | | |
| Patients graded, n (%) | 19 (63) | 698 (81) | 750 (79) | 327 (79) | 190 (76) |
| Score, mean (range) | 4.2 (0–11) | 2.3 (0–11) | 2.4 (0–12) | 2.3 (0–8) | 3.2 (0–10) |
| Patients with score ≥3, n (%) | 14 (74) | 291 (42) | 347 (46) | 139 (43) | 130 (68) |
| Year of transplantation, n (%) | | | | | |
| 2001–2005 | 8 (27) | 332 (38) | 373 (39) | 156 (38) | 105 (42) |
| 2006–2010 | 10 (33) | 256 (30) | 293 (31) | 129 (31) | 62 (25) |
| 2011–2015 | 12 (40) | 272 (32) | 283 (30) | 128 (31) | 84 (33) |
| Donor/recipient HLA compatibility, n (%) | | | | | |
| Related, matched | 14 (47) | 328 (38) | 377 (40) | 142 (34) | 84 (33) |
| Related, haploidentical | 1 | 22 | 22 | 10 | 6 |
| Related, other mismatch | 0 | 16 | 17 | 5 | 5 |
| Unrelated, matched | 12 (40) | 380 (44) | 404 (42) | 189 (46) | 114 (45) |
| Unrelated, mismatched | 3 (10) | 114 (13) | 129 (14) | 67 (16) | 42 (17) |
| Donor age, yr, median (range) (n = 2338) | 35 (20–74) | 39 (7–81) | 39 (10–77) | 37 (15–83) | 39 (18–71) |
| Stem cell source, n (%) | | | | | |
| Bone marrow | 6 (20) | 132 (15) | 135 (14) | 52 (13) | 29 (12) |
| Peripheral blood | 24 (80) | 726 (84) | 810 (85) | 360 (87) | 222 (88) |
| Bone marrow and peripheral blood | 0 | 2 | 4 | 1 | |

MDS indicates myelodysplastic syndrome; MPN, myeloproliferative neoplasm; ALL, acute lymphoblastic leukemia; CML chronic myelogenous leukemia; AML low risk, first remission; ALL low risk, first remission; MDS low risk, refractory anemia with ringed sideroblasts; MDS high risk, all others.

* Percentages in parentheses represent the percentage of patients in each weight classification if percentage is ≥10%.

[†] Includes Hodgkin lymphoma and non-Hodgkin lymphoma.

Table 2
Conditioning Regimens and Outcomes

| Parameter | Underweight (BMI <18.5) | Normal Weight (BMI 18.5–24.9) | Overweight (BMI 25.0–29.9) | Obese (BMI 30.0–34.9) | Very Obese (BMI ≥35.0) |
|---|----------------------------|----------------------------------|-------------------------------|--------------------------|---------------------------|
| Number of patients | 30 | 860 | 949 | 413 | 251 |
| Preparative regimen, n (%) | | | | | |
| MAC | 21 (70) | 294 (34) | 567 (60) | 258 (62) | 174 (69) |
| No TBI | 15 (50) | 74 (8) | 370 (39) | 88 (21) | 114 (45) |
| ≥1200 cGy TBI | 6 (20) | 220 (26) | 197 (21) | 170 (41) | 60 (24) |
| RIC | 9 (30) | 566 (66) | 382 (40) | 155 (38) | 77 (31) |
| No TBI | 0 | 305 (35) | 39 (4) | 15 (4) | 12 (5) |
| 200–450 cGy TBI | 9 (30) | 261 (30) | 343 (36) | 140 (34) | 65 (26) |
| GVHD prophylaxis, n (%) | | | | | |
| CSP/TAC + MTX | 14 (47) | 504 (70) | 537 (57) | 224 (54) | 159 (63) |
| CSP/TAC + MMF | 11 (37) | 242 (28) | 313 (33) | 127 (31) | 63 (25) |
| CSP/TAC + sirolimus ± other | 1 | 31 | 38 | 34 | 13 |
| Single agent | 1 | 36 | 22 | 11 | 5 |
| None | 1 | 10 | 5 | 4 | 1 |
| Other | 2 | 37 | 34 | 13 | 10 |
| Acute GVHD, n (%) | | | | | |
| Grade 0–I | 11 (37) | 253 (29) | 296 (31) | 125 (30) | 74 (29) |
| Grade II–IV | 19 (63) | 597 (69) | 648 (68) | 280 (68) | 176 (70) |
| Grade III–IV | 6 (20) | 106 (12) | 141 (15) | 53 (13) | 38 (15) |
| Day of onset of grade II–IV acute GVHD, median (range) | 25 (10–109) | 26 (3–151) | 27 (1–151) | 28 (6–128) | 27 (5–139) |
| Chronic GVHD*, n | 6 | 296 | 349 | 242 | 126 |
| Day of onset of chronic GVHD, median (range) | 202 (89–385) | 168 (80–2065) | 161 (50–1510) | 164 (83 – 1757) | 183 (74–1065) |
| Relapse, n (%) | 12 (40) | 272 (32) | 272 (29) | 102 (25) | 45 (18) |
| Day of onset, median (range) | 112 (75–949) | 158 (15–3277) | 149 (13–4423) | 154 (27–2943) | 145 (20 – 1678) |
| Survival, d, median (range) | 324 (15–5085) | 954 (1–5873) | 890 (4–5859) | 919 (4–5855) | 754 (9–5616) |
| Patients alive, n (%) | 10 (33) | 425 (49) | 443 (47) | 188 (46) | 114 (45) |
| Patients dead, n (%) | 20 (67) | 435 (51) | 506 (53) | 225 (54) | 137 (55) |
| Cause of death, n (%) | | | | | |
| Relapse-related | 8 (40) | 213 (49) | 216 (43) | 85 (38) | 34 (25) |
| Non-relapse-related | 12 (60) | 222 (51) | 290 (57) | 140 (62) | 103 (75) |

Numbers in parentheses (except for ranges) represent the percentage of patients in each weight classification if percentage is ≥10%.

CSP indicates cyclosporine; TAC, tacrolimus; MTX, methotrexate; MMF, mycophenolate mofetil.

* Classified based on the National Institutes of Health criteria [19].

Study Endpoints

Primary endpoints were mortality at 100 days post-transplantation, overall mortality, NRM, and relapse. Relapse was considered the cause of death if patients experienced relapse or disease progression, regardless of other intermediate events. All deaths without preceding relapse/disease progression were considered NRM. Additional factors analyzed by weight group included differences in weight, serum total protein, and serum albumin from pretransplantation values to values measured at the time of discharge to home.

Statistical Methods

The association between BMI and outcome was assessed using Cox regression for each time-to-event outcome: overall mortality, relapse, NRM, and day +100 mortality). For such models, BMI was modeled as a categorical variable (underweight versus normal versus overweight versus obese versus very obese) and also as a nonlinear continuous variable using restricted cubic splines [5]. When modeled as a spline, 5 knots were used at the 5th, 25th, 50th, 75th, and 95th percentiles of all BMI values. This type of analysis provides a flexible model that makes minimal assumptions regarding the functional form of the association between BMI and outcome, thereby allowing the data to specify this relationship. Given the relatively large sample size and thus the relatively large numbers of events (>400 events for each time-to-event outcome), there was considerable room for adjustment in each Cox regression model. As such, each Cox regression model was adjusted for bilirubin and creatinine levels at transplantation, patient cytomegalovirus serostatus, patient age at transplantation, type of donor (unrelated versus related versus identical twin), severity of disease (low versus high risk), conditioning regimen intensity (MAC versus RIC), stem cell source, year of transplantation, and patient/donor sex (a total of 13 degrees of freedom). *P* values from regression models were estimated using the Wald test. Statistical interactions between BMI and conditioning (categorized as RIC versus TBI-containing MAC versus non-TBI-containing MAC) were assessed for each outcome by including appropriate parameters into the regression models. A global test of interactions for each model was then conducted using the Wald chi-square test statistic.

Patients considered low risk were those with aplastic anemia, myelodysplastic syndrome subtypes refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS), acute myelogenous leukemia (AML) or acute lymphoblastic leukemia in first remission, chronic myelogenous leukemia in chronic phase, and Hodgkin lymphoma or non-Hodgkin lymphoma in remission. All other patients were considered high risk except for those with “other” diagnoses, which were not categorized by disease risk. Changes in laboratory values from pretransplantation to discharge to home (day +80 to +100) were compared among BMI groups using linear regression, adjusting for the same factors listed above. For graphical purposes, the probabilities of overall survival were summarized using Kaplan-Meier estimates. Probabilities of relapse and NRM were calculated using cumulative incidence estimates; NRM was considered a competing risk for relapse, and relapse was considered a competing risk for NRM.

RESULTS

Patient Distribution by BMI

Figure 1 illustrates the distribution of BMI pretransplantation. Only 34% of patients had a normal BMI, whereas 38% were overweight, 16% were obese, and 10% were very obese. Thirty patients (1%) were underweight.

Effect of BMI on Transplantation Outcome

The effects of BMI (as a categorical variable) on overall mortality, NRM, relapse, and day +100 mortality are summarized in Table 3. These results suggest an effect of BMI on each outcome examined, as evidenced by the global *P* values. In addition, the impact of BMI on NRM (as well as on “early” mortality, the majority of events for these endpoints being death without relapse) was most evident among underweight and very obese

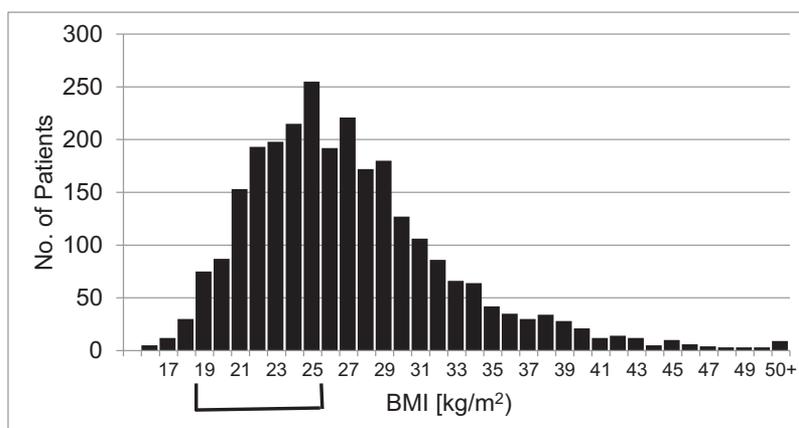


Figure 1. Frequency of BMI expressed as number of patients. The bracket on the x-axis represents the “normal” BMI range (18.5 to <25).

patients relative to those in the normal BMI group. The results further demonstrate an increased risk of overall mortality, day +100 mortality, and relapse in the underweight group relative to the normal BMI group.

Further assessment of these associations according to conditioning (as described in Statistical Methods) revealed evidence of a statistical interaction between BMI category and conditioning for NRM and the early-death outcomes (Table 3, *P* values for interaction). As such, separate regression models were fit for these 2 outcomes (Table 4). These results suggest that the detrimental impact observed in very obese patients is more pronounced in patients who received an MAC regimen, particularly one containing TBI. When classified by conditioning, the number of underweight patients is too small to allow for firm conclusions. Graphically, these associations by BMI category are depicted in Supplementary Figures S1 and S2.

The above modeling assumes that all patients within a particular BMI group behave the same regardless of whether the BMI is at the lower end or the upper end of the window that

defines the group. To avoid this relatively strong assumption, we allowed the association of BMI with outcome to vary in a continuous and nonlinear manner, as described in Statistical Methods.

These nonlinear associations are illustrated in Figures 2 and 3, either sorted by conditioning (Figure 2) or with BMI as a categorical variable (Figure 3). The results suggest that the detrimental effects on NRM and mortality are most pronounced at the extremes of the BMI values that were observed in this cohort of patients, and as with the categorical results summarized above and in Table 4, the effect on BMI appears to be greatest in the cohort that received TBI-containing MAC regimens. These curves display the hazard ratio (HR) of failure relative to a BMI of 21.75 (the midpoint of the normal BMI group). When testing the null hypothesis that the coefficients that compose a given curve are collectively equal to 0 (ie, a flat line at an HR of 1), the respective *P* values for NRM, day +100 mortality, relapse and overall mortality are shown in Figures 2 and 3.

Table 3
Association of Categorical BMI with Time-to-Event Outcomes

| Outcome | BMI category | HR | 95% CI | <i>P</i> Value |
|---------------------------------|--------------|------|-----------|-------------------|
| Overall mortality (1323 events) | Normal | 1 | — | — |
| | Underweight | 2.08 | 1.32-3.27 | .002 |
| | Overweight | .95 | .83-1.08 | .44 |
| | Obese | 1.00 | .84-1.17 | .95 |
| | Very obese | 1.15 | .95-1.40 | .15 |
| | | | | Global, .007 |
| | | | | Interaction, .24 |
| NRM (710 events) | Normal | 1 | — | — |
| | Underweight | 2.75 | 1.49-5.08 | .001 |
| | Overweight | 1.02 | .85-1.23 | .83 |
| | Obese | 1.13 | .90-1.42 | .28 |
| | Very obese | 1.68 | 1.31-2.15 | <.0001 |
| | | | | Global, <.0001 |
| | | | | Interaction, .007 |
| Relapse (728 events) | Normal | 1 | — | — |
| | Underweight | 1 | 1.13-3.61 | .02 |
| | Overweight | 2.02 | .71-1.01 | .06 |
| | Obese | .84 | .68-1.06 | .15 |
| | Very obese | .85 | .56-1.00 | .05 |
| | | | | Global, .009 |
| | | | | Interaction, .63 |
| Day +100 mortality (295 events) | Normal | 1 | — | — |
| | Underweight | 3.04 | 1.46-6.32 | .003 |
| | Overweight | 1.06 | .80-1.41 | .69 |
| | Obese | 1.06 | .74-1.52 | .74 |
| | Very obese | 1.41 | .95-2.09 | .09 |
| | | | | Global, .02 |
| | | | | Interaction, .06 |

Table 4
Association of Categorical BMI with Time-to-Event Outcomes by Conditioning Regimen*

| Outcome | BMI Group | RIC | | MAC, no TBI | | MAC, TBI | |
|-------------------|-------------|-------------------|---------|------------------|---------|-------------------|---------|
| | | HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value |
| NRM | Normal | 1 | | 1 | | 1 | |
| | Underweight | 3.50 (1.25-9.84) | .02 | 1.22 (.30-5.02) | .78 | 6.64 (2.50-17.66) | .0001 |
| | Overweight | 1.09 (.82-1.45) | .55 | .73 (.53-.99) | .04 | 1.67 (1.05-2.65) | .03 |
| | Obese | .86 (.59-1.25) | .42 | 1.01 (.70-1.47) | .94 | 2.17 (1.32-3.57) | .002 |
| | Very obese | 1.18 (.76-1.83) | .47 | 1.57 (1.07-2.31) | .02 | 3.30 (1.95-5.58) | <.0001 |
| Global P value | | | | .09 | | .003 | <.0001 |
| Day 100 mortality | Normal | 1 | | 1 | | 1 | |
| | Underweight | 3.43 (1.03-11.42) | .04 | 1.54 (.21-11.50) | .67 | 5.98 (1.89-18.89) | .002 |
| | Overweight | .81 (.52-1.25) | .34 | .94 (.56-1.56) | .80 | 2.20 (1.20-4.03) | .01 |
| | Obese | .61 (.33-1.13) | .12 | 1.13 (.62-2.06) | .69 | 1.76 (.87-3.57) | .12 |
| | Very obese | .60 (.27-1.35) | .22 | 1.21 (.61-2.41) | .58 | 3.45 (1.69-7.05) | .007 |
| Global P value | | .07 | | .92 | | .002 | |
| Day 150 mortality | Normal | 1 | | 1 | | 1 | |
| | Underweight | 2.52 (.77-8.24) | .13 | 2.84 (.87-9.33) | .08 | 5.16 (1.90-14.05) | .001 |
| | Overweight | .86 (.60-1.24) | .43 | .84 (.55-1.28) | .42 | 1.58 (.95-2.63) | .08 |
| | Obese | .60 (.36-1.00) | .05 | 1.09 (.66-1.81) | .73 | 1.38 (.76-2.50) | .29 |
| | Very obese | .83 (.46-1.51) | .55 | 1.19 (.66-2.13) | .56 | 3.09 (1.72-5.53) | .0002 |
| Global P value | | .15 | | .27 | | .0003 | |

BMI, body mass index; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; HR, hazard rate; CI, confidence interval.

* Number of events by conditioning regimen.

| BMI | RIC | MAC, no TBI | MAC, TBI |
|-------------|-----|-------------|----------|
| Normal | 294 | 346 | 220 |
| Underweight | 9 | 12 | 9 |
| Overweight | 382 | 370 | 197 |
| Obese | 155 | 157 | 101 |
| Very obese | 77 | 104 | 70 |

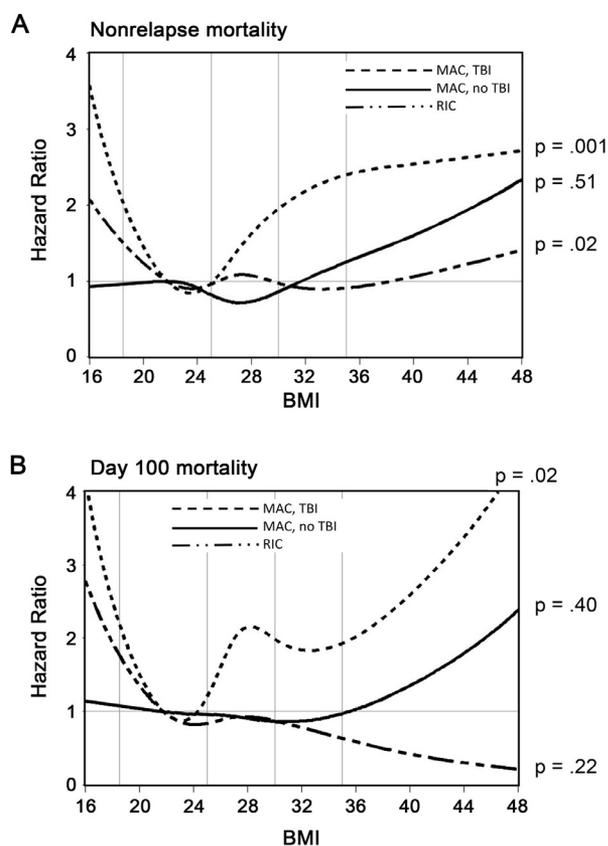


Figure 2. HR of failure relative to a BMI of 21.75 by intensity of conditioning regimen. Vertical lines represent categories of underweight, normal weight, overweight, obese, and very obese.

Laboratory Parameters

Additional clinical parameters that may reflect nutritional status during and after transplantation include changes in serum levels of albumin and total protein and in patient weight [6–10]. Changes in these values from pretransplantation to discharge to home (day +80 to +100) were compared using linear regression as described above. The mean changes among patients in the underweight, overweight, obese, and very obese groups were compared with the mean changes in the normal BMI group. As shown in Table 5, overweight patients had a greater increase in serum albumin level compared to normal weight patients; otherwise, there were no significant between-group differences in changes in serum albumin or total protein levels from pretransplantation to discharge to home. There was a significant difference in weight from pretransplantation to discharge to home, with underweight patients losing weight ($P = .03$) and overweight, obese, and very obese patients gaining weight ($P < .0001$ for each) relative to the change in weight among normal weight patients.

Nutritional Support

Underweight patients were more likely to be considered for enteral nutrition (EN) or parenteral nutrition (PN), especially during the early post-transplantation period. Detailed nutritional records, especially for patients who underwent HCT early in this cohort, were often incomplete; however, the medical records of the underweight patient group were reviewed in detail. Of the 30 underweight patients, 25 received PN during part of their initial hospital stay. The duration of PN for 19 patients was a median of 21 days (range, 6 to 67 days). Two of these patients also received EN during their hospitalization, 1 for 5 days and the other for 17 days. PN was always discontinued before discharge from the hospital, and

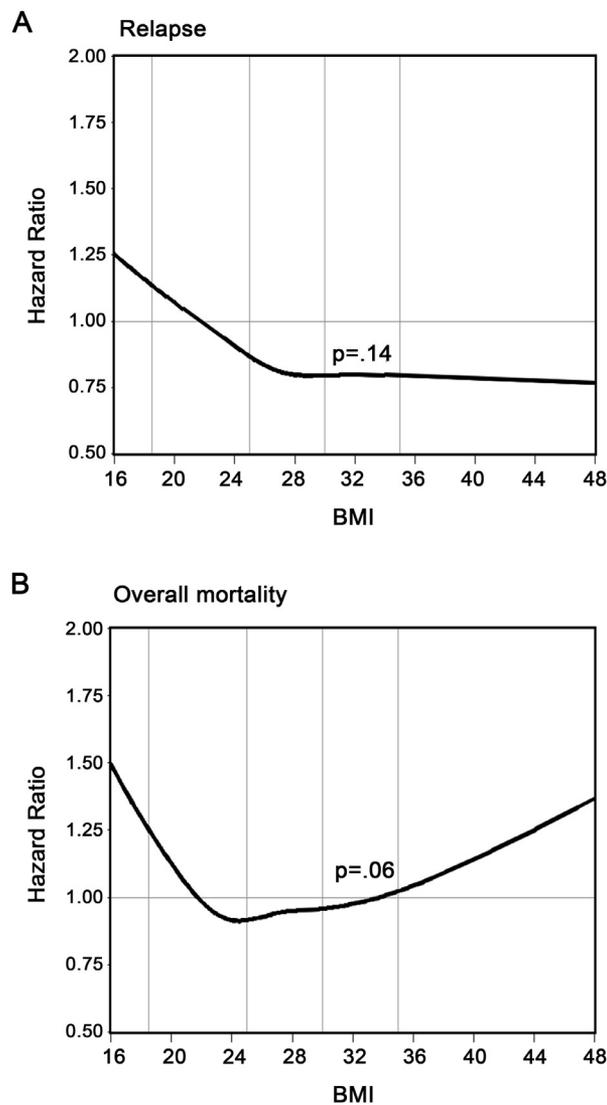


Figure 3. HR of failure relative to a BMI of 21.75.

Vertical lines represent categories of underweight, normal weight, overweight, obese, and very obese.

no underweight patient received EN or PN on an outpatient basis post-transplantation.

DISCUSSION

Previous studies assessing the impact of body habitus on outcomes of HCT have focused mainly on patients who are overweight or obese. According to the National Center for Health Statistics, in 2015–2016, 39.8% of US adults were obese based on BMI [11]. Less attention has been given to underweight patients. Results from the 2013–2014 National Health and Nutrition Examination Survey estimated that 1.4% of US adults age ≥ 20 years are underweight [12]. Patients at both extremes of weight have unique clinical problems when undergoing stem cell transplantation. In our analysis, we focused on the continuum of patient weight in estimating the risk of early (day +100) mortality, overall mortality, NRM, and relapse after HCT.

A variety of measures to assess body habitus have been reported in published data, including IBW, % IBW, % weight loss over time, body weight index, and BMI (Supplementary

Table S1). We evaluated BMI because most published studies in HCT recipients use this value. BMI was modeled as both a categorical variable using the 4 WHO weight categories (with the obese category further divided into obese and very obese) and as a nonlinear continuous variable to evaluate its effect on day +100 mortality, overall mortality, NRM, and relapse after HCT. Based on this analysis, BMI was significantly associated with NRM, affecting both extremes, very underweight and very obese. This association was most marked among patients who received a TBI-containing MAC regimen. BMI did not have a significant effect on relapse, and its impact on overall mortality was suggestive, with the greatest impact seen at the extremes of BMI but with a lower overall magnitude of effect relative to the association seen with NRM. When restricting the mortality analysis to 100 days after transplantation, the results were similar to those seen for NRM.

Clinical parameters of nutritional status have a limited effect on transplantation outcomes. Ferreira et al [9] and Rieger et al [13] evaluated changes in both serum albumin and total protein levels before and after transplantation, documenting decreases in both values that persisted through to discharge. In the study of Ferreira et al [9], higher serum albumin and total protein levels at discharge (not otherwise defined) were correlated with improved survival. That study was limited to 64 patients, however. In our study, we found no significant differences in serum albumin and total protein across BMI groups when comparing levels before transplantation and at discharge to home, usually between days +80 and +100.

Gleimer et al [2] analyzed the effect of BMI in 898 children and adults after a first allogeneic HCT. Outcomes evaluated included overall survival, NRM, relapse, and cumulative incidences of acute and chronic GVHD. Across BMI categories, only obese patients were at greater risk for NRM at 3 years compared with normal weight patients (HR, 1.43; $P = .04$), and obese patients had significantly lower relapse rates than normal weight patients (HR, .65; $P = .002$). There were no significant associations between BMI and overall survival, acute GVHD, or chronic GVHD.

In a review of CIBMTR data, Navarro et al [14] assessed the effect of BMI on transplantation outcomes in 4215 patients with AML undergoing a first HCT with either autologous stem cells ($n = 373$) or stem cells from related ($n = 2041$) or unrelated donors ($n = 1801$). Primary endpoints were overall survival, transplantation-related mortality (TRM), relapse, and leukemia-free survival (LFS). In a multivariate analysis of overall survival, the underweight group who received related donor transplants ($n = 32$) had a greater risk of mortality compared with normal weight patients (relative risk [RR], 1.92; $P = .002$). The underweight group also had an increased risk of TRM (RR, 2.23; $P = .014$), a higher risk of relapse (RR, 2.06; $P = .009$), and lower leukemia-free survival (RR, 2.09; $P < .001$) compared with the normal weight group. Among the unrelated donor and autologous transplant recipients, there were no statistically significant differences across the weight groups for any of the endpoints examined. In addition, there were no statistically significant differences in the rates of acute and chronic GVHD among the 4 weight groups in either allogeneic donor setting.

Additional studies are summarized in Supplementary Table S1. Given the heterogeneous patient populations studied and the variability in diagnoses, donors, transplantation regimens, and duration of follow-up, direct comparisons are difficult. Not all studies assessed underweight patients. Our present findings showing increased NRM in underweight patients are similar to our previously published data for a

Table 5
Association of Categorical BMI with Nutritional Parameters

| Outcome* | Variable | Estimate [†] | 95% CI | P Value |
|-----------------|-------------|-----------------------|----------------|----------------|
| Δ serum albumin | Normal | — | — | — |
| | Underweight | −.04 | −.28 to .19 | .72 |
| | Overweight | .05 | .003-.10 | .04 |
| | Obese | .01 | −.05 to .07 | .76 |
| | Very obese | .06 | −.01 to .14 | .10 |
| | | | | Global, .19 |
| Δ total protein | Normal | — | — | — |
| | Underweight | .15 | −.24 to .53 | .46 |
| | Overweight | −.02 | −.10 to .07 | .71 |
| | Obese | −.06 | −.16 to .04 | .27 |
| | Very obese | .04 | −.08 to .16 | .51 |
| | | | | Global, .58 |
| Δ weight | Normal | — | — | — |
| | Underweight | −5.98 | −11.20 to −.77 | .03 |
| | Overweight | 2.81 | 1.43-4.19 | <.0001 |
| | Obese | 4.55 | 2.78-6.32 | <.0001 |
| | Very obese | 8.25 | 6.14-10.36 | <.0001 |
| | | | | Global, <.0001 |

* Change in value from baseline (pretransplantation) to discharge home.

† Estimate represents the change in the listed group relative to the change in the normal BMI group.

group including both adults and children. By assessing BMI as a continuous nonlinear variable, the progressive effect of lower and higher patient weights on transplantation outcomes is readily apparent. Limiting the generalizability of our conclusions, however, is the relatively small number of patients with low BMI, with only 30 patients categorized as underweight.

Given the effects of both low BMI and high BMI on transplantation outcomes, the question is raised whether these risks can be reduced. Obesity has been well recognized as an adverse risk factor in calculating transplantation comorbidity scores; however, malnutrition is not factored into these analyses, likely due in part to the relatively low percentage of underweight patients who undergo transplantation [15]. Attempts to improve nutrition in underweight patients before or during transplantation have been proposed. Baumgartner et al [6] compared 90 adult AML patients who underwent myeloablative transplants and received PN with patients who did not receive nutritional therapy and showed that the patients who received PN had higher mortality, more infectious complications, and a greater risk of GVHD.

Consensus guidelines for recommending either EN or PN for HCT recipients have been published by both the American Society for Parenteral and Enteral Nutrition and the European Society for Parenteral and Enteral Nutrition [16,17]. An extensive review of available studies evaluating EN and PN in the HCT setting is provided in the American Society for Parenteral and Enteral Nutrition guidelines. Most of these studies involve small numbers of patients and are not well controlled. The European Society for Parenteral and Enteral Nutrition now recommends EN or PN during allogeneic HCT for undernourished patients; however, the level of evidence for this recommendation is rated as “very low.” In our experience with adult patients, EN is either refused or not well tolerated, whether patients are undernourished due to chemotherapy-associated anorexia or a preexisting eating disorder. Long-term PN also is often not practical, especially in the outpatient setting. Total gut rest for prolonged periods may also delay gut recovery [18]. Efforts to encourage patients to consider EN or PN are hindered by a lack of data demonstrating who would benefit most from nutritional support, the optimal route of administration, and timing and duration of therapy. Early education of patients and staff on the potential benefits of EN, along with

incorporation of EN into the overall HCT care plan, may increase patient acceptance of this modality of nutritional supplementation.

For overweight or obese patients, it is unreasonable to expect this population to lose significant weight while maintaining good nutritional status prior to transplantation. The National Marrow Donor Program defers potential stem cell donors who are very obese (BMI >40), but we are unaware of any stem cell transplant protocols that exclude patients from stem cell transplantation based on their BMI. For very obese patients, TBI-containing myeloablative conditioning regimens should be avoided, if possible, in an effort to decrease NRM in this subset of patients.

Thus, for both ends of the spectrum of patient weight before HCT, little can be done before or during transplantation, other than periodic short term EN or PN for undernourished patients or patients with severe GVHD. Patients need to be informed of their increased risk of NRM based on their BMI and the need to control their coexisting morbidities, such as hypertension, diabetes, and hyperlipidemia. All patients also benefit from frequent monitoring of their nutritional status by dietitians experienced with stem cell transplant recipients.

ACKNOWLEDGMENTS

The authors thank Chris Davis, Elizabeth Soll, Linda Glocking, Dr. Brenda Sandmaier, and Dr. Mohamed Sorrow for providing patient data from institutional databases.

Financial disclosure: This research was supported in part by the Biostatistics Shared Resource of the Fred Hutchinson/University of Washington Cancer Consortium (P30 CA015704).

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2018.10.006.

REFERENCES

- Deeg HJ, Seidel K, Bruemmer B, Pepe MS, Appelbaum FR. Impact of patient weight on non-relapse mortality after marrow transplantation. *Bone Marrow Transplant.* 1995;15:461–468.
- Gleimer M, Li Y, Chang L, et al. Baseline body mass index among children and adults undergoing allogeneic hematopoietic cell transplantation:

- clinical characteristics and outcomes. *Bone Marrow Transplant*. 2015;50:402–410.
- World Health Organization. *Obesity: preventing and managing the global epidemic: report of a WHO consultation. WHO Technical Report Series 894. Geneva, Switzerland: World Health Organization, 2000.*
 - Pasquini M. Why, When and Where to Report Conditioning Regimens. *Clinical Research Professionals/Data Management Conference: CIBMTR Summary Slides*. Available at: <http://www.cibmtr.org>. Accessed August 15, 2018.
 - Heinzel H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Comput Methods Programs Biomed*. 1997;54:201–208.
 - Baumgartner A, Zueger N, Bargetzi A, et al. Association of nutritional parameters with clinical outcomes in patients with acute myeloid leukemia undergoing haematopoietic stem cell transplantation. *Ann Nutr Metab*. 2016;69:89–98.
 - Espinoza M, Perelli J, Olmos R, Bertin P, Jara V, Ramirez P. Nutritional assessment as predictor of complications after hematopoietic stem cell transplantation. *Rev Bras Hematol Hemoter*. 2016;38:7–14.
 - Fuji S, Takano K, Mori T, et al. Impact of pretransplant body mass index on the clinical outcome after allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2014;49:1505–1512.
 - Ferreira EE, Guerra DC, Baluz K, de Resende Furtado W, da Silva Bouzas LF. Nutritional status of patients submitted to transplantation of allogeneic hematopoietic stem cells: a retrospective study. *Rev Bras Hematol Hemoter*. 2014;36:414–419.
 - Urbain P, Birlinger J, Lambert C, Finke J, Bertz H, Biesalski HK. Longitudinal follow-up of nutritional status and its influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2013;48:446–451.
 - Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. *NCHS Data Brief* 2017;1–8.
 - Fryar C.D., Carroll M.D., Ogden C.L. Prevalence of underweight among adults aged 20 and over: United States, 1960–1962 through 2013–2014. National Center for Health Statistics; 2016.
 - Rieger CT, Wischumerski I, Rust C, Fiegl M. Weight loss and decrease of body mass index during allogeneic stem cell transplantation are common events with limited clinical impact. *PLoS One*. 2015;10:e0145445.
 - Navarro WH, Agovi MA, Logan BR, et al. Obesity does not preclude safe and effective myeloablative hematopoietic cell transplantation (HCT) for acute myelogenous leukemia (AML) in adults. *Biol Blood Marrow Transplant*. 2010;16:1442–1450.
 - Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912–2919.
 - August DA, Huhmann MB. ASPEN clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enteral Nutr*. 2009;33:472–500.
 - Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36:11–48.
 - McDonald GB. How I treat acute graft-versus-host disease of the gastrointestinal tract and the liver. *Blood*. 2016;127:1544–1550.
 - Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease, I: Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2005;11:945–956.