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Relationship of Body Mass Index and Arm Anthropometry to Outcomes after Pediatric Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies

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A B S T R A C T

Although nutritional status may adversely affect various health outcomes, the relationship between anthropometry and outcomes after hematopoietic cell transplantation (HCT) has not been fully studied in children. We analyzed the impact of pre-HCT body mass index (BMI), arm muscle area, and arm fat area on outcomes in 733 patients age 2-18 years who underwent allogeneic HCT for a hematologic malignancy between 1985 and 2009. We evaluated these 3 variables according to patient group based on age- and sex-adjusted percentiles for BMI, arm muscle area (<5th, 5th-24th, 25th-94th, and ≥95th), and arm fat area (<25th, 25th-94th, and ≥95th). Cox proportional hazards regression models for event-free survival (EFS), relapse, and nonrelapse mortality (NRM) at 100 days and 3 years after HCT, as well as grade II-IV acute graft-versus-host disease (GVHD) and chronic GVHD, were performed using the 3 major variables and adjusted for covariates. BMI was <5th percentile in only 3% of patients and ≥95th percentile in 15% of patients, but outcomes for both groups were similar to those for the BMI 25th-94th percentile group. The BMI 5th-24th percentile group had lower EFS ($P = .01$) and higher relapse ($P = .003$) at day +100 post-HCT, but these associations did not hold at 3 years post-HCT. Arm muscle area was <5th percentile in 8% of patients, and arm fat area was <25th percentile in 10%. Analysis of arm muscle area showed that the <5th percentile group had lower EFS and higher NRM and relapse rate at day +100 ($P = .002$, .04, and .01, respectively) and 3 years ($P = .0004$, .008, and .01, respectively) post-HCT. Arm fat area <25th percentile was associated with lower EFS at day +100 (hazard ratio, 1.5; $P = .05$), but not at 3 years post-HCT. Anthropometry variables were not associated with acute or chronic GVHD. In conclusion, arm muscle area <5th percentile appears to be a stronger predictor than BMI of poor outcomes after HCT in children with hematologic malignancies.

INTRODUCTION

Poor nutritional status is known to adversely affect health outcomes. The role of nutritional status in children undergoing hematopoietic cell transplantation (HCT) is not fully understood. Early studies of pediatric HCT using ideal body weight showed poor survival in underweight patients after transplantation, but no difference in survival in overweight patients [1,2]. Since then, body mass index (BMI) has become a more commonly used index of nutritional status. In 2 studies, overweight patients (BMI ≥95th percentile) demonstrated decreased survival compared with non-overweight children [3,4].

BMI might not be the best indicator of nutritional status or body composition in pediatric HCT patients given that BMI only indicates weight relative to height (body size), and cannot discriminate between fat and muscle mass [5]. But body composition can be estimated by arm anthropometry, which measures peripheral tissue and provides an approximation of whole-body muscle and fat mass. Although arm anthropometry is not widely done, it is routinely performed at our center.

The purpose of the present study was to determine whether BMI and body composition as measured by arm anthropometry are associated with survival outcomes and the development of acute and chronic graft-versus-host disease (GVHD) in a large population of pediatric patients undergoing HCT for hematologic malignancies.

PATIENTS AND METHODS

Patient Selection

Between 1985 and July 1, 2009, 822 consecutive children age 2-18 years underwent myeloablative conditioning and allogeneic HCT for a hematologic malignancy at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle. Thirty-two of these patients were excluded from the present analysis, including 9 who received a T cell–depleted allograft, 6 who did not consent to follow-up, 5 who received ^{131}iodine therapy, 5 with Down syndrome, 4 who received 10-Gy single-fraction total body irradiation (TBI), and 3 identical twin donor allograft recipients. The remaining 790 patients or their responsible guardians consented to follow-up under Protocol 999.2, and the data were reviewed under Protocol 1782 approved by the FHCRC Institutional Review Board.

Anthropometric data were unavailable for 57 patients (23 for undocumented reasons, 20 for patient refusal or uncooperativeness, 9 not tested owing to direct hospital admissions, 4 for obesity, and 1 with missing data), leaving a total of 733 patients for analysis. Compared with the patients with anthropometric data, the 57 patients without anthropometric data were younger (7.5 years versus 10.4 years; $P < .001$) at time of transplantation, but there were no statistical differences in transplantation outcomes (data not shown).

Preparative Regimens, Stem Cell Sources, and Supportive Care

Transplantation preparative regimens included either chemotherapy or chemoradiotherapy as described previously [6-10]. Most chemotherapy-only

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regimens used cyclophosphamide 50 mg/kg/day for 4 days combined with busulfan 4 mg/kg/day for 4 days [6,8]. Most of the busulfan and cyclophosphamide doses were calculated using adjusted body weight if the patient's actual weight was >100% of ideal body weight, when dosing was based on per-kilogram weight. Since 1992, most busulfan doses have been adjusted based on pharmacokinetic levels [11]. Most TBI regimens included cyclophosphamide 60 mg/kg/day for 2 days. Between 1985 and 2000, TBI was delivered from dual opposing cobalt-60 sources at a dose rate in air of 5-8 cGy/min as fractionated TBI, with exposures of 2.0-2.75 Gy for 6-7 consecutive days or hyperfractionated exposures of 1.2 Gy 2-3 times daily for 4 consecutive days [6,9,10]. Starting in 2001, TBI has been delivered by a linear accelerator.

The allogeneic transplantation recipients received bone marrow, peripheral blood, or umbilical cord blood stem cells harvested from related or unrelated donors. All allogeneic transplantation recipients received prophylaxis for acute GVHD depending on the type of donor and protocol in use at the time of HCT and generally including either methotrexate or methotrexate and a calcineurin inhibitor, but less often including corticosteroids, antithymocyte globulin, mycophenolate mofetil, or monoclonal antibodies as additional prophylactic agents [12-14]. Acute and chronic GVHD were diagnosed, graded, and treated as described previously [15-18].

All surviving patients underwent evaluation for engraftment and chronic GVHD at 80-100 days after transplantation. Patients returned to the FHCRC for long-term follow-up at 1 year and electively thereafter. Follow-up after 1 year consisted of annual contact with referring physicians between 1985 and 1990, and questionnaires mailed annually to patients and their primary medical providers from 1991 to present.

Study Data

Data were obtained from the FHCRC clinical information database, transplantation flowsheets, nutritional records, and long-term follow-up records. Study data were collected through July 1, 2012.

BMI (in kg/m^2) was calculated based on patient height and weight at the time of HCT. Sex- and age-adjusted BMI was calculated using the 2000 Centers for Disease Control and Prevention's BMI for age growth charts to obtain percentile rankings [19]. Patients were divided into 4 BMI categories: underweight (<5th percentile), at risk for underweight (5th to <25th percentile), normal and at risk for overweight (25th to <95th percentile), and overweight (≥95th percentile).

Arm anthropometry was performed by registered dietitians. Mid-upper arm circumference was measured with flexible tape to the nearest 0.1 cm, and triceps skin fold thickness was measured with a Harpenden skinfold caliper as the average of 3 measurements taken to the nearest 0.2 mm at the halfway point between the acromion and olecranon process of the right upper arm. Arm muscle area and arm fat area *z*-scores were calculated according to the equations and age and sex-matched norms of Frisancho [20] and expressed as percentiles. Patients were divided into 4 arm muscle area categories: <5th percentile, 5th to <25th percentile, 25th to <95th percentile, and ≥95th percentile. Because of a limited number of patients in the <5% percentile category, arm fat area was collapsed into 3 categories: <25th percentile, 25th to <95th percentile, and ≥95th percentile.

Study Endpoints, Variables, and Statistical Methods

For the purpose of analysis, patient diagnoses at HCT were categorized into 4 groups: acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and juvenile myelomonocytic leukemia and myelodysplastic syndrome. Variables selected for adjustment included sex, race/ethnicity (non-Hispanic white versus other race/ethnicity), diagnosis, time from diagnosis to HCT (<1 year versus ≥1 year), age at HCT (2-9 years versus 10-18 years), TBI (yes/no), donor type (related versus unrelated), donor–recipient HLA-matching (matched or mismatched, defined as at least 1 antigen mismatch at HLA-A, -B, or -DRB1), acute GVHD prophylaxis (use of 1, 2, or 3 or more prophylactic drugs), and disease status. For the latter, good risk included ALL and AML in first or second complete remission (CR), CML in chronic phase, juvenile myelomonocytic leukemia and myelodysplastic syndrome, and myelodysplastic syndrome in refractory anemia or refractory anemia with ringed sideroblasts, and poor risk included ALL and AML in active relapse or third or greater CR, CML in acute phase or blast crisis, and myelodysplastic syndrome in refractory anemia with excess blasts or excess blasts in transformation.

Primary endpoints were nonrelapse mortality (NRM), relapse, and event-free survival (EFS) over the first 100 days and the first 3 years posttransplantation, and the development of grade II-IV acute GVHD and clinical extensive chronic GVHD. NRM was defined as death in CR. Relapse was defined as recurrence of disease in bone marrow. EFS was defined as survival without death, relapse, graft failure, or secondary malignancy.

All endpoints were adjusted for diagnosis, sex, race/ethnicity, age at HCT, TBI, donor type, and HLA matching. NRM, EFS, and relapse were also adjusted for disease status and time from diagnosis to HCT. Acute GVHD was also adjusted for acute GVHD prophylaxis.

Survival curves were estimated by the Kaplan-Meier method. Cox regression was used for hazard ratio (HR) analysis, with adjustment for covariates. NRM and relapse were treated as mutually competing risks. Death was treated as a competing risk for analysis of acute and chronic GVHD. Overall tests of significance reflect likelihood ratio tests; comparisons of individual levels to the reference level reflect Wald tests. All *P* values are 2-sided. Descriptive data were analyzed using SPSS software (IBM, Armonk, NY). Descriptive statistics are reported as mean and range.

RESULTS

Patient Population

Patient and transplantation characteristics are presented in Table 1. The study population comprised 733 patients, of whom 60% were male, 54% had ALL and 26% had AML, 56% were good risk, and 65% had received a HLA-matched transplantation from a sibling (41%), unrelated (37%), or other related (22%) donor. The distribution of patient BMI and arm anthropometry is shown in Table 2. Three percent of the patients were underweight (BMI <5th percentile), and 15% were overweight (BMI ≥95th percentile). Arm muscle area was very low (<5th percentile) in 8%, and arm fat area was low (<25th percentile) in 10%. Pearson correlation coefficients for the 3 measures were as follows: BMI with arm muscle area, $r = 0.60$, $P < .0001$; BMI with arm fat area,

Table 1
Patient and Transplantation Characteristics

Characteristic	Value
Number of patients	733
Age at HCT, yr, median (range)	9.2 (2.0-17.9)
Sex, n (%)	
Female	297 (40)
Male	436 (60)
Race/ethnicity, n (%)	
Non-Hispanic white	574 (78)
Other race/ethnicity	159 (22)
Diagnosis at HCT, n (%)	
ALL	395 (54)
AML	189 (26)
CML	89 (12)
Juvenile myelomonocytic leukemia	15 (2)
Myelodysplastic syndrome	45 (6)
Disease phase, n (%)	
Good	410 (56)
Poor	323 (44)
Donor type for first HCT, n (%)	
Related (parent or relative)	159 (22)
Unrelated	269 (37)
Sibling	305 (41)
HLA matching, n (%)	
Matched	475 (65)
Mismatched	258 (35)
Stem cell source at first HCT, n (%)	
Bone marrow	645 (88)
Peripheral blood	50 (7)
Cord blood	38 (5)
HCT preparative regimen, n (%)	
Fractionated 12-15.75 Gy TBI	637 (87)
Non–TBI-containing regimens	
Busulfan + cyclophosphamide	86 (12)
Other	10 (1)
Acute GVHD prophylaxis agents, n (%)	
1	103 (14)
2	562 (77)
3+	68 (9)
Acute GVHD grade, n (%)*	
0-I	190 (26)
II-IV	541 (74)
Clinical extensive chronic GVHD (yes/evaluable), n (%)	241/526 (46)

* Two patients were not evaluable for acute GVHD.

Table 2
Distribution of Arm Anthropometry Measurements by BMI

BMI	N	Arm Muscle Area, n (%)				Arm Fat Area, n (%)		
		<5th	5th-24th	25th-94th	≥95th	<25th	25th-94th	≥95th
<5th	21	11 (52)	10 (48)	—	—	14 (67)	7 (33)	—
5th-24th	67	24 (36)	28 (42)	15 (22)	—	21 (31)	46 (69)	—
25th-94th	533	22 (4)	173 (32)	324 (61)	13 (2)	40 (8)	395 (74)	97 (18)
≥95th	113	1 (1)	9 (8)	78 (69)	25 (22)	—	38 (34)	75 (66)
Total	733	58 (8)	220 (30)	417 (57)	38 (5)	75 (10)	486 (66)	172 (23)

$r = 0.68$, $P < .0001$; and arm muscle area with arm fat area, $r = 0.32$, $P < .0001$ (data not shown).

EFS

Transplantation outcomes by BMI and arm anthropometry are presented in Table 3. When categorized according to BMI, EFS at day +100 was 60% for the 5th-24th percentile group and 72% for the 25th-94th percentile group (Figure 1). As shown in Table 4, in multivariate analysis, the BMI 5th-24th percentile group was associated with a lower EFS at day +100 (HR, 1.7; $P = .01$), but this association was no longer significant (HR, 1.3; $P = .09$) at 3 years after HCT.

When categorized according to arm muscle area, EFS at day +100 was 52% for the <5th percentile group and 69% for the 25th-94th percentile group. At 3 years post-HCT, EFS had dropped to 22% for the arm muscle area <5th percentile group and 42% for the 25th-94th percentile group (Figure 2). In multivariate analysis, arm muscle area <5th percentile was significantly associated with decreased EFS at day +100 (HR, 2.0; $P = .002$) and 3 years (HR, 1.8; $P = .0004$) post-HCT.

When categorized according to arm fat area, EFS at day +100 post-HCT was 59% for the <25th percentile group and 70% for the 25th-94th percentile group. At 3 years post-HCT, EFS had dropped to 32% for the arm fat area <25th percentile group and to 42% for the 25th-94th percentile group. In multivariate analysis, arm fat area <25th percentile was associated with EFS at day +100 (HR, 1.5; $P = .05$), but not at 3 years (HR, 1.3; $P = .09$), post-HCT.

NRM

In multivariate analysis, BMI and arm fat area were not associated with NRM at day +100 or 3 years post-HCT. Among the arm muscle area groups, the <5th percentile group had a 26% NRM at day +100, compared with 16% for the 25th-94th percentile group. At 3 years post-HCT, NRM had increased to 38% for the <5th percentile group and 24% for the 25th-94th percentile group. In multivariate analysis, the HR of NRM at day +100 was nearly 2-fold higher for the arm muscle area <5th percentile group compared with the 25th-94th percentile group (HR, 1.88; $P = .04$), and this association was even more significant at 3 years (HR, 1.94; $P = .008$).

Relapse

Among the BMI groups, relapse at day +100 post-HCT was 21% for the 5th-24th percentile group and 11% for the 25th-94th percentile group. In multivariate analysis, the BMI 5th-24th percentile group was associated with a 2- to 3-fold increased risk of relapse at day +100 (HR, 2.5; $P = .003$), but the association was no longer significant at 3 years post-HCT (HR, 1.3; $P = .23$). In the arm muscle area <5th percentile group, 21% of patients had relapsed at day +100, representing a 2- to 3-fold increased risk compared with the 25th-94th percentile group (HR, 2.4; $P = .01$), and this association remained significant at 3 years post-HCT (HR, 1.8; $P = .01$). Arm fat area was not associated with relapse at day +100 or 3 years post-HCT.

Acute and Chronic GVHD

As shown in Table 3, BMI was associated ($P = .04$) with an increased incidence of acute GVHD, which rose from 48% in the <5th percentile group to 77% in the ≥95th percentile group, but arm muscle area and arm fat area were not associated with acute GVHD. We found no significant associations between chronic GVHD and BMI, arm muscle area, or arm fat area. None of the anthropometric measures tested here were associated with acute or chronic GVHD in multivariate analysis (data not shown).

Table 3
BMI, Arm Anthropometry, and Transplantation Outcomes

	N	EFS, Day +100	NRM, Day +100	Relapse, Day +100	Acute GVHD	Chronic GVHD*	EFS, 3 Year	NRM, 3 Year	Relapse, 3 Year
BMI, n (%)									
<5th	21	13 (67)	3 (14)	4 (19)	10 (48)	2/13 (15)	6 (29)	5 (24)	10 (48)
5th-24th	67	40 (60)	12 (18)	14 (21)	46 (69)	20/40 (50)	26 (39)	18 (27)	23 (34)
25th-94th	533	382 (72)	86 (16)	57 (11)	398 (75)	182/395 (46)	231 (43)	126 (23)	171 (32)
≥95th	113	74 (65)	22 (19)	17 (15)	87 (77)	37/78 (47)	42 (37)	31 (27)	40 (35)
P value		.10	.05	.71	.04	.16	.12	.16	.50
Arm muscle area, n (%)									
<5th	58	30 (52)	15 (26)	12 (21)	41 (71)	11/29 (38)	13 (22)	22 (38)	23 (40)
5th-24th	220	159 (72)	36 (16)	24 (11)	162 (74)	76/166 (46)	93 (42)	52 (24)	74 (34)
25th-94th	417	289 (69)	67 (16)	54 (13)	314 (75)	137/300 (46)	175 (42)	99 (24)	137 (33)
≥95th	38	31 (82)	5 (13)	2 (5)	24 (63)	17/31 (55)	20 (53)	6 (16)	11 (29)
P value		.009	.06	.21	.71	.78	.002	.08	.02
Arm fat area, n (%)									
<25th	75	44 (59)	13 (17)	15 (20)	48 (64)	16/48 (33)	24 (32)	20 (27)	31 (41)
25th-94th	486	341 (70)	78 (16)	62 (13)	356 (73)	160/351 (46)	204 (42)	115 (24)	159 (33)
≥95th	172	124 (72)	32 (19)	15 (9)	137 (80)	65/127 (51)	73 (42)	44 (26)	55 (32)
P value		.13	.16	.79	.16	.06	.13	.14	.68

* Chronic GVHD (clinical extensive divided by number evaluable).

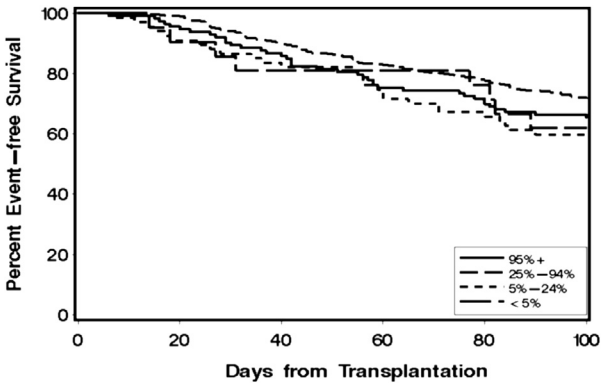

Figure 1. EFS by BMI percentile category: <5th, 5th-24th, 25th-94th, and ≥95th. The *P* values for unadjusted comparisons among the 4 categories were as follows: <5th versus 25th-94th, $P = .13$; 5th-24th versus 25th-94th, $P = .12$; ≥95th versus 25th-94th, $P = .09$). Adjusted *P* values are presented in Table 4.

Characteristics of the Low Arm Muscle Area Group

Mortality was 78% among the 58 patients in the arm muscle area <5th percentile group, higher (94%) in the 33 poor-risk patients and lower (56%) in the 25 good-risk patients. Before day +100 post-HCT, 6 patients died from regimen-related toxicity, 4 from relapse, 4 from grade IV acute GVHD, 4 from infections (2 cytomegalovirus, 2 fungal), and 3 from respiratory failure. After day +100, 17 patients died from relapse, 4 from infections (2 fungal, 1 cytomegalovirus, 1 staphylococcus), 1 from gastrointestinal hemorrhage, 1 from graft failure, and 1 from an unknown cause.

The distribution of BMI weight categories in the arm muscle area <5th percentile group was 19% (11 of 58) underweight, 41% at risk for underweight, 38% normal and at risk for overweight, and 2% overweight. At presentation for HCT, all of these patients had a normal serum creatinine level, and 14 patients had hypoalbuminemia (serum albumin <3.3 g/dL), 7 of whom had received total parental nutrition and/or nasogastric tube feeding. Seven other patients had received nutritional support for a history of gastrointestinal infections (n = 4) or weight loss, poor feeding, and stomatitis (n = 3).

DISCUSSION

This is the first study to report an association between arm anthropometry and transplantation outcomes in a large population of pediatric HCT recipients. A major finding of this study is that arm anthropometry is a better predictor of poor outcomes than the more commonly used BMI. Specifically, patients with pretransplantation arm muscle area <5th percentile had inferior EFS at day +100 and 3-years post-HCT owing to increased rates of relapse and NRM. Sarcopenia (low muscle mass) has been associated with toxicity in adult cancer patients receiving chemotherapy, and malnourished cancer patients are at increased risk for infection [21-23].

Our NRM data are consistent with these observations, in that among the group with arm muscle area <5th percentile, 14% died from infection, 10% died from regimen-related toxicity, and 5% died from respiratory failure; however, whether malnutrition increases the risk of relapse has not been clearly demonstrated. We could only identify 1 study showing an association of severely reduced protein energy reserves with an increased risk of relapse [24]. In our study, the 3 year posttransplantation relapse rate was almost 2-fold higher (HR, 1.81) in the arm muscle area <5th percentile

Table 4
Multivariate Analysis

	EFS to Day +100		NRM to Day +100		Relapse to Day +100	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
BMI						
<5th	1.62 (0.8-3.4)	.20	1.09 (0.3-3.6)	.88	1.88 (0.6-5.6)	.25
5th-24th	1.73 (1.1-2.6)	.01	1.36 (0.7-2.5)	.33	2.54 (1.4-4.7)	.003
25th-94th	1.0	–	1.0	–	1.0	–
≥95th	1.18 (0.8-1.7)	.38	1.31 (0.8-2.1)	.28	1.32 (0.8-2.3)	.32
Arm muscle area						
<5th	2.03 (1.3-3.2)	.002	1.88 (1.0-3.4)	.04	2.39 (1.2-4.8)	.01
5th-24th	0.99 (0.7-1.4)	.94	1.12 (0.7-1.7)	.59	0.97 (0.6-1.6)	.91
25th-94th	1.0	–	1.0	–	1.0	–
≥95th	0.59 (0.3-1.3)	.18	0.86 (0.3-2.2)	.75	0.43 (0.1-1.8)	.24
Arm fat area						
<25th	1.53 (1.0-2.3)	.05	1.36 (0.7-2.6)	.34	1.46 (0.8-2.6)	.22
25th-94th	1.0	–	1.0	–	1.0	–
≥95th	0.93 (0.7-1.3)	.66	1.07 (0.7-1.6)	.74	0.79 (0.4-1.4)	.42
	EFS to 3 Yrs		NRM to 3 Yrs		Relapse to 3 Yrs	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
BMI						
<5th	1.42 (0.8-2.4)	.20	1.32 (0.5-3.3)	.55	1.50 (0.8-2.9)	.23
5th-24th	1.33 (1.0-1.9)	.09	1.42 (0.9-2.3)	.18	1.32 (0.8-2.1)	.23
25th-94th	1.0	–	1.0	–	1.0	–
≥95th	1.17 (0.9-1.5)	.26	1.37 (0.9-2.1)	.13	1.19 (0.8-1.7)	.34
Arm muscle area						
<5th	1.83 (1.3-2.6)	.0004	1.94 (1.2-3.2)	.008	1.81 (1.1-2.9)	.01
5th-24th	1.01 (0.8-1.3)	.92	1.04 (0.7-1.5)	.85	1.09 (0.8-1.5)	.56
25th-94th	1.0	–	1.0	–	1.0	–
≥95th	0.74 (0.5-1.2)	.22	0.58 (0.3-1.3)	.20	0.87 (0.5-1.6)	.65
Arm fat area						
<25th	1.32 (1.0-1.8)	.09	1.53 (0.9-2.5)	.10	1.31 (0.9-2.0)	.19
25th-94th	1.0	–	1.0	–	1.0	–
≥95th	0.98 (0.8-1.2)	.88	1.04 (0.7-1.5)	.82	1.06 (0.8-1.4)	.73

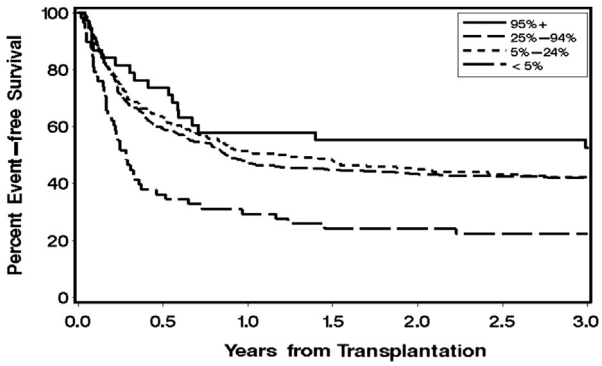

Figure 2. EFS by arm muscle area percentile category: <5th, 5th-24th, 25th-94th, and ≥95th. The *P* values for unadjusted comparisons among the 4 categories were as follows: <5th versus 25th-94th, $P = .0002$; 5th-24th versus 25th-94th, $P = .77$; ≥95th versus 25th-94th, $P = .22$). Adjusted *P* values are shown in Table 4.

group. This finding might be related to more aggressive underlying malignancies, despite our attempt to adjust for disease status in the multivariate analysis. Further investigation into the potential relationship between reduced muscle mass and risk of relapse may be warranted.

Underweight and overweight patients are generally considered at risk for poor outcomes. In our study, overweight patients had a lower EFS at day +100 post-HCT compared with non-overweight patients (65% versus 70%), but the difference was not significant in multivariate analysis. In contrast, underweight (BMI 5th-24th percentile) patients had significantly reduced EFS at day +100 (HR, 1.7; $P = .01$). Similarly, the very underweight (BMI <5th percentile) patients had a lower EFS at day +100 (HR, 1.6; $P = .20$), but this was not statistically significant, possibly owing to the small number of patients. Thus, patients with BMI <25th percentile appear to be at greater risk for decreased EFS at day +100 post-HCT compared with normal-to-overweight patients, but this risk did not extend to 3 years post-HCT.

Our findings regarding BMI and survival differ from those of 2 previous studies of pediatric HCT recipients [3,4], despite similar proportions of underweight and overweight patients. In our study, 3% of patients were underweight (BMI <5th percentile) and 15% were overweight (BMI ≥95th percentile), comparable to the 9% with BMI <5th percentile, 11% with BMI <10th percentile, and 11%-17% overweight in the previous studies [3,4]. Those 2 studies showed poorer survival in overweight children compared with non-overweight children. In a multicenter study of 1281 children with aplastic anemia, overall survival was lower in overweight children compared with non-overweight children (65% versus ≥69%) [4]. In a single-institution study of 325 children with various diseases (27% nonmalignant), overall survival and EFS at 5 years post-HCT were lower in overweight compared with non-overweight children (47% versus 60% [$P = .02$] and 42% versus 58% [$P = .02$], respectively) [3]. In our study, EFS at 3 years post-HCT was lower in overweight children compared with non-overweight children (37% versus 42%), but the difference was not statistically significant. One possible explanation for the lower survival seen in our study compared with previous studies is that the children in our cohort all had underlying malignancies, whereas the other study cohorts were entirely or partially composed of patients with nonmalignant diseases not at risk for relapse.

Taken together, the data suggest that the prognostic relevance of BMI on posttransplantation survival might be disease-specific. High BMI appears to be associated with lower survival in patients with nonmalignant disease, but for patients with malignant disease, our findings do not support any association of BMI with survival other than short-term EFS in the underweight BMI category.

Although BMI is the most commonly used index of body composition, it may lack discriminatory power as a predictor of posttransplantation outcome, given that it indicates weight relative to height (ie, body size) but cannot distinguish between fat and muscle mass. A previous study found that BMI was a poor predictor of nutritional status in the 30% of female children and 69% of male children with suboptimal nutritional status before HCT, as determined by body cell mass [5]. Eight percent of children in our cohort had low peripheral muscle mass, with arm muscle area <5th percentile, similar to a previous study reporting 7% of patients with muscle wasting before HCT [25]. The etiology of reduced muscle mass does not appear to be entirely related to energy intake, considering that 40% of the children with low arm muscle area in our cohort had a BMI >25th percentile. Muscle loss also might be related to infectious complications, the primary disease, or therapy. Weight loss often precedes a diagnosis of hematologic malignancy and frequently occurs during chemotherapy; for example, a study of childhood ALL showed a 5% reduction in the ratio of lean mass to total body weight after 6 months of therapy [26]. In our study, infection did not appear to be a major cause of muscle loss, given that only 7% of the low arm muscle area group had a gastrointestinal infection before HCT.

Our findings confirm that BMI does not increase the risk of acute GVHD. Barker et al. [4] found that BMI at the time of HCT did not increase the adjusted risk of grade III-IV acute GVHD. In this study, we did not find any association between grade II-IV acute GVHD and BMI or between anthropometry and chronic GVHD.

Arm anthropometry provides a simple, easily performed, and low-cost measurement of body composition. But although arm anthropometry provides an approximation of total body muscle mass, it does not provide a direct measure, as can be obtained by dual-energy X-ray absorptiometry (DEXA). Whether arm anthropometry is equivalent to DEXA as a measure of body composition has not been clearly established. Mid-upper arm circumference is highly correlated with lean body mass, but skinfold measurements may underestimate whole body fat as measured by DEXA [27,28]. Further investigation into the validity of arm anthropometry and DEXA scanning may be warranted.

In addition to measurements of body composition, identification of sarcopenia by biological markers may be of interest. During chemotherapy for childhood ALL, serum albumin was abnormally low in the majority of patients, and in another study, lean body mass from DEXA scans was correlated with increased serum creatinine concentration ($r = 0.52$; $P < .001$) [26,29]. In the present study, all patients in the arm muscle area <5th percentile group had a normal serum creatinine concentration, but 24% had a low serum albumin level at the time of HCT.

This study had several limitations, including its retrospective nature and a population with heterogeneous diagnoses and treatments. In addition, because nutritional status in children before HCT can be a surrogate for disease status or complications of previous therapy, it is possible that despite statistical adjustments for disease status, our findings may be related to other variables that were not considered. Population values were unavailable for BMI in

patients age <2 years because arm anthropometry in infants is unreliable, which limits the generalizability of our findings to this population. As discussed earlier, measurement of total body composition by DEXA might have yielded different results than those obtained by arm anthropometry. We were unable to evaluate the potential impact of differences in preparative regimen-specific chemotherapy doses or dose adjustments for overweight patients or based on pharmacokinetic levels, because these data are not routinely collected. Finally, underweight patients who have lost weight compared with baseline may fare differently than patients with a low baseline weight; however, adjusting for pretransplantation weight change was beyond the scope of this study.

CONCLUSION

Our data suggest that although low BMI is associated with lower day +100 EFS, low pretransplantation muscle mass as measured by arm anthropometry is a better predictor of reduced EFS, increased NRM, and increased relapse at both day +100 and 3 years post-HCT in children undergoing transplantation for hematologic malignancy. Given the potential impact of body composition on a child undergoing HCT, patients should undergo nutritional status assessment before HCT. Although not the focus of the present study, our findings suggest that patients with low BMI, and especially patients with pretransplantation muscle wasting, might benefit from increased preemptive nutritional monitoring and support. Further research on the optimal assessment of body composition and its role as a potential risk factor in transplantation recipients is needed.

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