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Limitations of body mass index to assess body composition due to sarcopenic obesity during leukemia therapy

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Abstract

Obesity as defined by body mass index percentile (BMI%) is strongly associated with relapse and poorer survival in childhood ALL. Whether BMI% accurately reflects body fat percentage (BF%) in this population is unknown. We conducted a prospective study assessing body composition during frontline ALL therapy. Dual-energy X-ray absorptiometry measured BF% and lean muscle mass (LMM) at diagnosis, end of Induction, and end of Delayed Intensification. Sarcopenic obesity (gain in BF% with loss of LMM) was surprisingly common during ALL treatment, resulting in poor correlation between changes in BMI% (expressed as Z-score) and BF% overall ($r=-0.05$) and within patients ($r=-0.09$). BMI Z-score and BF% changed in opposite directions in >50% of interval assessments. While BMI% at diagnosis is a suitable predictor of obesity/BF% for epidemiological studies, change in BMI% (as expressed as Z-score) does not reflect body composition. Studies evaluating obesity in leukemia should consider using direct measures of body composition.

Keywords

Childhood ALL; Obesity; Body Mass Index; DXA Scan; Body Fat; Adiposity

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DECLARATION OF INTERESTS

The authors have no conflicts of interest to disclose.

INTRODUCTION

Obesity has reached epidemic proportions in the United States[1] with a marked increase in obesity-associated cancers and cancer mortality,[2–4] including leukemia.[5,6] Body mass index (BMI)[7] is a metric frequently extrapolated from the general population to pediatric[8–11] (as age- and sex- adjusted BMI percentiles [BMI%] or Z-scores) and adult[4,12–15] oncology populations to assess the influence of obesity on leukemia incidence and clinical trial endpoints. In childhood acute lymphoblastic leukemia (ALL), greater BMI% has been associated with poorer initial disease response,[16] increased risk for relapse,[8] worse survival,[9] treatment-related toxicity,[9,17–19] and late effects in survivors.[20,21] A recent meta-analysis by Amakwanah et al has confirmed the adverse association of BMI%-defined obesity with poorer survival from childhood leukemias.[22] Yet, while BMI% is a convenient and accessible measure in the clinical setting, it does not always reflect true physiological overweight or obesity. This is because BMI is calculated from height and weight and thus does not differentiate between muscle and adipose tissue.[23] Thus, despite being a widely accepted surrogate for body fat and obesity among healthy children and adolescents,[24] BMI% has nonetheless been shown to yield erroneous results in characterizing body composition in various populations,[25–27] even in healthy children.[28]

In cancer therapy, such a discrepancy between “obesity” (defined by BMI% in children) and adiposity (actual body fat present) may be a vital distinction confounding assessments of obesity’s influence on cancer outcome. To our knowledge, no studies have validated BMI% as an adequate surrogate for body composition during leukemia therapy. This would be of particular interest in childhood ALL where cumulative time spent at an “obese” BMI% during the initial dose-intensive phases of pre-Maintenance chemotherapy is adversely associated with survival,[9] but where BMI% is also seen to fluctuate significantly throughout the same period.[29] Insight into the correlation of BMI% to body composition in those receiving ALL therapy is therefore necessary to understand the pathophysiology of this relationship and develop effective preventative or rescue strategies for obesity and its comorbidites in these patients. To this end, we undertook a specific analysis of body composition within this early treatment period to determine whether BMI is an effective surrogate for adiposity in childhood ALL at diagnosis (as relevant to studies of obesity-associated leukemia incidence) and during chemotherapy (as relevant to reports of obesity-associated outcomes).

METHODS AND MATERIALS

Study Population

Patients ten through 21 years of age newly diagnosed with National Cancer Institute/Rome High-Risk B-Precursor ALL (HR-ALL) or T-cell ALL (T-ALL) were prospectively enrolled in a clinical trial studying body composition and bone health. Subjects were enrolled within 24 hours from chemotherapy initiation, and were treated with similar frontline Children’s Oncology Group (COG) regimens (modified CCG1961[30] (with substitution of PEGylated L-asparaginase for L-asparaginase), AALL0232 [31], AALL1131[32], AALL0434[33]) using a four-drug Induction and successive blocks of dose-intensive chemotherapy on an

augmented Berlin-Frankfurt-Münster platform (Supplemental Figure 1). Of note, all but one patient with T-ALL was treated according to a HR-ALL regimen (AALL0232-based) which included dexamethasone and high-dose intravenous methotrexate, the remaining patient received AALL0434. All subjects uniformly received a 28 day Induction regimen using vincristine, PEGylated L-asparaginase, anthracycline (daunorubicin or doxorubicin), and a glucocorticoid (either prednisone 60 mg/m^2/day for 28 days or dexamethasone 10 mg/m^2/day for 14 days). All subjects then entered the dose-intensive sequential phases of Consolidation, Interim Maintenance (IM), and Delayed Intensification (DI) before continuing to either a second Interim Maintenance or Maintenance. Due to treatment-associated toxicity and mortality, not all subjects were able to complete all imaging and assessments. Subjects who completed fewer than two assessments were excluded from analyses of change in body composition (Supplemental Figure 2, CONSORT diagram). In addition to body composition and BMI, demographic and treatment information including age, sex, self-reported ethnicity, leukemia phenotype, and treatment regimen were collected for the cohort. The clinical trial was registered nationally (NCT#01317940), approved by the Institutional Review Board, and documented informed consent obtained prior to study enrollment for all subjects.

Assessment of Body Composition

Subjects underwent three serial assessments (Supplemental Figure 1): at diagnosis (within 96 hours from start of chemotherapy), at end of the Induction phase (~28–35 days later), and at the end of DI (~7–9 months after diagnosis). In accordance with the study aims, body composition was first assessed at diagnosis to enable evaluation of BMI's utility for epidemiology studies of ALL incidence. This measurement then also provided a baseline for serial measurements of body composition throughout subsequent therapy. As the primary focus this study was to explore the relationship of BMI to adiposity in order to better understand obesity's adverse influence on outcomes, and not to determine the contributing factors to obesity itself (i.e. steroids or other), assessment of body composition was limited to the periods in which obesity was previously reported to exert a major effect: prior to the end of Induction[16] and by the end of the final dose-intensive pre-Maintenance phase.[9] For BMI, height and weight were measured by Scale-Tronix instruments (accuracy for weight ±0.01 kilograms). Raw BMI scores were converted to a BMI% and associated Z-score using age- and sex- specific norms from the Centers for Disease Control and Prevention (CDC), which are available for children <20 years of age.[7] BMI% was then further classified as lean weight (<85th percentile), overweight (85th–4th percentile), or obese (≥95th percentile) by the CDC criteria. Underweight patients (<5th percentile) were included in the lean weight BMI category for purposes of this analysis. Percentage of total body fat (BF%) and lean muscle mass (LMM) was measured using the gold-standard of dual-energy X-ray absorptiometry (DXA) to limit the introduction of even moderate variability inherent in non-radiologic, indirect measures of BF% and LMM (e.g. as is found with bioelectric impedence,[34–36] skin folds,[34,36–38] and waist-circumfrence[38–40]). A fan beam DXA densitometer (Delphi W; Hologic, Inc., Waltham, MA) in array mode was used and scans were analyzed with the manufacturer's software; the coefficients of variation for these measurements are between 1.2 and 5%.[41–43]

Statistical Analyses

The primary endpoints for the analysis were BMI (as Z-score) and BF%. Changes in LMM and bone density by DXA were analyzed as potential confounding factors of a BMI Z-score:BF% correlation. The primary methods of analyses were based on ordinary least squares analysis of variance and regression. We assessed differences in mean values of these parameters at the three evaluation time-points using mixed effect analysis of variance, where subject was the random effect and time-point the fixed effect. We assessed the correlation between BMI z-score and BF% using least squares linear regression methods either unstratified, stratified on time-point, or stratified on subject, as appropriate for overall, within time-point, and within subject analyses, respectively. Partial correlation coefficients are reported for the latter two analyses. All reported p-values are two-sided, with significance set at $p<0.05$. Analyses performed using Stata Release 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

RESULTS

Baseline Characteristics Of Cohort

A description of the cohort (n=50) is provided in Table I. Subjects were mostly in mid-adolescence, male (30/50), and conforming to our institution demographic, predominantly of Hispanic ethnicity (41/50). The majority of subjects were diagnosed with B-Precursor ALL (41/50), although all subjects were treated using similar chemotherapy regimens. Reflective of the obesity rates in the adolescent Hispanic general population [1], half the subjects were either overweight (12/50) or obese (13/50) by BMI% at study entry. Of 38 patients with DXA results at diagnosis, mean BF% was similar in males and females (BF% males 28.4±9.6%, females 28.2±8.6%), though this was due to an overall higher BMI Z-score in the boys ($p=0.036$). After adjusting for BMI Z-score, girls had a 4.8±2.1 percentage point higher BF% than boys ($p=0.033$). Among the 50 enrolled subjects, there were 128 paired BMI and BF% measurements, 31 subjects with measurement at three time-points, 16 at two time-points (Diagnosis+End of Induction n=5; End of Induction+End of DI, n=11), and 3 at one time-point only (Diagnosis, n=2; End of DI, n=1).

Correlation between Overall BMI Z-score and BF%

In analysis of the study's primary aim, we found a significant correlation between BMI z-score (which reflects BMI%) and BF% over the entire 128 pairs of measurements, ($r = 0.66$, $p<0.0001$, Figure 1). The partial correlation adjusting for time-point was also significant (partial $r = 0.74$, $p<0.0001$), but the partial correlation within subjects was not (partial r −0.22, $p=0.055$); hence, there are strong correlations between BF% and BMI Z-score overall and within each time point, but not within individual subjects. Despite age not varying significantly over the short duration of the study, we nonetheless repeated the analyses with raw BMI and found similar results in mangitude and significance (overall $r=0.61$, $p<0.0001$; within time-point 0.67, $p<0.0001$; and within subjects −0.13, $p=0.25$, respectively).

Change in Body Composition during Therapy

Among 47 evaluable patients, change in BMI Z-score and change in BF% could be computed for 78 adjacent time-point pairs (36 for Induction, 42 for post-Induction). In the cohort, BMI Z-score differed significantly at the three time-points, albeit with only small changes of unclear clinical relevance (Figure 2A, Table II). Conversely, BF% evidenced significant and large increases between each successive time-point (Figure 2A, Table II). As changes in bone mineral content (BMC) contributed <1% to differences in body composition between time-points, the discordance between BMI Z-score and BF% was found to be due to the development of sarcopenic obesity during therapy (fat gain concurrent with loss of lean mass), thereby explaining the absence of correlation between BMI Z-score and BF% within subject noted above. During Induction, weight loss resulting in loss of BMI Z-score was found to be not from loss of fat mass or BMC, but instead due to a coexisting significant decrease in LMM (Table II). Following Induction, this trend continued with both BF% and fat mass continuing to increase without recovery of lean mass. As a result, change in BF% was not correlated with change in BMI Z-Score (which is reflective of change in BMI%) either overall (Figure 2B), within time-points, or within patient ($r = -0.05$, $r = 0.02$, $r = -0.09$, respectively, all not significant). In over half of these (58%, 45/78), the change in BMI Z-score was discordant with the change in BF%, mostly reflecting increasing BF% during decreasing BMI Z-score (Figure 2B).

DISCUSSION

Our primary finding is that changes in BMI% during ALL therapy do not accurately reflect changes in body composition. In fact, a clinician using change in BMI% (or Z-score) to counsel a patient on weight management during ALL therapy would be wrong about the body composition over half of the time. The association of BMI Z-score to body fat noted here has additional implications for clinical research efforts focused on obesity and leukemia. Our results show BMI Z-score to be a reasonable approximation of body fat percentage at the time of diagnosis, thereby providing support for use of this measure in epidemiological studies evaluating the incidence of obesity-associated pediatric leukemia. Conversely, our data caution against the use of BMI as a surrogate measure for obesity as either a predictor or specific endpoint on clinical trials. The discordance between BMI Z-score and body fat in our cohort strongly suggests that BMI may be a poor indicator for studies of the prevalence of obesity[29] or obesity-associated risks[18,19] during therapy. We found that much of the discrepancy noted between BMI and body composition was due to the development of a high prevalence of sarcopenic obesity in the cohort, wherein large gains in body fat were not reflected in BMI Z-score due to concurrent muscle loss. To our knowledge, this is the first report using the gold standard of DXA to longitudinally evaluate the validity of BMI Z-score to define obesity in a pediatric population during ALL therapy and confirms the general findings reported by Murphy et al across a mixed cohort of children with cancer. [44] Moreover, we present here the first description of sarcopenic obesity in children being treated on modern irradiation-sparing ALL chemotherapy regimens.

Our data raise significant questions regarding the import of BMI-associated outcomes during therapy.[9] The most recent hypothesis for increased relapse risk in ALL implicates a direct interaction of adipocytes and related adipokines with leukemia cells [45,46] and/or body fat-related pharmacodynamic changes.[47–49] The increase in adiposity during therapy even in many patients defined as “lean” by BMI% indicates more patients may be at risk for adiposity-associated toxicity and relapse than previously suggested by use of BMI alone. Likewise, a direct effect of adiposity on leukemia sensitivity to chemotherapy as seen in pre-clinical experiments suggests a broader such group might benefit from targeted obesity-directed interventions irrespective of BMI%. The loss of lean muscle mass, primarily skeletal muscle, may also have independent implications for outcome as well. In adults, sarcopenic obesity as seen here has been associated with adverse survival for a variety of hematologic and other malignancies.[50–53]. One cannot disregard the importance of adequate nutrition during chemotherapy. Both underweight and overweight affect the immune system in different but profound ways; in addition to the direct effects on leukemia described above, under- or overnutrition may affect tolerance of chemotherapy, risk for severe infection, and other key factors affecting outcome.[54–56] Yet, despite lower energy intake as compared to healthy controls, children receiving intensive leukemia therapy were found to remain significantly overweight by both BMI and anthropometry.[57] With increasing evidence supporting the influence of body composition on leukemia survival, accurate assessment and a better understanding of the limitations of current surrogate measures are crucial.

The dissociation between BMI Z-score and adiposity is one with implications that extend to obesity research in ALL survivors as well.[58–60] In adults survivors of pediatric ALL, BMI % has been similarly used historically to determine the prevalence of obesity[61] and raise concern for associated long-term health consequences. Yet BMI’s correlation to obesity in ALL survivors may be as misleading as to what we found during therapy itself. A study recent by Karlage et. al.[38] calculated an approximate 50% false negative rate using BMI% to predict elevated body fat in adult survivors ten years from diagnosis. Even though a large portion of that survivorship cohort was defined obese by BMI, mean body fat was actually lower than that reported separately in the NHANES general population.[62] In fact, some planned future studies in cancer survivors will rely not on BMI% alone but use direct measures of adiposity instead [63]. Our findings during therapy complements those of the survivorship study to further reflect the concern for the validity of BMI% as a surrogate measure of body composition and shows, in actuality, this discordance begins during therapy. Longitudinal studies of children on-therapy should therefore similarly use more direct measures of body composition and avoid BMI% as an imprecise surrogate.

Our study provides the first description of the poor correlation of change in BMI% as a marker of changes in body composition in a pre-adolescent and adolescent population receiving frontline ALL therapy. While our study period was selected to coincide with treatment phases thought to be most susceptible to the adverse influence of obesity on ALL survival, we recognize this includes phases wherein fat gain was exacerbated by steroid exposure. Nonetheless, our primary aim was to assess the accuracy of BMI Z-score as an anthropometric biomarker for future research in obesity and ALL, and in this respect, the poor correlation of the measure along with the opposing directions of weight loss and fat

gain is of concern to both clinicians and researchers. We also focused our study on pre-adolescents and adolescents as a representative population at greatest risk due to increased rates of obesity [1] and poorer leukemia outcomes.[64] We recognize that by limiting our study to this specific age range, caution must be used when extrapolating to other ages ranges. Despite similar glucorticoid exposures, behavior and dietary changes are likely different in both younger patients with NCI/Rome standard-risk ALL receiving less dose-intensive regimens[65] and, on the other extreme, adult populations utilizing distinct regimens[66,67] and/or sufferig increased treatment-related morbidity.[68] Lastly, while no internal disagreement by ethnicity was seen in our results, and while our use of DXA eliminates the assessment bias common within anthropometric estimates of BF%,[69] we would note the majority of our population was Hispanic, a group already at high risk for obesity.[1] The discordance between BMI% as a validated measure of overweight/obesity in the general population and its lack of precision in this leukemia population highlights the need for careful re-assessment of whether BMI Z-score is an acceptable research tool within cancer populations. The use of DXA for this research study has demonstrated BMI% to be too imprecise a surrogate for research or clinical care, but we acknoweldge that DXA is not readily available in many smaller centers and internationally. Preliminary data supports the potential use of mid-arm circumference and triceps skin folds as anthropometric means of assessment, [38,70,71] but further validation is necessary to correlate these measures with body composition in children receiving adipogenic therapy for ALL. Longitudinal research is needed to determine the most precise, cost-efficient, and widely available surrogate markers of obesity to minimize morbidity during therapy and in survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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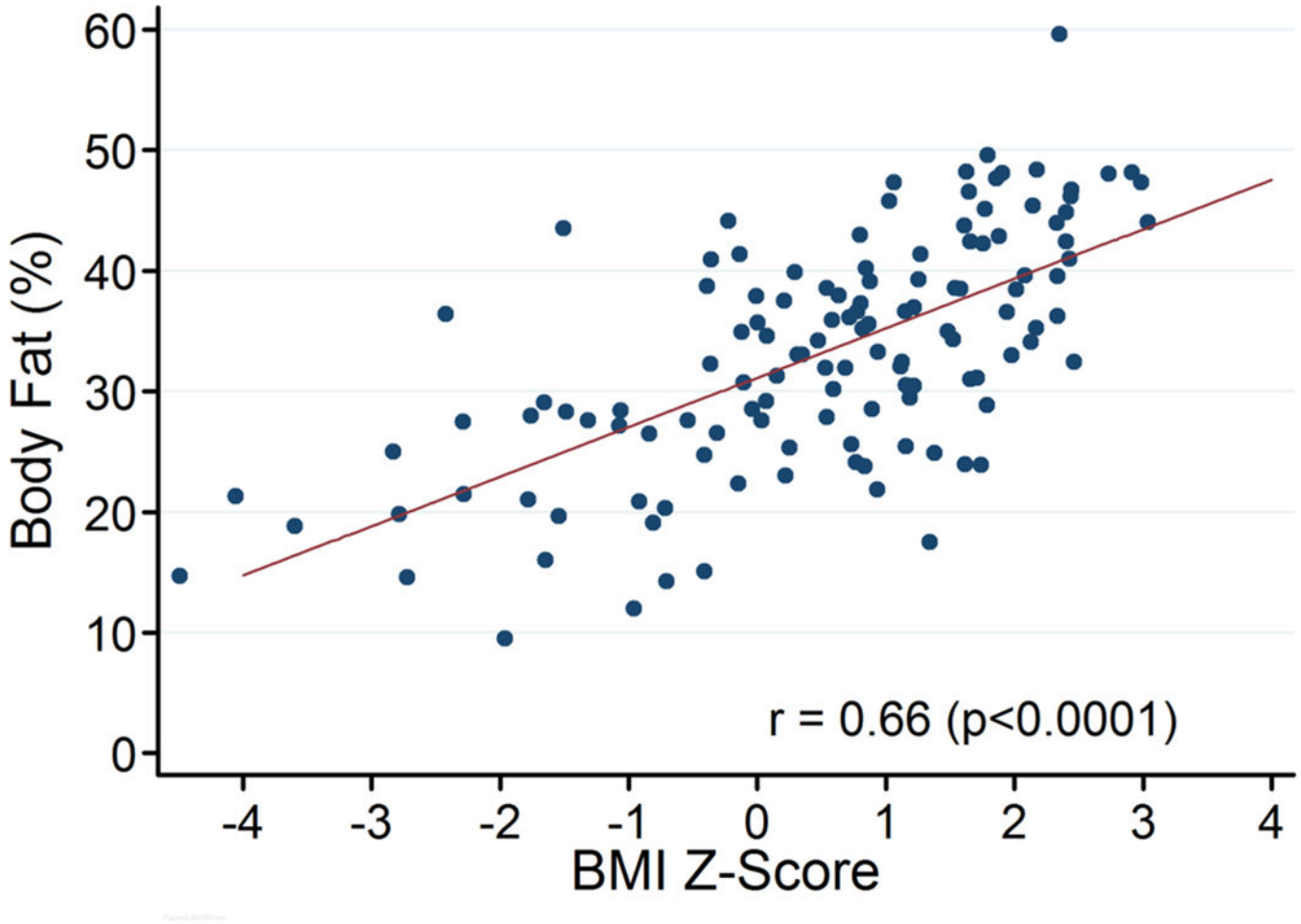

Figure 1. Correlation of body fat percentage and BMI Z-score

Correlation of body fat percentage by DXA to BMI Z-score (as is directly related to BMI%) across all assessments.

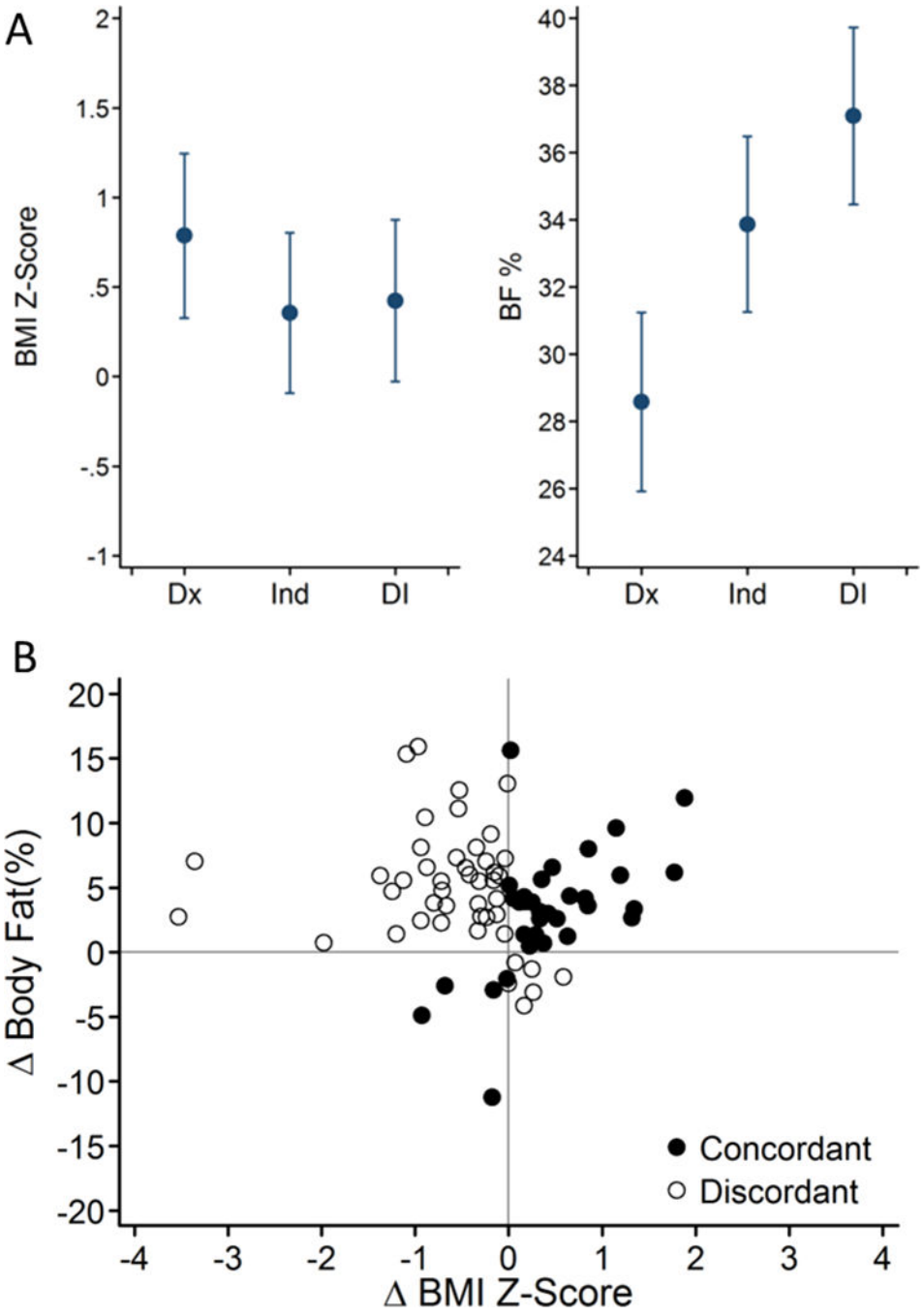

Figure 2. Direction of change for BMI% and body fat during therapy

(A) BMI Z-Score and BF% for cohort at each study time-point (mean±SD). **(B)** Change in BF% versus change in BMI Z-score between two successive time-points. *p<0.05 from preceeding time-point, **p<0.001 from preceeding time-point.

Table I

Characteristics of cohort at study entry[a]

Characteristic	N (%)
Age (Years)	
Mean, Median	14.7, 14.6
Range	9.9–19.6
Sex	
Male	30 (60)
Female	20 (40)
Ethnicity	
Hispanic	41 (82)
Non-Hispanic	9 (18)
Leukemia Phenotype	
B-Precursor ALL	41 (82)
T-cell ALL	9 (18)
Chemotherapy Regimen	
CCG1961	1 (2)
AALL0232	22 (44)
AALL1131	25 (50)
AALL0434	1 (2)
Other	1 (2)
Body Mass Index Category[b]	
Lean	25 (50)
Overweight	12 (24)
Obese	13 (26)
Body Mass Index Percentile (BMI%)[b,c]	
Mean, Median	70.5, 87.5
IQR[d]	47.5 (48.4–95.9)
Range	0.02–99.9
Body Fat Percentage (BF%)[c]	
Mean, Median	28.3, 28.7
IQR[d]	25.9 (15.1–41.0)
Range	9.5–44.0

[a] Includes those enrolled at diagnosis (n=38) and at end of Induction (n=12);

[b] BMI category determined according to population norms for BMI% according to the Centers for Disease Control and Prevention (BMI kg/m^2), see methods.

[c] In those with assessment of body fat at diagnosis (n=38);

[d] IQR = interquartile range (25^{th}–75^{th}).

Table II

Change in body composition during therapy

Measure of Body Composition[a]		At Diagnosis (mean±SE)	End of Induction (mean±SE)	End of Delayed Intensification (mean±SE)	p[b]
Body Mass Index Percentile (BMI%)		70.5±5.5	61.6±5.2	62.8.±5.2	<0.001
Fat Mass	**(%)**	28.6±1.3	33.9±1.3	37.1±1.3	<0.001
	(kg)	19.4±1.7	20.9±1.7	24.1±1.7	<0.001
Lean Mass	**(%)**	68.1±1.3	62.7±1.2	59.8±1.3	<0.001
	(kg)	41.6±1.6	35.6±1.6	36.4±1.6	<0.001
Bone Mass	**(%)**	3.28±0.094	3.43±0.091	3.10±0.092	<0.001
	(kg)	1.99±0.080	1.94±0.080	1.86±0.080	<0.001

[a] Body mass index percentile calculated from weight and height at time of visit according to CDC age- and sex- norms. Other parameters directly assessed via dual-energy X-ray absorptiometry.

[b] p-value for percentages calculated from mixed-effect analysis of variance across time-points (see methods for additional detail).