Impact on Survival and Toxicity by Duration of Weight Extremes During Treatment for Pediatric Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group

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Terms in [blue](#) are defined in the glossary, found at the end of this article and online at www.jco.org.

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A B S T R A C T

Purpose

Previous studies regarding the influence of weight on event-free survival (EFS) and treatment-related toxicity (TRT) in childhood acute lymphoblastic leukemia (ALL) considered only weight at diagnosis. Inasmuch as weight varies substantially over treatment, we hypothesized its impact on EFS is instead determined by cumulative time spent at an extreme weight during therapy and on TRT by weight at the time of toxicity.

Patients and Methods

In a cohort of 2,008 children treated for high-risk ALL in Children's Oncology Group study CCG-1961, we determined the effect on EFS of cumulative time receiving therapy at an extreme weight (either obese or underweight) between end of induction and start of maintenance therapy. We also evaluated the association between weight category and incidence and patterns of TRT during 13,946 treatment courses.

Results

Being obese or underweight at diagnosis and for $\geq 50\%$ of the time between end of induction and start of maintenance therapy resulted in inferior EFS (hazard ratios, 1.43 and 2.30, respectively; global $P < .001$). Normalization of weight during that period resulted in mitigation of this risk comparable to never being obese or underweight. Obese or underweight status at start of each treatment course was significantly associated with specific patterns of TRT.

Conclusion

Influence of weight extremes on EFS and TRT is not set at diagnosis as previously reported but is moderated by subsequent weight status during intensive postinduction treatment phases. These observations suggest that weight is a potentially addressable risk factor to improve EFS and morbidity in pediatric ALL.

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INTRODUCTION

Intensification of therapy for childhood acute lymphoblastic leukemia (ALL) has achieved 5-year survival approaching 90%¹; however, subsets of patients remain at greater risk for both treatment-related toxicity (TRT) and poorer [event-free survival](#) (EFS) from combinations of factors relating to host, disease, and treatment.²⁻⁴ Previous reports addressing the impact of weight on TRT and EFS in acute leukemia were limited by considering patient weight only surrounding the time of diagnosis.⁵⁻¹⁰ Furthermore, although Butturini et al⁵ described an association between obesity at diagnosis and survival in children treated for ALL on Children's On-

cology Group (COG) protocols, reports from other consortia have not supported this observation.^{9,11} Patients underweight at diagnosis in developing countries have been found to have inferior outcomes,^{12,13} but this too has not been replicated in studies of patients treated in developed countries.^{5,9,11} Therefore, it remains controversial whether a relationship between weight and EFS exists and, if so, whether it applies only to those who are obese or to those who are underweight as well. Because weight varies considerably over the course of therapy for pediatric ALL,¹⁴ one potential explanation for these conflicting reports is the effect of changes in weight during treatment, an effect that has not been previously examined to our

knowledge. We therefore hypothesized that the impact of weight on EFS is not determined exclusively at diagnosis but rather results from continued exposure to an extreme weight during the subsequent critical period of intensified therapy before maintenance.¹⁵ We hypothesized a similar effect on the incidence and patterns of acute TRT, which would not be determined by weight at diagnosis but rather by weight surrounding the period of acute toxicity. The purpose of this study was to evaluate the effect of weight variations during treatment on EFS and development of TRT in a large cohort of children treated in a cooperative-group setting for high-risk ALL.

PATIENTS AND METHODS

Study Cohort

The study population consisted of patients enrolled onto CCG (Children's Cancer Group) 1961, the frontline COG therapeutic trial open to enrollment from 1996 to 2002 for children age ≥ 1 year diagnosed with high-risk ALL according to National Cancer Institute/Rome criteria. CCG-1961 was designed to address the question of whether further intensification in postinduction therapy in the form of increased duration and/or intensity could improve outcome in children classified as rapid early responders (RERs) based on morphologic response via bone marrow evaluation on the eighth day of induction therapy. In brief, the study used a

four-drug induction (vincristine, prednisone, asparaginase, and daunorubicin) to assess regimens of differing intensity (through incorporation of additional cytotoxic agents) and/or duration (through repetition of intensive courses) in children who were RERs and compare two forms of anthracycline in children who were slow early responders (SERs). In general, children received an induction phase followed by intensive therapy for a total of 6 to 11 months depending on treatment arm. They then completed a prolonged maintenance phase of primarily oral chemotherapy. Regimen details and overall outcomes have been reported.¹⁵ Institutional review board approval and informed consent were obtained as per federal regulations and local requirements.

Study Database

The database included 2,057 patients treated in CCG-1961 (Fig 1). Patients were excluded from the analysis for the following reasons: unresolvable errors in height or weight at diagnosis ($n = 12$), outside of the pediatric age range (age ≥ 21 years; $n = 5$), lost to follow-up ($n = 1$), and randomly assigned to treatment with B43-pokeweed antiviral protein immunotoxin, which was terminated early for lack of study drug availability (SERs only; $n = 31$). Height and weight values were systematically corrected for clear reporting errors (eg, numeric transpositions and metric system conversion errors), with interpolation of missing values performed for a small number of treatment courses (123 of 13,946; $< 1\%$ of courses). Weight status by z score and percentile was determined as per guidelines from the Centers for Disease Control and Prevention (CDC) using body mass index (BMI) for children age 2 to 20 years and weight for length for those age < 2 years.^{16,17} The extreme-weight categories

Fig 1. CONSORT diagram. CCG, Children's Cancer Group; CDC, Centers for Disease Control and Prevention; ICU, intensive care unit; PAP, pokeweed antiviral protein. (*) One patient could not be unambiguously classified as either $< 50\%$ underweight or $< 50\%$ obese. Analyses that either excluded the patient or classified the patient into either category produced results that differed negligibly. Analysis excluding this patient is presented.

Table 1. Patient Demographic and Clinical Characteristics at Diagnosis (N = 2,008)

Characteristic	Weight Category at Diagnosis								P*
	All Patients		Normal/Overweight		Underweight		Obese		
	No.	%	No.	%	No.	%	No.	%	
Overall cohort	2,008	100.0	1,612	80.3	117	5.8	279	13.9	—
Sex									
Male (referent)	1,201	59.8	953	59.0	74	63.2	174	62.4	
Female	807	40.2	659	41.0	43	36.8	105	37.6	
Age, years									.428
Mean		10.2							
Range		1-20							
Median		11							
1 to 9 (referent)	750	37.3	605	37.5	55	47.0	90	32.3	
10 to 12	496	24.7	403	25.0	28	23.9	65	23.3	
13 to 15	513	25.5	401	24.9	24	20.5	88	31.5	
≥ 16	249	12.4	203	12.6	10	8.5	36	12.9	
Race/ethnicity									< .001
White (referent)	1,341	66.8	1,111	68.9	80	68.4	150	53.8	
Hispanic	401	20.0	298	18.5	18	15.4	85	30.4	
African American	129	6.4	89	5.5	13	11.1	27	9.7	
Other/unknown	137	6.8	114	7.1	6	5.1	17	6.1	
WBC count, × 10 ⁹ /L									.151
Mean		93,418							
Range		0-1,000,000							
Median		53,300							
< 50,000 (referent)	951	47.4	780	48.4	48	41.0	123	44.1	
≥ 50,000	1,057	52.6	832	51.6	69	59.0	156	55.9	
Leukemia phenotype									.049
Pre-B cell (referent)	1,314	65.4	1,045	64.8	80	68.4	189	67.7	
Pre-T cell	406	20.3	338	21.0	13	11.1	55	19.7	
Missing	288	14.3	229	14.2	24	20.5	35	12.5	
CNS disease status									.228
1 or 2 (referent)	1,849	92.1	1,490	92.4	109	93.2	250	89.6	
3	83	4.1	62	3.8	4	3.4	17	6.1	
Missing	76	3.8	60	3.7	4	3.4	12	12.5	
Treatment regimen received									.045
A (control arm)	320	15.9	258	16.0	15	12.8	47	16.8	
B (longer duration)	321	16.0	264	16.4	26	22.2	31	11.1	
C (intensified therapy)	323	16.1	263	16.3	18	15.4	42	15.1	
D (longer and intensified)	363	18.1	291	18.1	17	14.5	55	19.7	
Augmented SER (idarubicin)	426	21.2	338	20.9	27	23.0	61	21.9	
Unknown/not following protocol	255	12.7	198	12.3	14	11.9	43	15.4	
Treatment response category									.913
RER (referent)	1,416	70.5	1,139	70.7	83	70.9	194	69.5	
SER	571	28.4	457	28.3	32	27.4	82	29.4	
Unknown	22	1.1	16	1.0	2	1.7	3	1.1	
BMI at diagnosis, kg/m ² †									NA
Median			17.8		14.0		27.9		
Inter-95th percentile range‡			14.4-25.9		11.3-17.3		18.4-44.2		

Abbreviations: BMI, body mass index; NA, not applicable; RER, rapid early responder; SER, slow early responder.

*Likelihood ratio χ^2 test for distribution of predictors across weight category.

†Weight categories based on BMI percentile, which is age and sex dependent. Hence, there is some overlap in raw BMI values among categories.

‡32.5th to 97.5th percentile.

were defined per CDC thresholds of BMI percentile for children underweight (< fifth percentile) or obese (≥ 95th percentile), with the reference group consisting of those normal/overweight (fifth to 95th percentile). Median follow-up from study entry was 8.5 years among patients who were alive and clinically disease free at last recorded contact.

Statistical Methods

The distribution of patients among the three weight categories (underweight, normal/overweight, and obese) at diagnosis was compared using the χ^2 test for each predictor listed in Table 1. The primary end point for outcome analysis was EFS, defined as the time from study entry to no achievement of remission, disease relapse, or death resulting from any cause. Patients without an observed

event were censored at the time of last contact. In addition, conditional analyses were performed using EFS measured from the start of maintenance among patients who reached maintenance. The primary method of analysis for impact of weight category and other predictors on EFS was Cox proportional hazards regression analysis stratified by protocol treatment arm. The percent time spent at an extreme weight category during premaintenance therapy cycles was computed as the course length–weighted proportion of courses during which the patient was classified as underweight or obese, with patients classified as ≥ 50% cumulative time underweight, < 50% cumulative time underweight, normal/overweight throughout, < 50% cumulative time obese, or ≥ 50% cumulative time obese. These categories were then used to investigate the effect of cumulative time at an

extreme weight on EFS from the start of maintenance after adjusting for weight category at diagnosis. To rule out the possibility that the observed effect of cumulative time spent at weight extremes was an artifact because of clustering of patients near the border of the underweight and obese categories at diagnosis (ie, whether patients who changed weight category were those only slightly obese or underweight), we repeated the analysis dividing BMI at diagnosis into both seven and nine weight categories. We also verified the model by including BMI percentile at diagnosis as a continuous linear-quadratic element instead. Examination of failure rates (relapse or death) before the start of maintenance in each weight group was performed to assess differences for patients who did not survive to maintenance.

To evaluate the impact of concurrent weight on acute TRT, each patient's weight was classified at the start of each phase into obese, underweight, or normal/overweight categories. Primary end points for the analysis of TRT were the occurrences during each course of: grade 3 to 4 nonhematologic toxicities as defined by the CCG Toxicity and Complications Criteria (TCC); hematologic toxicity as reflected by the surrogate measure of hematologic support (ie, transfusion of blood products, elective use of hematopoietic growth factors); documented infections; use of other supportive care interventions (antimicrobial treatments, intravenous analgesics, parenteral nutrition); delay in start of treatment phase; and number of hospital and intensive care unit (ICU) days. The CCG-TCC define grade 3 performance toxicity as a Karnofsky score < 50% and grade 3 weakness as causing functional impairment. These end points were analyzed during the period from diagnosis through the first three cycles of maintenance. The primary method of analysis was an end point-specific multivariable linear or logistic regression model. The variables listed in Table 1 were included as candidate predictors in the multivariable EFS and TRT models (TRT analyses also contained treatment phase). Predictors were initially screened in univariable analyses, and those with $P < .15$ via likelihood ratio test were included in a preliminary multivariable model. The final model for each end point (Appendix Table A1, online only) was determined by a reverse stepwise selection of predictors until all remaining covariates had likelihood ratio $P < .05$. This model was then verified by testing whether reintroducing previously eliminated predictors would significantly improve the model. Use of formal repeated measure methods in the TRT analyses had a negligible effect on the results. Unless otherwise stated, P values refer to two-sided tests. Statistical computations were performed with STATA software (version 11; STATA, College Station, TX).

RESULTS

Of the 2,008 evaluable children, 279 (14%) were obese and 117 (6%) were underweight at diagnosis. Demographic, disease, and treatment

characteristics by weight category are listed in Table 1. No significant differences in the presence of CNS disease, elevated WBC count by continuous or categorical variable, or classification as SER versus RER were found among the three weight groups, although T-cell phenotype was somewhat less common among underweight patients. Patients who identified themselves as Hispanic were more prevalent in the obese category, whereas Caucasians were slightly underrepresented in that category. These differences were not found to be of independent statistical significance consistently across the multivariable models.

Survival by Weight Category at Diagnosis

The 5-year EFS rates ($\pm$ standard deviation [SD]) for patients obese and underweight at diagnosis were $64\% \pm 3\%$ and $65\% \pm 5\%$, respectively, as compared with $74\% \pm 1\%$ for normal/overweight patients (univariable $P = .002$; Fig 2A). Subsequent multivariable analysis demonstrated worse EFS for patients who were either obese or underweight at diagnosis (hazard ratio [HR], 1.40; 95% CI, 1.13 to 1.73 and HR, 1.33; 95% CI, 0.97 to 1.83, respectively; global $P = .005$). This analysis reflects an additional > 3 years of follow-up as compared with the earlier report by Butturini et al.⁵ Inspection for differences among weight categories in rate of early treatment failure or death during the premaintenance period resulted in reported events for seven (6.0%) of 117 patients underweight at diagnosis, 22 (7.9%) of 279 patients obese at diagnosis, and 100 (6.2%) of 1,612 patients normal/overweight at diagnosis. However, formal statistical analysis to detect a statistically significant difference among groups was precluded by the relative rarity of events and resultant lack of power.

Survival by Cumulative Time in Weight Category

Analysis of EFS from the start of maintenance was conducted for the subcohort of 1,581 patients alive and disease free at that time. Of these, 644 patients (40.7%) spent some time premaintenance at an extreme weight (obese, $n = 393$; underweight, $n = 251$), whereas 937 patients (59.3%) were normal/overweight for the entire time. In this group, children who spent $\geq 50\%$ of the time either obese or underweight demonstrated inferior EFS as compared with those who had reduced exposure to either weight extreme (univariable $P = .008$; Fig

Fig 2. Five-year event-free survival (EFS) by weight status at diagnosis and during therapy. Kaplan-Meier plots of EFS by (A) weight category at diagnosis (EFS as measured from diagnosis; $n = 2,008$) or (B) weight category over time during postinduction therapy (EFS as measured from beginning of maintenance; $n = 1,581$). Both plots demonstrate significantly worse EFS of patients in either weight extreme category as compared with normal/overweight patients.

Table 2. Risk for Event by Cumulative Time at Weight Extreme Versus Weight at Diagnosis for Patients Surviving to Start of Maintenance (n = 1,581)

Weight Category at Diagnosis	Underweight $\geq 50\%$ Time			Underweight $< 50\%$ Time			Always Normal/Overweight			Obese $< 50\%$ Time			Obese $\geq 50\%$ Time		
	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
Underweight	33	2.30	1.46 to 3.63	60	1.09	0.68 to 1.76	—	—	—	—	—	—	—	—	—
Normal/overweight	50	1.09	0.65 to 1.83	108	0.52	0.32 to 0.83	937	1 (referent)	—	146	1.04	0.74 to 1.48	42	1.51	0.95 to 2.41
Obese	—	—	—	—	—	—	—	—	—	54	0.99	0.62 to 1.58	151	1.43	1.04 to 1.96

NOTE. On basis of multivariable Cox proportional hazards model stratified on treatment regimen. Global likelihood ratio *P* value resulting from excluding both weight category and cumulative time spent main effects was *P* < .001. Test of interaction between cumulative time and weight category at diagnosis was not statistically significant (*P* = .451), and inclusion in model revealed identical trend. Bold font indicates unadjusted 95% CIs not overlapping event-free rate equivalent to 1. Abbreviation: HR, hazard ratio.

2B). Five-year EFS rates ($\pm$ SD) for children who were either obese or underweight $\geq 50\%$ of the time were $73\% \pm 3\%$ and $70\% \pm 5\%$, respectively, compared with children who spent $< 50\%$ of their time obese or underweight ($77\% \pm 3\%$ and $82\% \pm 3\%$, respectively) or were normal/overweight throughout ($80\% \pm 1\%$).

However, multivariable analysis (Table 2) revealed the greatest risk for an event was in patients who presented obese or underweight and then remained in their respective extreme weight category for $\geq 50\%$ of the premaintenance phases ($\geq 50\%$ obese: HR, 1.43; 95% CI, 1.04 to 1.96 and $\geq 50\%$ underweight: HR, 2.30; 95% CI, 1.46 to 3.63; global *P* < .001). In contrast, children who were diagnosed obese or underweight but normalized their weight for $>$ half of premaintenance therapy had similar risk as compared with children who were never obese or underweight. Interestingly, a protective effect was found for those who started in the normal weight category at diagnosis but became underweight for $<$ half the premaintenance period (HR, 0.52; 95% CI, 0.32 to 0.83). In the analyses of finer categorizations of BMI at diagnosis and BMI as a continuous linear-quadratic element in the model, the cumulative time-spent effect re-

mained significant at *P* $\leq$.004, indicating the effect was not attributable to differences in the distribution of weights at diagnosis.

Treatment-Related Toxicity by Weight Category

The 2,008 children in the cohort were reflected in 13,946 courses of treatment. Multivariable regression models are summarized in Table 3. For overall grade 3 to 4 toxicity, there was a statistically significant association between weight category and risk of toxicity (*P* = .008), with trends toward higher rates of TRT at both extremes of weight. Examination of individual toxicities revealed a risk profile of toxicity specific to weight category. Both hepatic and pancreatic toxicities were more common among obese patients (odds ratio [OR], 1.32; 95% CI, 1.15 to 1.51 and OR, 1.53; 95% CI, 1.22 to 1.92, respectively; both *P* < .001). In contrast, pulmonary toxicity (broad spectrum ranging from supplemental oxygen to mechanical ventilation) and fungal infections were substantially more common among underweight patients (OR, 2.07; 95% CI, 1.31 to 3.29; *P* = .003 and OR, 2.24; 95% CI, 1.24 to 3.32; *P* = .001).

Table 3. Risk for Grade 3 to 4 Nonhematologic Toxicity and Supportive Care Use by Weight Category During Intensive Treatment (n = 13,946 cycles)

Reported Toxicity or Supportive Care Measure*	Frequency†		Weight Category‡						P§
			Underweight		Normal/Overweight	Obese			
	No.	%	OR	95% CI		OR	OR	95% CI	
Any grade 3 to 4 toxicity	3,860	28	1.12	0.95 to 1.32	1	1.18	1.06 to 1.31	.008	
Hepatic	1,685	12	1.04	0.83 to 1.31	1	1.32	1.15 to 1.51	< .001	
Pancreatic	603	4	0.77	0.50 to 1.17	1	1.53	1.22 to 1.92	< .001	
Pulmonary	201	1	2.07	1.31 to 3.29	1	0.68	0.43 to 1.10	.003	
Infectious	2,645	19	1.23	1.02 to 1.47	1	0.99	0.88 to 1.12	.094	
Fungal	259	2	2.24	1.51 to 3.32	1	1.10	0.78 to 1.57	.001	
Bacteremia	1,312	9	1.25	0.99 to 1.58	1	1.13	0.96 to 1.33	.078	
Other	1,270	9	1.44	1.15 to 1.82	1	0.96	0.81 to 1.13	.008	
Antifungal therapy	813	6	1.61	1.24 to 2.08	1	0.91	0.74 to 1.14	.001	
Any hematologic support	5,986	43	1.76	1.45 to 2.15	1	0.93	0.81 to 1.06	< .001	
Platelet	3,598	26	1.50	1.24 to 1.82	1	1.05	0.92 to 1.20	< .001	
Packed RBCs	5,650	41	1.81	1.49 to 2.20	1	0.91	0.79 to 1.04	< .001	
Hematopoietic growth factor	586	4	1.41	1.04 to 1.91	1	0.81	0.62 to 1.06	.019	
Parenteral nutrition	751	5	2.09	1.64 to 2.65	1	0.79	0.62 to 1.01	< .001	
Performance status	73	< 1	3.12	1.60 to 6.09	1	1.36	0.74 to 2.53	.010	
Muscle strength	634	5	0.61	0.40 to 0.93	1	1.33	1.08 to 1.64	< .001	

Abbreviation: OR, odds ratio.

*Toxicities graded per Children's Cancer Group Toxicity and Complications Criteria as routinely reported by institution.

†Frequency of end point across all courses.

‡ORs based on multivariable logistic regression.

§Likelihood ratio test *P* value < .05 indicates statistically significant overall association between weight category and specified end point. With exception of overall infections, only statistically significant associations with toxicity/supportive care measures are shown.

95% CI, 1.51 to 3.32; $P = .001$). Limitations in data reporting prevented analysis of type or site of fungal infection and of potential overlap among patients with pulmonary toxicity and fungal infections. Underweight children were also more likely to experience hematologic toxicity, as evidenced by increased delivery of hematologic support (OR, 1.76; 95% CI, 1.45 to 2.15; $P < .001$), including transfusion of blood products and use of hematopoietic growth factors. Explanations were not evident for the divergence in the risk for weakness in the obese (OR, 1.33; 95% CI, 1.08 to 1.64; $P < .001$) or performance toxicity in the underweight (OR, 3.12; 95% CI, 1.60 to 6.09; $P = .010$).

Weight was associated with statistically significant but clinically negligible 1-day prolongations of durations of treatment course, hospital stay, and ICU stay as well as need for ICU care (all preceding end points with $P < .001$). The greater use of antifungal medication in the underweight group was consistent with the increased risk for fungal infection in that group. The increased use of parenteral nutrition in the underweight group was similarly consistent. No significant difference in the use of parenteral analgesia was found ($P = .246$). Of the demographic characteristics included in the analysis (Table 1), older age at start of course ($P = .008$), female sex ($P < .001$), and race/ethnicity ($P < .001$) were all associated with statistically significant increased overall risk for grade 3 to 4 toxicity.

DISCUSSION

To our knowledge, this is the first consortium study to characterize the impact of weight during therapy, in contrast to weight at diagnosis, on EFS and TRT. By using analyses designed to reflect the clinical experience of variations in weight to evaluate EFS (ie, as cumulative exposure) and TRT (ie, in proximity to event), we present here a more accurate and complete depiction of the influence of weight than has previously been reported. With this approach, we found that only those children with sustained underweight or obese status during intensive phases of treatment for high-risk ALL were at significantly greater risk for relapse or death and development of TRT. For patients who remained either obese or underweight for $>$ half of premaintenance therapy, the risk for eventual relapse or death was up to double that of patients remaining at normal weight throughout treatment. Conversely, for patients who began treatment obese or underweight and subsequently attained normal/overweight status, this risk was reduced to be equivalent to having normal weight throughout. These findings may provide an explanation for the inconsistency among earlier reports, which did not account for weight changes during therapy. Moreover, obese or underweight patients were found to be at higher risk for distinct toxicity profiles, an important independent consideration in efforts to reduce morbidity resulting from effective but toxic treatment regimens.

An important implication of these findings is the identification of a risk factor potentially amenable to intervention. In contrast to most prognostic indicators in childhood ALL, which are innate to the host (eg, age and sex) and/or disease (eg, presenting WBC count, leukemia phenotype, and chromosomal alterations) and therefore fixed, weight represents a modifiable risk factor. The mechanism for its effect on EFS is unclear. Possibilities include pharmacokinetic variations in chemotherapy,¹⁸⁻²² direct influence of adipose tissue on leukemia resistance,^{18,23,24} differences in protein synthesis and hematopoietic reserves causing reduced target-dose delivery,²⁵⁻²⁸ and others yet unidentified. The discrete pattern of

toxicity among weight groups also suggests different underlying mechanisms for these effects. Whereas increased hepatic and pancreatic toxicities in obese patients could have resulted from the direct effects of adiposity on these organs,^{29,30} the increased infectious toxicity in underweight patients was more likely a result of the established influence of protein-energy malnutrition on immunity.³¹ Interventions focused on either weight extreme will require unique approaches. For underweight patients, nutritional repletion is feasible, and better nutrition is associated with improved survival in developing countries,³² but the high prevalence of obesity in the developed world³³ poses a growing challenge for pediatric oncologists that requires a complex, multidisciplinary approach to address effectively. Certain populations may be at disproportionate risk. For instance, the higher prevalence of obesity among Hispanic populations in the United States³⁴ and in our cohort may contribute to their poorer outcome in pediatric ALL,³⁵ although this effect was not found in an earlier small cohort.³⁶ Prospective investigation is needed to explore mechanisms of treatment failure in obese and underweight patients, further characterize at-risk groups, and develop interventions to improve outcomes.

Secondary analyses such as this possess the common limitation of relying on anthropomorphic measurements (eg, BMI) as surrogates for body composition and may not accurately reflect the distribution of body fat or changes in lean muscle mass.^{37,38} Nonetheless, BMI is universally available, inexpensive, and readily transferable to clinical practice. Prospective research would benefit, however, from correlating BMI with sophisticated body composition assessments such as dual-energy x-ray absorptiometry.³⁹ Although our study focused only on exposure to extreme weights, we recognize weight is a continuum; examination of children overweight (85 to 95 percentile), however, demonstrated identical trends in the pattern of toxicity and risk for an event. Because the database did not contain the dosage of chemotherapy delivered, we were unable to answer whether some of the adverse association of obesity with outcome was attributable to calculation of chemotherapy doses according to ideal, rather than actual, body weight, a determination not specified in the protocol and left to individual clinicians during the study period.

This study identifies a subset of patients who do not seem to be fully benefiting from therapeutic advances in pediatric ALL. Our results contrast sharply with those of previous studies in ALL by shifting the focus on weight beyond the period of diagnosis to accurately reflect the experience of patients as they progress through therapy. Furthermore, we show improved outcomes associated with normalization of weight, thereby providing potential opportunity for prospective investigation into nutritional interventions. Pending these future efforts, this study provides support for nutritional monitoring and early intervention during the initial intensive treatment phases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Data analysis and interpretation: All authors

Manuscript writing: All authors

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GLOSSARY TERMS

event-free survival: calculated from the date of diagnosis to the date of the first event, which is resistance, relapse, death, or second malignant neoplasm.

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Appendix

Table A1. Summary of Predictors in Multivariable Models for TRTs and EFS

Reported Toxicities and Supportive Care Measures†																	EFS†	
Predictor in Final Multivariable Model for Each End Point*	Nonhematologic Toxicities				Hematologic Supportive Care										Survival From Diagnosis (N = 2,008)	Survival From Start of Maintenance (n = 1,581)		
	Any Grade 3 to 4 Toxicity	Hepatic	Pancreatic	Pulmonary	Any Infection			Any Hematologic Support			Packed RBCs	Hematopoietic Growth Factor	Parenteral Nutrition	Performance Status			Muscle Strength	
					Any	Fungal	Bacteremia	Other	Antifungal Therapy	Support								Platelets
Sex	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Age at diagnosis (categorical)	X		X		X		X							X				
Age at phase (categorical)	X	X					X		X		X			X			NA	
Race/ethnicity	X	X		X	X		X	X	X	X	X	X			X			
WBC count (categorical)	X	X	X						X	X	X	X					X	
Leukemia phenotype	X	X		X													X	
CNS disease status at diagnosis					X		X		X	X	X	X		X		X	X	
CRT																		
Treatment response category					X		X		X	X	X	X		X				
Weight							X		X	X	X	X		X				
Weight category#	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Course type§	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	NA	
Cumulative time spent in weight category																		

NA

Abbreviations: CRT, cranial radiation therapy; EFS, event-free survival; NA, not applicable; TRT, treatment-related toxicity.

*Potential predictors as listed in Table 1. Notably, although CRT was prescribed for subsets of patients within protocol, it was included as an independent potential predictor to capture any additional patients who may have received CRT outside of protocol. CRT was not found to be of independent statistical significance in any multivariable model.

†Logistic regression was used for analyses of TRTs. Cox proportional hazards regression stratified by CCG (Children's Cancer Group) 1961 protocol treatment regimen received was performed for analyses of EFS. Sex was not found to be significant in univariable or multivariable model of survival from start of maintenance.

‡Weight category at start of each phase was used in analyses of reported TRT end points; weight category at diagnosis was used in survival analyses from diagnosis.

§Treatment phase (ie, course type: induction, consolidation, interim maintenance, delayed intensification, maintenance) was added to model to control for baseline TRT associated with differences in course intensity.

||Percent time spent in weight category was calculated from diagnosis to start of maintenance. This analysis included only subset of patients who lived to start of maintenance phase.