The negative impact of being underweight and weight loss on survival of children with acute lymphoblastic leukemia

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ABSTRACT

Body mass index and change in body mass index during treatment may influence treatment outcome of pediatric patients with acute lymphoblastic leukemia. However, previous studies in pediatric acute lymphoblastic leukemia reported contradictory results. We prospectively collected data on body composition from a cohort of newly diagnosed Dutch pediatric patients with acute lymphoblastic leukemia (n=762, age 2-17 years). Patients were treated from 1997-2004 and the median follow-up was 9 years (range, 0-10). Body mass index at diagnosis was expressed as age- and gender-matched standard deviation scores and on the basis of these scores the patients were categorized as being underweight, of normal weight or overweight. Multivariate analyses showed that patients who were underweight (8%) had a higher risk of relapse [hazard ratio: 1.88, 95% confidence interval (1.13-3.13)], but similar overall survival and event-free survival as patients who had a normal weight or who were overweight. Patients with loss of body mass index during the first 32 weeks of treatment had a similar risk of relapse and event-free survival, but decreased overall survival [hazard ratio: 2.10, 95% confidence interval (1.14-3.87)] compared to patients without a loss of body mass index. In addition, dual X-ray absorptiometry scans were performed in a nested, single-center cohort. Data from these scans revealed that a loss of body mass consisted mainly of a loss of lean body mass, while there was a gain in the percentage of fat. In conclusion, being underweight at diagnosis is a risk factor for relapse, and a decrease in body mass index early during treatment is associated with decreased survival. In addition, loss of body mass during treatment seems to consist mainly of a loss of lean body mass. This study was approved by the Medical Ethical Committee in 1996 (trial number NTR460/SNWLK-ALL-9).

Introduction

Acute lymphoblastic leukemia (ALL) is the most frequently occurring malignancy in childhood. Currently, the 5-year overall survival exceeds 85%.[1] Apart from the characteristics of the leukemia itself, clinical factors that determine treatment response remain important, such as patients' compliance and inter-individual variance of pharmacokinetics.[2] The latter is determined by genetic variation, but also by body composition. It has been shown that obesity is associated with altered drug distribution and a subsequent higher mortality rate in adult cancer.[3] Previous studies in pediatric ALL showed contradictory results, i.e. some studies show that weight at diagnosis does not influence survival, while others suggest that being underweight or overweight at diagnosis of ALL has an influence on survival[4-14] (Table 1).

Body composition changes extremely during the treatment of pediatric ALL due to the use of corticosteroids,[15,16] but also due to other factors such as the catabolic effect of the disease itself, stress,[17] nutritional changes and impaired exercise capacity.[11,15,18] This change in body composition may differ between patients and could affect outcome. So far, only two studies have addressed the association between therapy-related change of body composition and outcome.[11,14] One study was conducted in only high-risk pediatric ALL patients[14] and the other was a report from Guatemala.[11]

It should be noted that previous studies used body mass index (BMI) as a primary measure and it is generally appreciated that this index is only a proxy of body composition.[19] It has been shown that dual-energy X-ray absorptiometry (DEXA) provides a more reliable estimate of body composition by discriminating the relative contribution of bone, fat and lean body (muscle) mass.[20]

The aim of this study was to examine the influence of BMI and its change on treatment outcome in a cohort of Dutch pediatric ALL patients, including an evaluation of change of body composition by DEXA in a nested, single-center cohort.

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Methods

Study population

This study included newly diagnosed pediatric ALL patients, aged 2-17 years, treated according to the Dutch Childhood Oncology Group (DCOG) – ALL9 protocol, between January 1997 and November 2004 in seven pediatric oncology centers in the Netherlands.[21] The patients were stratified at diagnosis into non-high-risk and high-risk treatment groups as previously described.[21]

For the current study, patients with syndromes or pre-existent diseases affecting the locomotor system were excluded (Figure 1) as these influence body composition and/or leukemia outcome.[22] Patients were prospectively evaluated from diagnosis to November 2012 at the central DCOG office. The Medical Ethical Committee approved the study in 1996. Written informed consent was obtained according to the Helsinki agreement from all caregivers and patients aged ≥12 years (trial number NTR460/SNWLK-ALL-9).

Body composition

Height and weight were measured at diagnosis (T0), after 32 weeks of treatment at the start of ALL maintenance therapy (T1), at the end of treatment (T2, 109 weeks) and 1 year after the end of treatment (T3) (Figure 1).

Height was measured using a Harpenden stadiometer and weight with a standard clinical scale. Absolute values of BMI were calculated as weight (m)/height (kg)^2.[23] A Z-score for age and gender was calculated for weight, height and BMI with reference values for healthy Dutch peers, and was expressed as a standard deviation score (SDS: Z-score).[24-26]

On the basis of the BMI_{SDS} at diagnosis, patients were divided into categories: obese and overweight (>1.1 $_{SDS}$), normal weight (–1.8$_{SDS}$ to 1.1$_{SDS}$), and underweight(<–1.8$_{SDS}$).[24,25,27]

Change of BMI was measured between diagnosis and 32 weeks of treatment (T0 to T1), and between diagnosis and cessation of antileukemic treatment (T0 to T2). Patients were included in the analysis if BMI was measured at 32 weeks (range, 30-40) or at 109 weeks (range, 104-114). BMI change was analyzed into categories: BMI_{SDS} loss or BMI_{SDS} gain.

To assess the relative contribution of body composition components to the change of BMI over time, the percentage (%) fat and total lean body mass (organs and muscle tissue) were measured by DEXA (GE Lunar Prodigy, LUNAR Corporation, Madison, WI, USA). DEXA scans were taken in patients ≥4 years, as reference values for healthy peers are only available from the age of 4 years.[28,29]

Statistical analysis

The χ^2 test was used to compare frequencies in patients' variables between categories of BMI and its changes. The two sample t-test or analysis of variance (ANOVA) was used to compare normally distributed, continuous patients' variables between BMI categories.

The primary outcomes of interest were complete remission rate, event-free survival, cumulative incidence of relapse and overall survival. The 10-year survival curves for event-free and overall survival were estimated using the Kaplan-Meier methodology[30] and the two-sided Mantel-Haenszel log-rank test.[31] Univariate and multivariate Cox-regression analyses were used to estimate the hazard ratio (HR) of BMI categories for event-free and overall survival.[32] To estimate the 10-year cumulative incidence of relapse curves, a competing risks model was used with death and second malignancy as competing events.[33] All multivariate regression analyses including BMI at baseline or BMI change were adjusted for non-high-risk or high-risk group, and BMI at diagnosis as a continuous variable (only for BMI change).

Table 1. Overview of literature assessing the influence of body composition on outcome in pediatric ALL by multivariate analysis.

Year	Author (Reference)	Patients (N)	Age (range, years)	Measures	Outcome ↓CRR	↓EFS	↑CIR	↓OS	↑TRM
1994	Viana MB(10)	128	1-15	Weight for height at Dx	<-2 SDS		<-2 SDS		
1994	Reilly JJ(9)	78	1-13	Weight for height at Dx			<-0.5 SDS		
1998	Weir J(8)	1025	0-15	BMI at Dx		No		No	
		NA		BMI change[b]		No	No	No	
2001	Hann I(7)	2090	1-15	BMI at Dx		No			
2006	Baillargeon J(6)	322	2-18	BMI at Dx		No		No	
2006	Hijiya N(5)	621	1-19	BMI at Dx		No	No	No	
2006	Hijiya N(5)	NA		BMI change[c]		No	No	No	
2007	Butturini AM(4)	4260 and 1733 *	2-20	BMI at Dx		≥ 95th	≥ 95th	≥ 95th	No
2011	Gelelete(12)	181	<10	BMI at Dx		>1 SDS			
2013	Aldhafiri FK(13)	1033	2-15	BMI at Dx		No			
2013	Antillon(11)	241	1-18	TSFT/MUAC at Dx				TSFT and MUAC < 10th	
2013	Antillon(11)	241		TSFT/MUAC changed				Decrease	
2014	Orgel(14)	2008	1-20	BMI at Dx		≥ 95th < 5th			≥ 95th < 5th
2014	Orgel(14)	1581	1-20	BMI change[a]		95th ≥ or < 5th ≥50% time			
2014	den Hoed MAH, current study	762	2-17	BMI at Dx	No	No	≤-1.8 SDS	No	No
		508		BMI change[e]		No	No	Decrease	

N: *number; SDS: standard deviation score; th: amount of percentile; BMI: body mass index for age and gender (SDS or Z-score); Dx: at diagnosis; CRR: complete remission rate; CIR: cumulative incidence of relapse; EFS: event-free survival; OS: overall survival; TRM: treatment related mortality (including infection, toxicity, relapse, death before first complete remission); NA: not available; "no": no association found; empty cells indicate that the outcome was not assessed in the study; TSFT: triceps skin fold thickness; MUAC: mid upper arm circumference. *: Verification cohort; **: Correction of BMI for variables associated with survival outcomes; [a]: percentage time between end of induction and start of maintenance spent in weight category; [b]: change after diagnosis; c: BMI change during entire treatment period; [d]: BMI change after 6 months of treatment; [e]:BMI change after 32 weeks of treatment.*

Statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and R version 2.15.2 (The R Foundation for Statistical Computing). *P* values ≤0.05 (two-sided) were considered statistically significant.

Additional information on the methods is available in the *Online Supplementary Appendix*.

Results

Patients' demographics

Of the 859 patients registered in the DCOG-ALL9 protocol, 762 (463 males, 61%) were eligible for the current study (Figure 1, *Online Supplementary Table S1*). The median age at diagnosis of the patients included was 5.0 years (range, 1.5-17.3). Complete remission was achieved after induction in 744 (98%) patients. The median follow-up was 9 years (range, 0.1-10). At 10 years the cumulative incidence of relapse of the patients included was 17% (SE 1%), the event-free survival rate was 78% (SE 2%) and the overall survival rate was 85% (SE 1%); these values are similar to those previously published for the whole DCOG-ALL-9 group by Veerman *et al.*[21]

The nested, single-center subset (n=72) in which DEXA total body scans were performed was representative of the total cohort with respect to gender, risk group, white blood cell count, genetics and extramedullary mass, but the patients were older than those in the total cohort (median age 8.5 *versus* 4.7 years; *P*<0.001). This was due to the inclusion age for DEXA-scan evaluation, as reference values for healthy peers are only available from the age of 4 years.[28,29] Mean %fat and lean body mass at diagnosis did not differ according to gender (*P*=0.429 and *P*=0.063, respectively), age at diagnosis (*P*=0.209 and *P*=0.131), risk group (*P*=0.525 and *P*=0.491), immunophenotype (*P*=0.583 and *P*=0.499) or white blood cell count (*P*=0.928 and *P*=0.428) at diagnosis.

Body mass index at diagnosis

BMI_{SDS} data were available for 738 patients (97%) (Figure 1). At diagnosis, 584 patients (79%) had a normal weight,

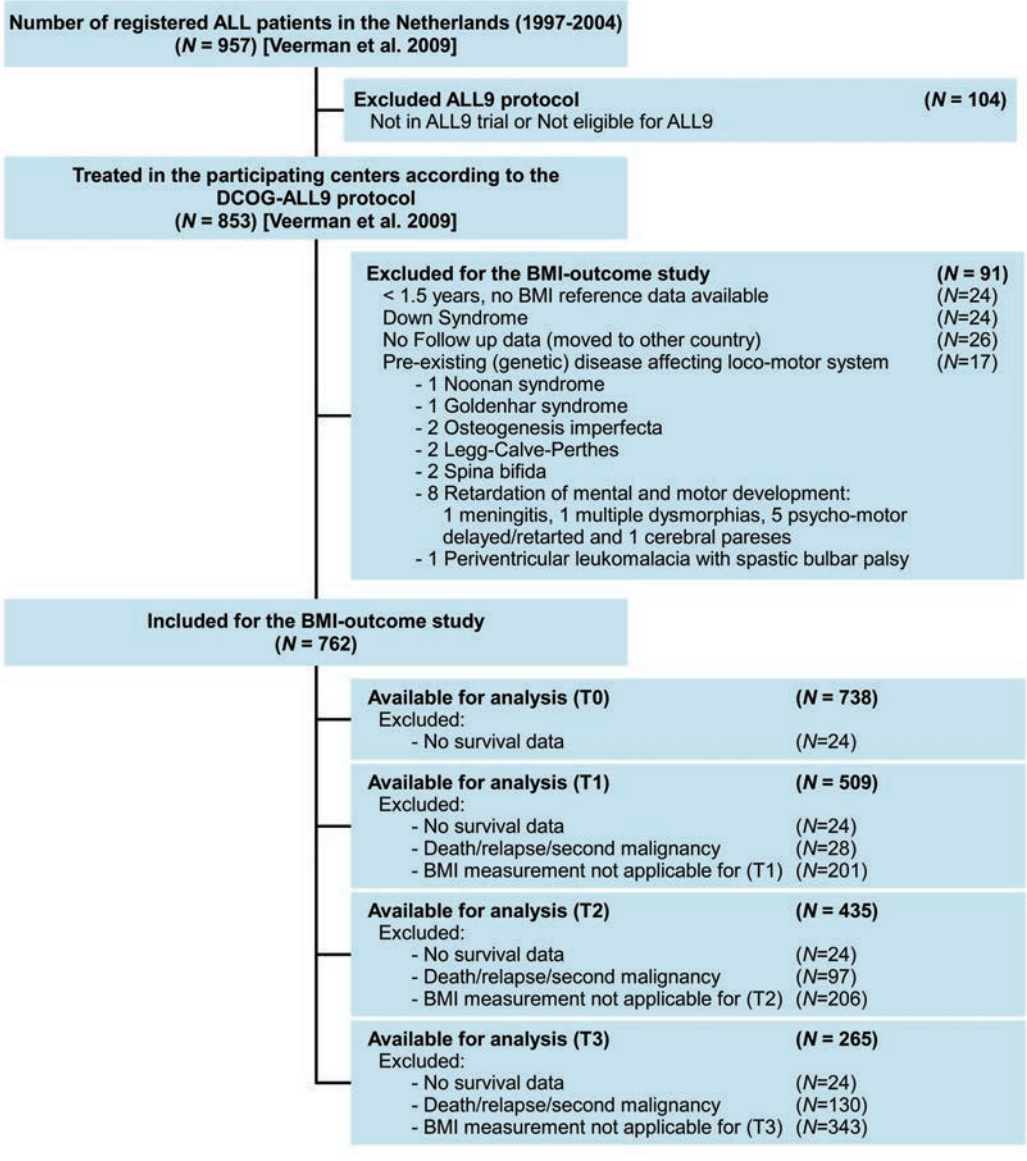


Figure 1. CONSORT diagram of the inclusion of patients in the current BMI-outcome study. ALL: acute lymphoblastic leukemia; DCOG: Dutch Childhood Oncology Group; BMI: body mass index.

59 (8%) were underweight, and 95 (13%) were overweight or obese. As only 2% of the patients were obese (BMI_{SDS} ≥2.3), overweight and obese patients were combined in all analyses. BMI categories did not differ between patients who were stratified into the non-high risk or high-risk protocols (*P*=0.51). However, younger patients (<10 years) more often had a normal weight, while older patients were more likely to be over- or underweight (*P*=0.016) (Table 2). Body composition data showed that patients who were underweight at diagnosis (n=7) were characterized by both low %fat [mean -1.19 (1.04); *P*<0.01] and a low lean body mass [mean -1.75 (0.62), *P*=0.06] compared to overweight patients. Inversely, overweight patients (n=10) had both a high %fat [mean 1.08 (0.85); *P*<0.01] combined with a relative high lean body mass [mean -0.33 (0.93); *P*=0.06].

Body mass index at diagnosis and outcome

The complete remission rate did not differ between patients in different BMI_{SDS} categories (Table 3). Underweight patients were more likely to have experienced a relapse by 10 years of follow up (cumulative incidence of relapse: 31% in underweight patients *versus* 18% in normally weighted/overweight patients; *P*<0.01) (Figure 2, Table 3). In multivariate analysis, after adjustment for risk group and age, patients who were underweight had an almost 2-fold higher risk of relapse as compared to those who were not underweight [cumulative incidence of relapse: HR 1.88; 95% confidence interval (CI): 1.13-3.13].

Being underweight at diagnosis was not associated with overall or event-free survival (Figure 2, Table 3). There was no effect modification by age ≥10 years, gender or risk-group protocol.

Of the ALL patients who died, all subjects who were underweight died of leukemia (n=10), whereas patients who had a normal weight or were overweight died of infection (n=20), toxicity (n=6), leukemia (n=79) or other causes (n=3) (*Online Supplementary Table S2*).

Change in body mass index

A second BMI measurement at 32 weeks of treatment was available for 508 patients (Figure 1). In 28 cases the dropout of patients at 32 weeks was caused by relapse, death, or second malignancy, whereas in 201 patients, BMI was not documented within the aimed range of 5 weeks (T1) (Figure 1). The patients with or without a BMI measurement at 32 weeks did not differ with regards to gender, age at diagnosis, risk group or white blood cell count at diagnosis. However, patients with a BMI measurement at 32 weeks of therapy were less likely to have T-ALL, (12.6% *versus* 36.4%; *P*<0.01). A third BMI measurement was available for 435 patients at cessation of treatment (T2) (Figure 1). The lack of data at cessation of treatment was caused by relapse, death, or second malignancy in 97 patients, whereas in 206 patients, BMI was not measured at cessation of treatment in the range of 104-114 weeks (Figure 1). As compared to patients without a BMI measurement at cessation of treatment, patients with a BMI measurement had a similar gender distribution, but they were more often younger than 10 years at diagnosis (17.2% *versus* 27.7%; *P*=0.001); were more likely to have common ALL (68.1% *versus* 89.2%; *P*<0.01); were more less often at high-risk (23.3% *versus* 38.2%); and had lower white blood cell counts [8.1x10^9/L (range, 0.2-650) *versus* 13.4x10^9/L (range, 0.3-926); *P*=0.001].

BMI_{SDS} increased significantly during the first 32 weeks of therapy [mean 0.85 (SD 0.94); *P*<0.001]. An increase of one BMI_{SDS} (T1-T0) is equivalent to a gain of 2.27 kg (95% CI 2.01-2.54) or an increase of 1.67 BMI units (95% CI 1.58-1.75). This increase in BMI in our cohort was shown to be due not only to an increase in body weight but also to a

Table 2. Characteristics of patients divided according to BMI category.

	BMI groups at diagnosis							BMI change*				
	Underweight		Normal weight		Overweight			Decrease		Increase		
	N	(%)	N	(%)	N	(%)	*P*	N	(%)	N	(%)	*P*
BMI (SDS)												
≤ -1.8	-		-		-		NA	2	(4%)	47	(96%)	NA[a]
-1.8 – 1.1	-		-		-			60	(15%)	333	(85%)	
> 1.1	-		-		-			25	(38%)	41	(62%)	
Gender												
Male	33	(7%)	355	(79%)	62	(14%)		57	(18%)	254	(82%)	
Female	26	(9%)	229	(80%)	33	(11%)	0.503[a]	30	(15%)	167	(85%)	0.366[c]
Age at diagnosis (median, range)	5.0	(1.6-15.6)	5.1	(1.5-17.3)	5.1	(1.6-16.6)	0.310[b]	4.0	(1.5-17.1)	5.1	(1.5-16.8)	0.035[d]
Age group (> 10 years)												
No	39	(7%)	469	(81%)	69	(12%)		71	(18%)	334	(82%)	
Yes	20	(12%)	115	(71%)	26	(17%)	0.016[a]	16	(16%)	87	(84%)	0.631[c]
Risk group stratification												
Non-high-risk	45	(8%)	404	(79%)	65	(13%)		44	(12%)	310	(88%)	
High-risk	14	(6%)	180	(80%)	30	(14%)	0.508[a]	43	(28%)	111	(72%)	<0.001[c]
Immunophenotype												
BCP-ALL	54	(9%)	445	(78%)	74	(13%)		69	(16%)	358	(84%)	
T-ALL	3	(2%)	107	(82%)	20	(16%)	0.025[a]	18	(29%)	45	(71%)	0.016[a]
White blood-cell count												
WBC (x10^9/L) (median, range)	7.4	(1.2-246.0)	10.2	(0.2-926.0)	8.9	(0.7-590.0)	0.610[b]	23.2	(1.0-590.0)	9.3	(0.2-650.0)	<0.001[d]

*BMI: body mass index; SDS: standard deviation score; BCP: B-cell precursor; WBC: white blood cell count; a: analyses were performed with ANOVA; b: analyses were performed with the Kruskal-Wallis test: c: analyses were performed using the χ^2 test; d: analyses were performed with the Mann-Withney U test; *BMI increase or decrease was measured in the first 32 weeks of treatment.*

Table 3. Influence of change in BMI on treatment outcomes.

	N	(%)	Complete Remission N	(%)	CIR Univariate $HR_{F\&G}$	(95%CI)	CIR Multivariate $HR_{F\&G}$	(95%CI)	EFS Univariate HR	(95%CI)	EFS Multivariate HR	(95%CI)	OS Univariate HR	(95%CI)	OS Multivariate HR	(95%CI)
Baseline BMI																
BMI ≤ -1.8 SDS	59	(8%)	58	(98%)	**1.94**	**(1.18 -3.19)***	**1.88**	**(1.13 -3.13)***	1.29	(0.77 -2.15)	1.28	(0.76 -2.15)	1.11	(0.58 -2.13)	1.10	(0.57 -2.10)
BMI > -1.8 SDS	679	(92%)	652	(96%)	**1**		**1**		1		1		1		1	
BMI change – 32 weeks																
BMI <0 SDS (decrease)	87	(17%)	NA		1.29	(0.76 -2.19)	1.45	(0.82 -2.57)	1.37	(0.82 -2.27)	1.51	(0.89 -2.58)	**1.96**	**(1.10 -3.48)***	**2.10**	**(1.14 3.87)***
BMI ≥0 SDS (increase)	421	(83%)	NA		1		1		1		1		**1**		**1**	
BMI change – 109 weeks																
BMI <0 SDS (decrease)	75	(17%)	NA		0.98	(0.44 -2.19)	1.37	(0.57 -3.08)	0.96	(0.42 -2.15)	1.31	(0.56 -3.03)	0.75	(0.21 -2.70)	0.47	(0.12 -1.78)
BMI ≥0 SDS (increase)	360	(83%)	NA		1		1		1		1		1		1	

*Multivariate analyses were adjusted for (log) age of diagnosis, risk group and baseline BMI $_{SDS}$. N: number; BMI: body mass index; SDS: standard deviation score; CIR: cumulative incidence of relapse; EFS: event- free survival; OS: overall survival; HR: hazard ratio; $HR_{F\&G}$: sub-distribution hazard ratio and associated 95% CI for Fine-Gray regression; 95% CI: 95% confidence interval; *P value <0.05.*

delay in growth [T1-T0 mean $height_{SDS}$ -0.44 (SD 0.47); *P*<0.01 and T1-T0 mean $weight_{SDS}$ 0.38 (SD 0.69); *P*<0.01] (*Online Supplementary Figure S1*).

Patients in the non-high-risk group had a more prominent increase in BMI during the first 32 weeks of therapy than had high-risk patients (T1-T0: SDS non-high-risk +0.98 *versus* high-risk +0.55; *P*<0.01), but ultimately there was no difference in increase in the BMI at the end of therapy between the high-risk and non-high-risk groups (T2-T0: non-high-risk: +0.98 SDS *versus* high-risk: +0.87 SDS; *P*=0.36). During the first 32 weeks of therapy 17% (n=87) of the patients had a decrease in BMI_{SDS}; these patients had a median increase of 0.7 kg in weight (range, -5.50 - 3.50) and a median loss of -0.58 BMI units (range, -4.20 - 0.33). Patients who had a decrease in BMI_{SDS} (T1-T0) were more often high-risk patients (*P*<0.001) and were relatively younger (*P*<0.04) (Table 2). Almost all patients who were underweight at diagnosis (n=49) had an increase in BMI during the first 32 weeks of therapy (n=47, 96%).

DEXA-scan data from the nested subset showed that this increase in BMI could be explained by an increase in $\%fat_{SDS}$ [T1-T0: +1.22 (0.90); *P*<0.01]. Lean body $mass_{SDS}$ remained stable [T1-T0: -0.01 (1.25); *P*=0.97]. Interestingly, in patients with a decrease in BMI in the first 32 weeks of treatment (n=8), $\%fat_{SDS}$ still tended to increase, but there was a predominant loss in lean body $mass_{SDS}$ (*Online Supplementary Figure S2*). Between discontinuation of therapy and 1 year thereafter (T3-T2), BMI_{SDS} decreased significantly (mean 0.78 to 0.61; *P*<0.01), but remained higher when compared to that of healthy peers [mean 0.61 (1.15); *P*<0.01].

Change in body mass index and outcome

The decrease in BMI in the first 32 weeks was associated with an impaired overall survival [HR: 1.96 (1.10-3.48)]. This association remained significant after adjustment for baseline BMI, age at diagnosis and risk group [HR: 2.10 (1.14-3.87)] (Figure 3, Table 3). The causes of death in patients with a decrease in BMI were treatment toxicity (n=4), second malignancy (n=1) and leukemia (n=11). In patients who died, the site of the first relapse (*P*=NA) and the time between relapse and death (*P*=0.495) were similar in patients whose BMI did or did not decrease. Patients whose BMI decreased seemed to have a higher incidence of death after relapse than had patients without a decrease in BMI [n=14 (88%) *versus* n=38(58%)] (*Online Supplementary Table S3*).

A decrease in BMI_{SDS} (T1-T0) was not associated with event-free survival [adjusted HR: 1.51 (0.89-2.58)] or cumulative incidence of relapse [adjusted $HR_{F\&G}$: 1.29 (0.76-2.19)] (Figure 3, Table 3). A decrease in BMI between diagnosis and end of therapy (T2-T0) was not associated with event-free survival, cumulative incidence of relapse or overall survival (Table 3). There was no effect modification by age ≥10 years, gender or risk-group protocol in any of the analyses.

During DCOG-ALL9 treatment, the causes of death in patients with a decrease in BMI were treatment toxicity (n=1), second malignancy (n=1) and leukemia (n=7) (*Online Supplementary Table S2*).

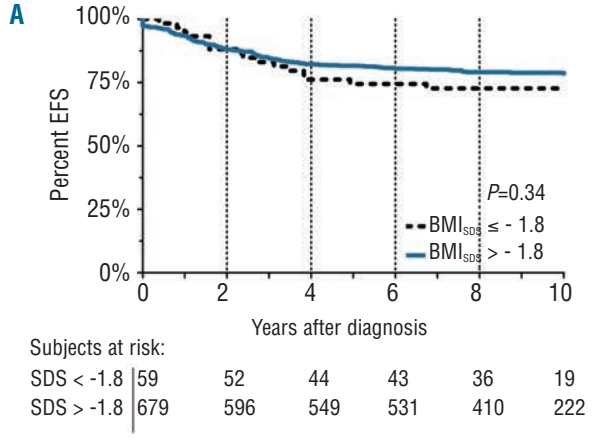
Discussion

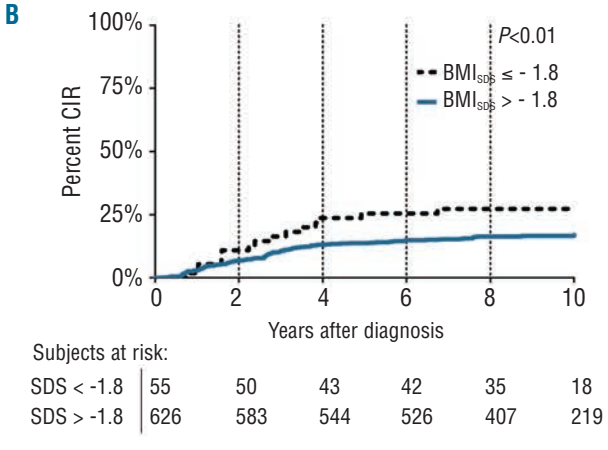
The current study shows that being underweight at diagnosis is associated with a higher relapse rate, and that a decrease in BMI during therapy, which seems to be due to a loss of lean body mass, is associated with decreased overall survival in children with ALL.

So far, contradictory results have been reported on the impact of BMI at diagnosis on outcome in children with ALL (Table 1). Studies that showed that baseline BMI was not associated with outcome included small numbers of patients in BMI subgroups, or only analyzed the influence of being overweight on survival.[5-8,13] Studies that reported baseline undernourishment as a determinant of impaired survival were mostly conducted in developing countries or had small numbers in the BMI subgroups.[9-11] In those series, patients were, in addition to their disease status and treatment, also coping with additional risk factors for poor outcome such as malnutrition and poor socioeconomic risk factors. Our study underscores that the fact of being underweight at baseline needs to be taken into account in survival analyses in pediatric ALL. This confirms the findings of a recently performed study in a large cohort of high-risk pediatric ALL patients that showed an impaired event-free survival in patients who were underweight at baseline.[14]

In our cohort, patients who were underweight at diagnosis were more likely to relapse, but this did not eventually lead to an inferior survival. It is unknown what determines this influence of baseline weight on relapse occurrence. It is conceivable that several factors may be involved, including impaired immune function, reduced absorption of treatment medication, and decreased drug-protein

binding,[34,35] which are all in general determined by genetic variation. Patients who were underweight at diagnosis in our study showed a low lean body mass as well as a low %fat compared to normal or overweight patients. All these factors might produce variations in drug pharmacokinetics;[34] however, the impact of weight status on pharmacokinetics and pharmacodynamics remains under debate in pediatric oncology as there are conflicting reports.[5,36] In the current study underweight patients had a higher incidence of relapse, but interestingly, did not experience many (toxic) events as the event-free survival was similar for both BMI groups (underweight or not underweight). Our





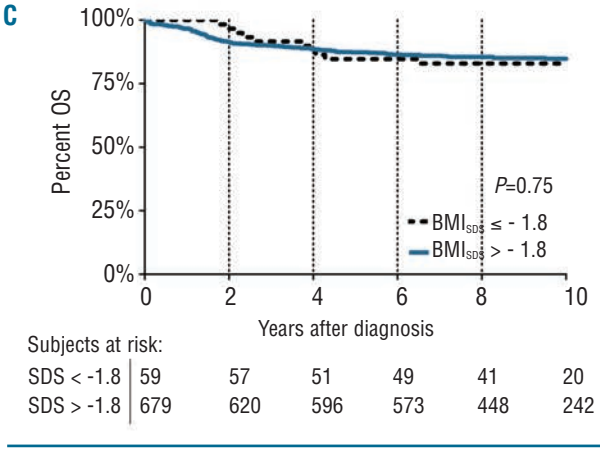
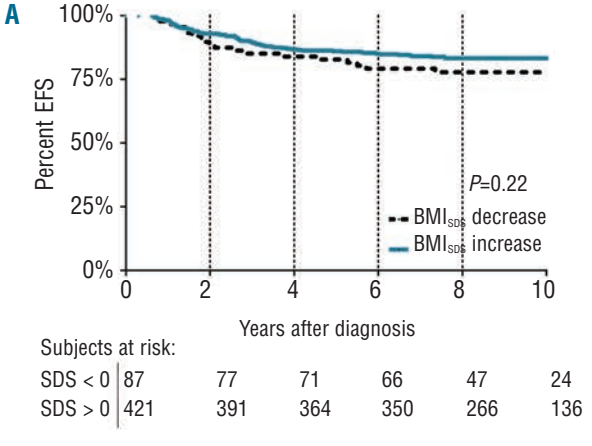
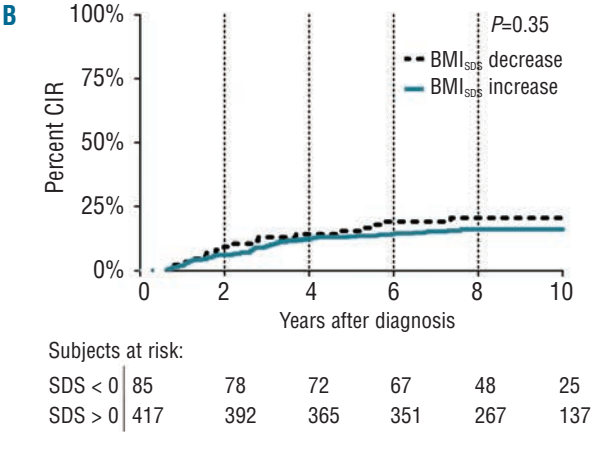


Figure 2. Outcomes according to BMI measured at the time of ALL diagnosis. (A) Kaplan-Meier analysis for event-free survival (EFS), (B) cumulative incidence of relapse (CIR) and (C) overall survival (OS). BMI categories: underweight (BMI$_{SDS}$ ≤ -1.8, N=59) and other weight (BMI$_{SDS}$ > -1.8, N=679). BMI: body mass index; SDS: standard deviation score.





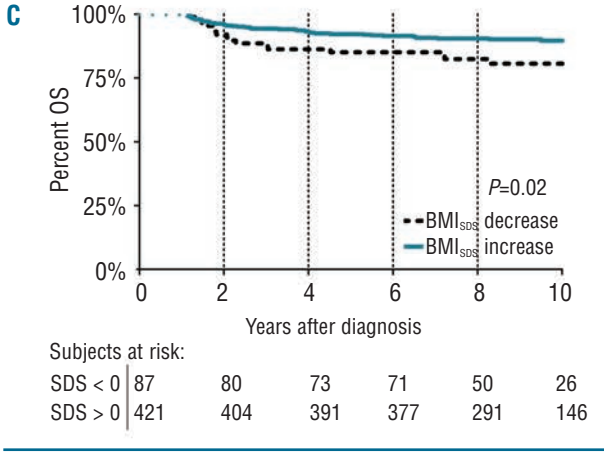


Figure 3. Landmark analyses for outcomes according to BMI change during the first 32 weeks of treatment. (A) Kaplan-Meier estimates for BMI change during 32 weeks of treatment (T1-T0) for event-free survival (EFS), (B) cumulative incidence of relapse (CIR) and overall survival (OS). BMI categories were: BMI decrease (< 0 BMI$_{SDS}$) and BMI increase (≥ 0 BMI$_{SDS}$). BMI: body mass index; SDS: standard deviation score.

hypothesis is that the observed lack of serious toxicity in combination with the higher incidence of relapse in underweight patients may be related to minor delays and mild dosage deviations of treatment which were based on doctors' choice.[37] The underweight group of ALL patients may have been considered frail by pediatricians, as has been described in adults[38] That underweight patients received less therapy is further underscored by the fact that a higher proportion of such patients could be salvaged, as shown by the equal overall survival of patients who were underweight and those who were not underweight. This may illustrate that, rather than the aggressive tumor biology, the cumulative effect of mild therapy adjustments over time may determine the higher incidence of relapse. This is in contrast to other reports, in which it was suggested that being underweight at diagnosis might also be a reflection of the biological aggressiveness of the leukemia or the "illness state".[17]

In this study we also analyzed the effect of BMI *change* during therapy on treatment outcome in pediatric ALL. One previous study in 241 ALL patients in South America revealed that a decrease in body fat, measured by triceps skin fold thickness and mid upper arm circumference, was associated with a higher risk of mortality.[11] Another study showed impaired event-free survival when patients were underweight for ≥50% of the time between diagnosis and starting maintenance therapy[14] (Table 1). We found that a decrease in BMI during the first 32 weeks of treatment was associated with increased mortality. To our knowledge this is the first report that shows that even in patients with a decrease in BMI, the %fat increased while the muscle mass substantially decreased. How exactly this decrease affects survival is unknown. We found that, after a relapse, the salvage of patients with a decrease in BMI was more difficult than that of patients without a decrease in BMI; i.e. of the 87 patients with a decreased BMI, 14/17 (82%) patients who suffered a relapse died. In contrast, 38/66 (58%) patients without a decrease in BMI (n=421) died after having a relapse.

Our findings underscore the possible value of supportive care and lifestyle interventions for patients who are underweight at diagnosis and/or have a decrease in BMI in the first 32 weeks of treatment. The results from our nested study suggest that pediatric ALL patients could benefit from interventions that enhance lean body mass in addition to commonly used interventions, such as nasogastric-tube feeding including adequate nutrients to avoid a catalytic state. We also stress the importance of physical exercise programs early during treatment.[39] Furthermore, our findings suggest that in the future it would be interesting to base chemotherapy dosing schedules on lean body mass[40] rather than on body surface area to optimize pharmacodynamics in children.[41] However, in order to design such strategies, it is necessary to unravel the true nature of weight status in individual patients and confirm the herewith identified effects of being underweight, loss of weight and change in body composition in larger cohorts of ALL patients.

Previous studies suggested that being underweight or overweight is associated with a compromised outcome in children with ALL,[4,9-12,14] indicating that "extremes" matter. This has also been shown in pediatric acute myeloid leukemia.[42,43] This U-shaped association seems logical as both weight status and weight change affect and/or can be affected by disease severity. Overweight patients may have a compromised outcome as a result of a deficient immune response due to higher levels of sex steroids, insulin, insulin-like growth factor and inflammatory parameters and have an increased risk of comorbidities related to their excess weight.[15,44] Butturini *et al.* showed that obesity (>95th percentile ≈ 30 kg/m^2) was an independent predictor of relapse and mortality in 4260 children with ALL.[4] In the current study, we were not able to associate obesity with survival, as only 2% of our population suffered from obesity (>2.3 SDS ≈ BMI >30 kg/m^2). We found no association between being overweight at baseline and outcome (*data not shown*), but the degree of excess weight (>1.1 SDS ≈ BMI >25 kg/m^2) may not have been extreme enough to influence survival.

We made an attempt to include the development of BMI after 32 weeks in the analyses by evaluating longitudinal BMI data. We found that decreases in BMI between the start, 32 weeks and 109 weeks of treatment were associated with a decreased overall survival (*data not shown*). We lost a very high percentage of patients with BMI decrease in the first 32 weeks due to death after relapse, which hampered proper statistical analysis of the effect of BMI change after 32 weeks. We, therefore, appreciate the fact that even larger cohort studies are necessary to confirm our results.

We further realized that it is important to adjust for risk groups in the analyses, as there is a difference in treatment strategy for patients who are or are not at high risk during the first 32 weeks of treatment. Multivariate analysis revealed independent effects of BMI and BMI change on treatment outcome; even within the risk groups the effects of BMI and BMI change on outcome were in the same direction.

In conclusion, this study confirms that being underweight at diagnosis is a risk factor for relapse. A decrease in BMI early during treatment is associated with increased mortality. This suggests that pediatric ALL patients who are underweight at the time of diagnosis, and pediatric ALL patients with an early decrease in BMI might benefit from cautiousness when adjusting treatment, but also from including exercise interventions in addition to standard diets with high-quality nutrients during ALL treatment.

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Authorship and Disclosures

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