Body mass index during and early after therapy for pediatric acute lymphoblastic leukemia is associated with obesity in survivors

The current 5-year survival rate for childhood acute lymphoblastic leukemia (ALL) exceeds 90% with risk-adaptive therapy, effective central nervous system (CNS) control without cranial radiotherapy (CRT), and improved supportive care.[1] However, survivors remain vulnerable to chronic health conditions.[2] In recent protocols, the prevalences of obesity and musculoskeletal disorders have surpassed those of neurocognitive impairment and cardiopulmonary dysfunction.[2] Childhood obesity contributes to cardiometabolic disorders in adulthood, making it a key focus in survivorship research.[3] Disease risk classification, specific treatments such as glucocorticoids and CRT, genetics, unhealthy diet, and physical inactivity can contribute to obesity among survivors, and survivors with a high polygenic risk score (PRS) experience an increase of up to 53-fold in severe obesity.[4,5] A prior study of body mass index (BMI) in ALL used single-time point BMI, which cannot capture dynamic treatment-related weight changes.[6] Moreover, survivors experience additional biological and therapy-related factors that may further modify obesity persistence into adulthood. Therefore, we modeled longitudinal BMI trajectories and calculated BMI areas under the curve (AUC) above the overweight/obesity threshold with variable observation periods to characterize the dynamic and cumulative overweight/obesity burden, enabling early identification of high-risk patients for timely intervention during therapy. This study was approved by the St. Jude Institutional Review Board. Informed consent or assent was obtained from each patient or from their legal guardian, as appropriate to the patient's age.

Eligible survivors (N=881) were treated in St. Jude Total Therapy Studies X-XV (1980-2006)[1,7-12] and participated in the St. Jude Lifetime Cohort Study (SJLIFE) with a completed initial on-campus evaluation.[13] Data from the Total Therapy Studies and SJLIFE were sequentially linked for individual participants (*clinicaltrials gov. Identifier: NCT00760656*). Exclusion criteria included age <2 years at ALL diagnosis (N=76) and having Down syndrome/Turner syndrome (N=10), relapsed disease (N=66), transplantation (N=37), secondary malignant neoplasms requiring treatment before the SJLIFE visit (N=5), and missing BMI data during therapy (N=9). Therefore, 678 patients were evaluated.

Patient demographics, treatment exposures, and lifestyle data were obtained from medical records and protocol databases.[13] The BMI-PRS included 2.09 million genome-wide common variants.[4] Genetic ancestry was determined by using k-means clustering implemented in Admixture,[14] based on genotype data and the 1,000 Genomes reference populations. Height and weight were collected at diagnosis (±3 days), end of induction (±7 days), 6 months (±14 days), 12 months (±14 days), 18 months (±30 days), 24 months (±30 days), end of therapy (±30 days), and annually thereafter (±180 days) until 5 years off-therapy. Survivorship outcomes were obtained at the first SJLIFE visit. BMI was converted to an age- and sex-adjusted Z-score by using Centers for Disease Control and Prevention growth charts. For patients aged >20 years, Z-scores were based on reference data for individuals aged 20 years. Survivors were categorized by BMI as follows: <18.5 kg/m^2: underweight; 18.5-24.9 kg/m^2: normal weight; 25.0-29.9 kg/m^2: overweight, and ≥30.0 kg/m^2: obese.

Latent classes were identified using a latent process mixed model, assigning each patient to the class with the highest posterior probability. Missing BMI values during treatment were imputed using the last observation carried forward (LOCF) method. The optimal number of latent classes was determined using Bayesian and Akaike Information Criteria and clinical relevance. Total AUC, representing exposure to overweight/obesity, was calculated as the area above a BMI Z-score of 1.036 (85th percentile) by integrating BMI Z-scores across measurement intervals. Analyses were performed in R version 4.3.1. Latent profiles were modeled using BMI Z-scores from diagnosis to 5 years off-therapy and from diagnosis to 1 year post-diagnosis. AUC were calculated for three periods: diagnosis to 5 years off-therapy, diagnosis to 1 year post-diagnosis, and diagnosis to end of induction therapy. A web application for predicting a patient's latent class and calculating the BMI AUC is available at https://sjbiostat.shinyapps.io/BMIzExplorer/. Associations of BMI latent classes and AUC with weight status were evaluated using multinomial logistic regression. Statistical significance was set at P<0.05.

Characteristics of the 678 patients included in the analysis and their longitudinal changes in weight, height, and BMI Z-scores from diagnosis until 5 years off-therapy are shown in *Online Supplementary Tables S1* and *S2*, respectively. The median time from end of therapy to first SJLIFE evaluation was 17.47 years (range, 6.08-33.42 years). The percentage of overweight/obese patients increased from 16.4% at diagnosis to 35.2% at off-therapy and 44.6% at 5 years off-therapy, and it continued rising to 63.3% in survivors.

We identified four BMI trajectory classes from diagnosis to 5 years off-therapy (Figure 1A). The low-slow group was characterized by persistently low BMI with a gradual increase (N=404, 59.6%). The medium-slow group showed mid-range BMI at diagnosis with a slow upward trend (N=180, 26.5%). The low-fast group began treatment with a lower BMI but experienced a rapid increase during and shortly after therapy (N=65, 9.6%). The high-slow group started with a higher BMI that gradually increased (N=29, 4.3%). These patterns may reflect differences in baseline nutritional status, treatment-related metabolic effects, or activity limitations during therapy. For BMI trajectories from diagnosis to 1 year post-diagnosis, most patients were in the "normal" group (N=393, 58.0%), followed by the "medium" (N=151, 22.3%), "low" (N=108, 15.9%), and "high" (N=26, 3.8%) groups (Figure 1B).

Multivariable models evaluating associations between BMI trajectories, host and treatment factors, and BMI Z-scores or weight-status categories in survivors included sex, race/ethnicity, attained age, and CRT (the only treatment factor significant in univariate analysis). BMI latent classes and BMI AUC were significantly associated with BMI categories and BMI Z-scores at survivorship in all models (Tables 1 and 2). From diagnosis to 5 years off-therapy, the "high-slow" group had the highest risk of overweight and obesity, followed by the "low-fast" and "medium-slow" groups,

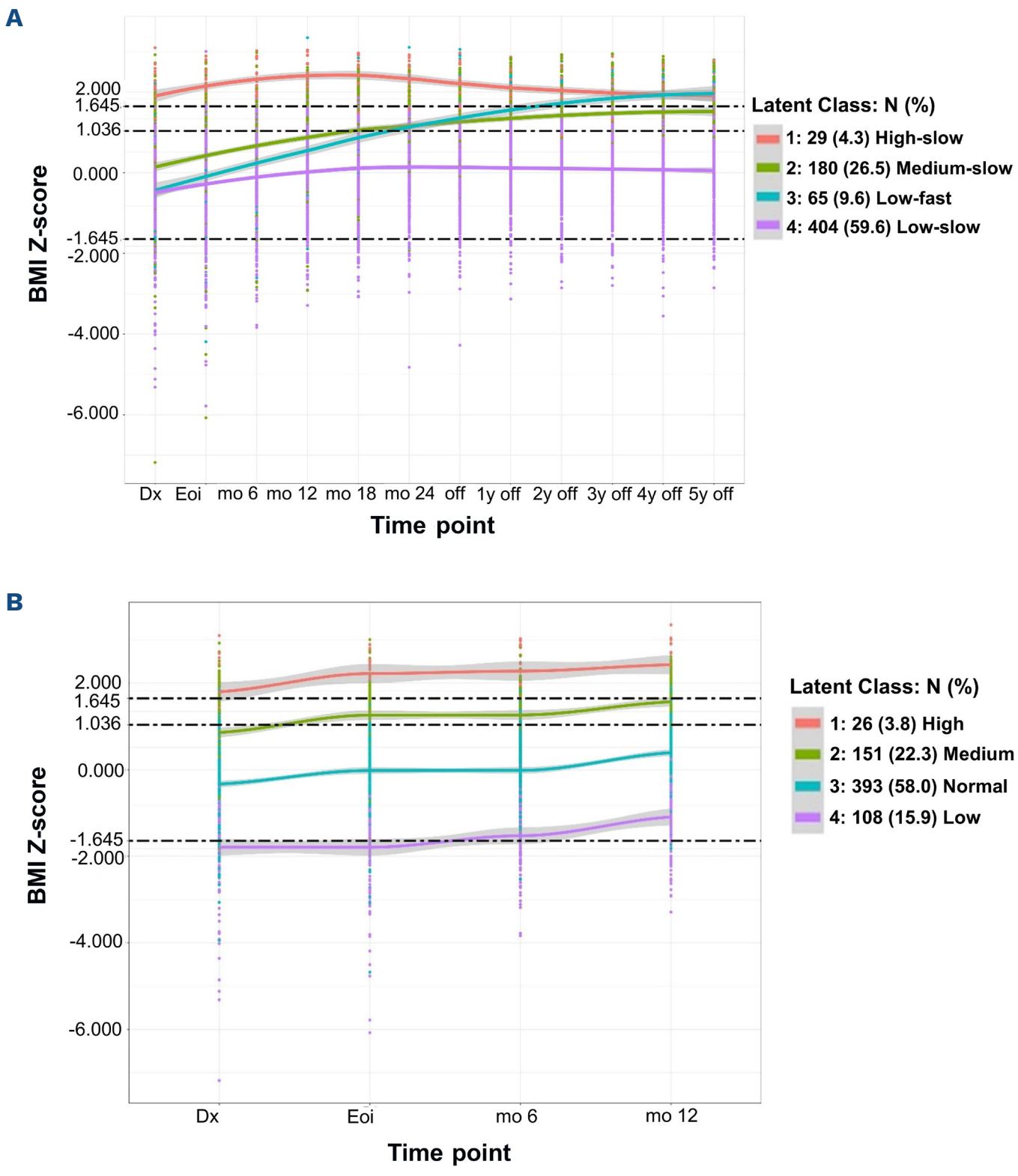


Figure 1. Longitudinal body mass index trajectory patterns in childhood acute lymphoblastic leukemia survivors, showing trajectories from diagnosis to 5 years off-therapy and from diagnosis to 1 year post-diagnosis. (A) Trajectories from diagnosis to 5 years off-therapy (off). (B) Trajectories from diagnosis to 1 year post-diagnosis. ALL: acute lymphoblastic leukemia; BMI: body mass index; Dx: diagnosis; Eoi: end of induction; mo: month; y: year.

Table 1. Association of host, treatment factors, and body mass index trajectory pattern with overweight/obesity categories and body mass index Z-score in survivors.

Overweight/obesity categories in survivors							
Factor	**N**	**Overweight**			**Obesity**		
		OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
BMI trajectory from diagnosis to 5 years off-therapy							
Sex							
Female	339	-	-	-	-	-	-
Male	339	1.65	1.10-2.48	0.016	1.22	0.79-1.89	0.400
Attained age	678	1.07	1.03-1.12	<0.001	1.15	1.10-1.20	<0.001
Race/ethnicity							
Non-Hispanic White	566	-	-	-	-	-	-
Non-Hispanic Black	77	1.48	0.74-2.97	0.300	1.73	0.85-3.51	0.130
Hispanic, Asian, or other	35	1.11	0.49-2.48	0.800	0.31	0.09-1.06	0.062
Cranial radiotherapy							
No	465	-	-	-	-	-	-
Yes	213	2.00	1.21-3.31	0.007	2.39	1.42-4.04	0.001
Latent class profile							
Low-slow	404	-	-	-	-	-	-
Medium-slow	180	2.71	1.59-4.62	<0.001	14.20	8.26-24.30	<0.001
Low-fast	65	5.18	1.92-14.00	0.001	32.70	12.70-84.30	<0.001
High-slow	29	6.70	1.26-35.70	0.026	76.60	16.80-349.00	<0.001
BMI trajectory from diagnosis to 1 year post-diagnosis							
Sex							
Female	339	-	-	-	-	-	-
Male	339	1.63	1.09-2.44	0.019	1.20	0.79-1.81	0.400
Attained age	678	1.09	1.04-1.13	<0.001	1.16	1.11-1.21	<0.001
Race/ethnicity							
Non-Hispanic White	566	-	-	-	-	-	-
Non-Hispanic Black	77	1.69	0.84-3.39	0.140	2.31	1.17-4.56	0.016
Hispanic, Asian, or other	35	1.06	0.48-2.36	0.900	0.29	0.09-0.94	0.039
Cranial radiotherapy							
No	465	-	-	-	-	-	-
Yes	213	2.06	1.25-3.41	0.005	2.54	1.54-4.19	<0.001
Latent class profile							
Normal	393	-	-	-	-	-	-
Low	108	0.38	0.22-0.66	<0.001	0.12	0.06-0.24	<0.001
Medium	151	1.90	1.10-3.27	0.020	4.23	2.51-7.13	<0.001
High	26	4.04	0.36-45.90	0.300	58.80	7.54-458.00	<0.001
BMI Z-score in survivors							
Factor	**N**	**β**		**95% CI**		**P**	
BMI trajectory from diagnosis to 5 years off-therapy							
Sex							
Female	339	-		-		-	
Male	339	-0.01		-0.15 to 0.12		0.900	
Attained age	678	0.04		0.03-0.06		<0.001	
Race/ethnicity							
Non-Hispanic White	566	-		-		-	
Non-Hispanic Black	77	0.13		-0.08 to 0.35		0.200	
Hispanic, Asian, or other	35	-0.24		-0.55 to 0.06		0.120	
Cranial radiotherapy							
No	465	-		-		-	
Yes	213	0.19		0.03-0.35		0.023	

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BMI Z-score in survivors				
Factor	**N**	**β**	**95% CI**	***P***
BMI trajectory from diagnosis to 5 years off-therapy				
Latent class profile				
Low-slow	404	-	-	-
Medium-slow	180	1.00	0.86-1.20	<0.001
Low-fast	65	1.30	1.00-1.50	<0.001
High-slow	29	1.60	1.20-1.90	<0.001
BMI trajectory from diagnosis to 1 year post-diagnosis				
Sex				
Female	339	-	-	-
Male	339	0.00	-0.15 to 0.14	>0.900
Attained age	678	0.05	0.04-0.07	<0.001
Race/ethnicity				
Non-Hispanic White	566	-	-	-
Non-Hispanic Black	77	0.27	0.05-0.50	0.018
Hispanic, Asian, or other	35	-0.31	-0.63 to 0.01	0.055
Cranial radiotherapy				
No	465	-	-	-
Yes	213	0.24	0.07-0.40	0.006
Latent class profile				
Normal	393	-	-	-
Low	108	-0.87	-1.10 to -0.67	<0.001
Medium	151	0.58	0.40-0.76	<0.001
High	26	1.40	0.98-1.70	<0.001

BMI: body mass index; OR: odds ratio; CI: confidence interval

when compared with the “low-slow” group (*P*≤0.026 for all). From diagnosis to 1 year post-diagnosis, the “high” group had the highest risk of obesity when compared to the “normal” group (*P*<0.001). The “medium” group had an increased risk of both overweight and obesity in survivors (*P*≤0.020), whereas the “low” group exhibited protective effects (*P*<0.001). For the association of overweight/obesity AUC with overweight and obesity in survivors, a larger overweight/obesity AUC derived from all models (from diagnosis to 5 years off-therapy, from diagnosis to 1 year post-diagnosis, and from diagnosis to end of induction therapy) showed a significantly increased risk of overweight and obesity in survivors (*P*≤0.012 for all) (Table 2). Across the BMI trajectory and AUC models, CRT and older age at SJLIFE assessment were significantly associated with an increased risk of both overweight and obesity (*P*≤0.007 for all) (Tables 1 and 2).

The BMI-PRS was available for 599 of the 678 survivors (88.4%). Higher PRS was associated with significantly greater odds of overweight and obesity in both trajectory models and all AUC models (*P*≤0.007 for all) (*Online Supplementary Table S3*). Even after adjusting for PRS, the associations of BMI trajectories and AUC with overweight and obesity risk remained significant.

Our findings showed that the prevalence of overweight and obesity increased steadily over survival time, from 16.4% at diagnosis to 63.3% at the first SJLIFE visit, which is higher than that in a previous meta-analysis (34-46% at ≥10 years off-therapy).[3] There were associations of BMI trajectories and overweight/obesity AUC with the overweight and obesity categories and BMI Z-scores in long-term survivors across multiple time frames. These associations, along with older age at SJLIFE assessment and CRT, remained significant even after adjustment for BMI-PRS, a powerful predictor of severe obesity. In the trajectory models, survivors in the “high-slow” and “high” categories, as compared with those in the “low-slow” and “normal” categories, respectively, had substantially higher obesity risks (odds ratios: 76.6 and 58.8, respectively) than were found in the healthy population, showing that obese children are approximately five times more likely than non-obese children to be obese adults.[6] Treatment factors, such as glucocorticoids, CNS-directed therapy, and a sedentary lifestyle may exacerbate weight gain during and after therapy.[3,15] AUC analysis further supported the trajectory models, showing that more extensive overweight/obesity - even during induction therapy alone - was associated with a higher risk of long-term obesity. CRT, especially at a younger age, was a major contributor to reduced adult height and increased BMI resulting from growth hormone deficiency and central precocious puberty.[5] The shift away from CRT towards intrathecal therapy in modern protocols is expected to reduce these effects.[1,5] However, even survivors of ALL treated without

Table 2. Association of host, treatment factors, and overweight/obesity area under the curve with overweight/obesity categories and body mass index Z-score in survivors.

Overweight/obesity categories in survivors							
Factor	**N**	**Overweight**			**Obesity**		
		OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Area under the curve (at diagnosis, end of induction, off-therapy, and 5 years off-therapy)							
Sex							
Female	328	-	-	-	-	-	-
Male	329	1.41	0.94-2.13	0.100	0.92	0.59-1.44	0.700
Attained age	657	1.07	1.03-1.12	0.001	1.15	1.10-1.20	<0.001
Race/ethnicity							
Non-Hispanic White	550	-	-	-	-	-	-
Non-Hispanic Black	73	1.41	0.69-2.89	0.300	-1.68	0.81-3.49	0.200
Hispanic, Asian, or other	34	1.01	0.44-2.31	>0.900	0.19	0.05-0.72	0.015
Cranial radiotherapy							
No	451	-	-	-	-	-	-
Yes	206	2.15	1.30-3.57	0.003	3.04	1.82-5.06	<0.001
Overweight/obesity AUC	657	1.28	1.15-1.43	<0.001	1.65	1.48-1.85	<0.001
Area under the curve (at diagnosis, end of induction, and 1 year post-diagnosis)							
Sex							
Female	338	-	-	-	-	-	-
Male	339	1.47	0.98-2.19	0.061	0.92	0.61-1.39	0.700
Attained age	677	1.07	1.02-1.11	0.002	1.12	1.07-1.16	<0.001
Race/ethnicity							
Non-Hispanic White	565	-	-	-	-	-	-
Non-Hispanic Black	77	1.45	0.73-2.87	0.300	1.75	0.90-3.39	0.100
Hispanic, Asian, or other	35	1.02	0.46-2.27	>0.900	0.28	0.08-0.90	0.033
Cranial radiotherapy							
No	464	-	-	-	-	-	-
Yes	213	2.08	1.27-3.41	0.004	2.90	1.80-4.68	<0.001
Overweight/obesity AUC	677	2.34	1.47-3.74	<0.001	4.55	2.90-7.14	<0.001
Area under the curve (at diagnosis and end of induction)*							
Sex							
Female	339	-	-	-	-	-	-
Male	339	1.54	1.04-2.29	0.033	0.98	0.66-1.46	>0.900
Attained age	678	1.06	1.02-1.10	0.005	1.10	1.06-1.14	<0.001
Race/ethnicity							
Non-Hispanic White	566	-	-	-	-	-	-
Non-Hispanic Black	77	1.56	0.79-3.06	0.200	2.04	1.07-3.87	0.030
Hispanic, Asian, or other	35	1.06	0.48-2.33	0.900	0.28	0.09-0.92	0.035
Cranial radiotherapy							
No	465	-	-	-	-	-	-
Yes	213	2.03	1.24-3.31	0.005	2.73	1.70-4.37	<0.001
Overweight/obesity AUC × 10	678	1.22	1.05-1.43	0.012	1.52	1.31-1.76	<0.001
BMI Z-score in survivors							
Factor	**N**	**β**		**95% CI**		***P***	
Area under the curve (at diagnosis, end of induction, off-therapy, and 5 years off-therapy)							
Sex							
Female	328	-		-		-	
Male	329	-0.10		-0.24 to 0.05		0.200	
Attained age	657	0.04		0.03-0.06		<0.001	

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BMI Z-score in survivors				
Factor	**N**	**β**	**95% CI**	***P***
Area under the curve (at diagnosis, end of induction, off-therapy, and 5 years off-therapy)				
Race/ethnicity				
Non-Hispanic White	550	-	-	-
Non-Hispanic Black	73	0.15	-0.08 to 0.38	0.200
Hispanic, Asian, or other	34	-0.34	-0.66 to -0.02	0.038
Cranial radiotherapy				
No	451	-	-	-
Yes	206	0.33	0.16-0.49	<0.001
Overweight/obesity AUC	657	0.14	0.12-0.15	<0.001
Area under the curve (at diagnosis, end of induction, and 1 year post-diagnosis)				
Sex				
Female	338	-	-	-
Male	339	-0.10	-0.24 to 0.05	0.200
Attained age	677	0.04	0.02-0.05	<0.001
Race/ethnicity				
Non-Hispanic White	565	-	-	-
Non-Hispanic Black	77	0.20	-0.04 to 0.43	0.100
Hispanic, Asian, or other	35	-0.32	-0.66-0.01	0.059
Cranial radiotherapy				
No	464	-	-	-
Yes	213	0.33	0.16-0.51	<0.001
Overweight/obesity AUC	677	0.43	0.36-0.51	<0.001
Area under the curve (at diagnosis and end of induction)*				
Sex				
Female	339	-	-	-
Male	339	-0.07	-0.22 to 0.08	0.300
Attained age	678	0.03	0.02-0.05	<0.001
Race/ethnicity				
Non-Hispanic White	566	-	-	-
Non-Hispanic Black	77	0.26	0.02-0.49	0.035
Hispanic, Asian, or other	35	-0.32	-0.66 to 0.02	0.062
Cranial radiotherapy				
No	465	-	-	-
Yes	213	0.31	0.13-0.49	<0.001
Overweight/obesity AUC × 10	678	1.20	0.97-1.50	<0.001

The total cohort comprised 678 patients. Sample sizes varied because of missing body mass index (BMI) data at certain time points: for the area under the curve (AUC) model from diagnosis to 5 years off-therapy (with BMI measured at diagnosis, end of induction, off-therapy, and 5 years off-therapy), N=657; for the AUC model from diagnosis to 1 year post-diagnosis (with BMI measured at diagnosis, end of induction, and 1 year post-diagnosis), N=677; and for the AUC model from diagnosis to end of induction therapy (with BMI measured at diagnosis and end of induction), N=678. *As AUC during induction were small, they were multiplied by 10 for analysis. CI: confidence interval.

CRT have demonstrated an increased obesity risk when compared to controls.[6] As the association between BMI AUC and survivorship obesity emerges as early as induction, preventive interventions by a multidisciplinary team including a dietitian, a physical therapist, a pharmacist, a social worker, child life specialists, and clinicians should begin during this phase.

This study has limitations, including potential selection bias from evaluating only survivors who completed an on-site visit and missing socioeconomic, environmental, or lifestyle data during therapy. Nevertheless, effect directions remained consistent after adjustment for CRT and PRS. Further prospective studies are warranted to minimize these confounders.

In conclusion, BMI trajectories and overweight/obesity exposure during ALL treatment and early survivorship are independently associated with long-term obesity in survivors. These findings support the implementation of early, multidisciplinary interventions - including nutritional counseling, physical activity promotion, and behavioral support- beginning as early as induction therapy to prevent or treat obesity in this vulnerable population.

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No conflicts of interest to disclose.

Contributions

KS, KKN, and HI conceived the study. KS, GCZ, DS, KKN, and HI contributed to the study design. KS, GCZ, NL, AN, KP, TY, JLB, PY, CLW, SBD, AD, YS, SCK, GTA, CHP, MMH, DS, KKN, and HI were involved in data acquisition, analysis, interpretation, manuscript editing, and review. GCZ and DS performed the statistical analysis. KS, NL, GCZ, DS, KKN, and HI prepared the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data-sharing statement

The SJLIFE data that support the findings of this study are openly available at https://www.stjude.cloud/research-domains/cancer-survivorship.

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