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Can Weight Gain Predict the Outcome of Childhood Leukemia?

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Abstract

Background: This study aimed to assess whether weight gain predicts the outcome of childhood leukemia.

Methods: This is a cohort study on patients with leukemia aged 2 to 19 years. Data was gathered by a form consisting of age, sex, baseline and final weight, height, Body Mass Index (BMI), and poor outcome (mortality plus occurrence). We used the Receiver Operator Characteristic (ROC) curve and the Area under the Curve (AUC) to define the cut-off points. Data analysis was performed in SPSS software version 19.

Results: 114 patients enrolled in the study, including 68 (59.6%) boys and 46 (40.4%) girls. Ten patients (8.7%) died, and 14 (12.2%) experienced a recurrence. Overall, 16 (14.1%) patients had poor outcomes. In this study, most patients had annual weight gain (95.6%), and all had height gain. AUC of weight and height gain at the diagnosis and the end regarding poor outcome were 0.672 and 0.718, respectively. The cut-off points of weight and height gain for poor outcomes were 1.2 % per month (14.5% annual weight gain, and 0.32 % per month (3.8% annual height gain), respectively. Besides, 60% of patients with weight loss had poor outcomes, and the results revealed that weight loss of more than 12% per year causes poor outcomes.

Conclusions: According to the results, weight and height gain during the treatment period can be related to a better outcome in children and adolescents with leukemia, irrespective of weight, height, and BMI at the diagnosis. Therefore, anthropometric indices may be associated with outcomes.

Key Words: Body mass index, Child, Height, Leukemia, Weight.

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1- INTRODUCTION

Cancer is uncommon in individuals younger than 20 years (1). Leukemia (incidence rate=8-62/million), lymphoma (incidence rate=3-23/million), and central nervous system tumors (incidence rate=2-22/million) are the most common cancers in children from 0 to 14 years old (1, 2).

Meanwhile, cancer is the second most common cause of death in children in developed countries. Based on incorporating precise diagnostic procedures and improvement of multimodal treatment strategies, the probability of cure is raised dramatically (3, 4).

In Iran, the incidence of childhood cancer is 48 - 112 and 51 - 144 per million among girls and boys, respectively (2). It is reported to cause 4% of deaths among under-five children and 13% among those with 5 to 15 years of age (5).

In the United States, more than 3000 new leukemia cases annually, accounting for 25% of all malignancies, are diagnosed in patients younger than 20 years. The prevalence of Acute Lymphoblastic Leukemia (ALL), Acute Myelogenous Leukemia (AML), and Chronic Myelogenous Leukemia (CML) are 75%, 20%, and <5%, respectively (6).

Although ALL is the most common cancer in childhood, its etiology in most patients is unknown (1). The overall 5-year-survival in 2011–2017 was reported as 84.7% in children and 85.9% in adolescents with cancer (7).

Obesity (body mass index (BMI) > 95th percentile) is a common health problem worldwide. The prevalence of overweight and obesity in the previous studies in under 18-year-old individuals was 3.2-11.9% (8). Aside from its well-known long-term complications, it may also affect cancer incidence and cure; however, the precise mechanisms that underlie this association remain elusive (9). To the best of our knowledge, despite the association between obesity and the relapse of certain adult cancers, limited evidence exists on its association with leukemia relapse in children (10).

Although the choice of appropriate risk-directed therapy is the most important prognostic factor according to the subtype of ALL, the initial white blood count, the patient's age, the rate of response to initial therapy, and the effect of BMI on treatment outcomes at diagnosis is controversial (1, 11-13). Therefore, this study aimed to assess whether weight gain predicts the outcome of childhood leukemia.

2- MATERIALS AND METHODS

2-1. Participants

This is a retrospective cohort study on records of patients with ALL aged 2 to 19 years who were diagnosed from January 2010 to January 2017 and referred to the 17 Shahrivar Hospital in Rasht, Iran. Data was gathered from June 2021 to June 2022. Patients were compared regarding their baseline characteristics and outcomes. Outcomes were categorized into successful treatment and death (either due to relapse or treatment-related mortality (TRM)) or relapse per se. Also, we compared good (survival) and poor outcomes (death and/ or relapse).

2-2. Procedure

Data were gathered by a form asking information regarding age, sex, baseline and final weight, height, BMI, initial White Blood Cell Count (WBC), immunophenotypes, outcomes, and Minimal Residual Disease (MRD) at the end of the remission induction phase. Weight was measured in light indoor clothing and barefoot or with stockings. Participants were weighed to the nearest 0.1 kg with an electronic scale (Girmi, Germany) calibrated daily at the beginning

of each working day. Height was measured to the nearest 0.1 cm with a tape meter in an erect, vertical position, with parallel feet and the shoulders and bottom touching the wall. Height and weight were used to calculate BMI (kg/m^2). We classified the z-score of BMI <-2, -2 - +1, +1 - +2, +2-+3, >+3 as wasting, normal, and at risk for being overweight, overweight, and obese (14).

Relapse was evaluated and defined as the return of more than 5% of lymphoblast in the bone marrow or localized leukemic cell infiltration at any site.

Initial WBC was divided into <50000 (standard risk) and ≥ 50000 (high risk). Using flow cytometry, MRD was indicated as negative or positive if the results of bone marrow assessment were <0.01 and ≥0.01, respectively. Immunophenotypes were reported as B-cell or T-cell acute leukemia based on the flow cytometry results.

2-3. Data Analysis

Data was analyzed using SPSS software version 19 (SPSS Inc., Chicago, Ill., USA). Data was reported by descriptive statistics including frequency, percent, mean, and standard deviation (SD). The Shapiro-Wilk test indicated the normality distribution of quantitative variables. Non-normally distributed quantitative variables were shown as a median and interquartile range [IQR]. T-test, Mann-Whitney U, chi-square, and Fisher's exact tests, as well as Spearman correlation coefficients, were used to analyze data. We used the Receiver Operator Characteristic (ROC) curve to define the cut-off points. P-value< 0.05 indicates statistical significance.

3- RESULTS

This study enrolled 114 patients, including 68 (59.6%) boys and 46 (40.4%) girls. The majority of patients were diagnosed at the age of 2-5 years. The mean duration of follow-up in patients was 38 months. **Table 1** shows the characteristics of patients at the diagnosis and end.

Ten patients (8.7%) died, and 14 (12.2%) experienced a recurrence. Overall, 16 (14.1%) patients had poor outcomes, including mortality and/or recurrence.

Meanwhile, 17.5%, 71.0%, 7.8%, and 3.5% of patients were wasting, normal, at risk of being overweight, and overweight based on z-BMI at diagnosis, respectively. No one was in the obese group. No significant association was found between z-BMI at diagnosis and poor outcomes (P=0.303) (**Table 2**).

In this study, 11% of patients had WBC count≥ 50000, 10.1% MRD≥0.01, 92.1% B-cell, and 7.1% T-cell phenotypes. There was no significant difference between the occurrence of the poor outcome in terms of WBC count (p=0.670), MRD (p= 0.149), and immunophenotyping (p=0.990). Also, assessing the poor outcomes based on z-BMI in the above mentioned variables was not significant (P> 0.050). In this study, most patients had annual weight gain (95.6%), and all had height gain. Although weight and height gain were significant in terms of mortality (P=0.040 and p=0.020, respectively), there was no significant relationship between increased BMI and mortality (P>0.050).

The AUC for the percentage of weight, height, and BMI changes from the diagnosis to the end due to mortality were 0.693, 0.721, and 0.633, respectively. The percentage of weight gain per month regarding death was 0.9%. The annual weight gain cut-off point was almost 12% (sensitivity=70.0% and specificity=70.3%, P=0.040).

The percentage of height gain at the diagnosis and the end per month regarding death was 0.32%. The cut-off point of annual height gain was 3.8% (sensitivity=67.3%, specificity=67.9%, p=0.020).

Table-1: Demographic characteristics and anthropometric indices at the diagnosis and end

Variable	N	Minimum	Maximum	Mean	Std. Deviation
Age at the diagnosis (years)	114	2.0	17.5	6.1	3.7
Age at the diagnosis (month)	106	22.0	211.0	72.7	44.1
Age at the end (years)	114	4.0	21.0	9.1	3.7
Age at the end (month)	98	55.0	226.0	104.0	40.5
Weight at the diagnosis	114	10.0	85.0	22.8	14.7
Z-score of weight at the diagnosis	114	-4.6	2.9	-0.3	1.2
Height at the diagnosis	114	80.0	179.0	114.9	23.6
Z-score of height at the diagnosis	114	-3.4	3.8	0.1	1.2
BMI at the diagnosis	114	10.8	39.1	15.9	3.6
Z-score of BMI at the diagnosis	114	-7.3	2.7	-0.7	1.6
Weight at the end	114	12.0	116.0	30.9	16.0
Z-score of weight at the end	114	-5.0	2.9	-0.3	1.4
Height at the end	114	98.0	189.0	128.9	20.2
Z score of height at the end	114	-4.5	3.5	-0.6	1.3
BMI at the end	114	12.0	40.1	17.5	4.1
Z score of BMI at the end	114	-4.6	2.8	-0.1	1.4
WBC count at the diagnosis	109	760.0	635000.0	33742.7	89523.3
MRD at the end	109	1.0	2.0	1.9	0.3

Table-2: comparing outcome results based on the classifications of zBMI.

Variable			outcome		P-value
			Good outcome	Poor outcome	
Classifications based on zBMI	wasting	number	18	2	0.303
		percent	18.4%	12.5%	
	normal	number	71	10	
		percent	72.4%	62.5%	
	At the risk of overweight	number	6	3	
		percent	6.1%	18.8%	
	Overweight	number	3	1	
		percent	3.1%	6.3%	
Total		Count	98	16	
		percent	100%	100.0%	

The AUC of monthly height gain at the diagnosis and the end regarding recurrence was 0.718. The cut-off point of annual height gain was almost 10.0% (sensitivity = 64.3%, specificity = 69.0%, P=0.008); but there was no significant relationship between the effect of weight gain and increased BMI on the recurrence (p>0.05).

The AUC of weight and height gain at the diagnosis and the end regarding poor outcome were 0.672 and 0.718 (p=0.020

and p=0.050, respectively). The cut-off point of weight gain for poor outcomes was 1.2 % per month (14.5% annual weight gain) (sensitivity = 75.0% and specificity = 60.6 %). The cut-off point of height gain for poor outcomes was 0.32 % per month (3.8% annual height gain) (sensitivity = 62.5%, specificity = 70.0 %). Besides, 60% of patients with weight loss had poor outcomes, and the results demonstrated that weight loss of more than 12% per year causes poor outcomes **(Fig. 1)**.

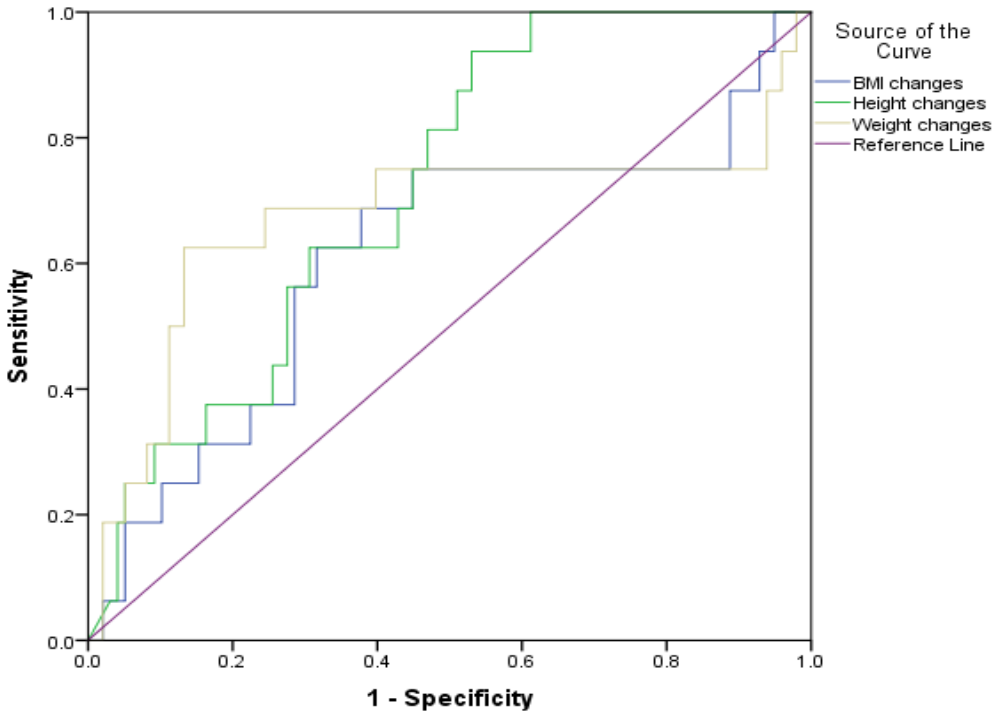

Fig. 1: The ROC curve regarding anthropometric indices for poor outcomes

4- DISCUSSION

ALL is a heterogeneous disease, and many genetic or environmental factors affect its pathogenesis, course, and outcome. Age and WBC at diagnosis, presence of certain cytogenetic abnormalities, immunophenotyping, and response to initial treatment are among the most important prognostic factors related to the outcome (15). As weight, height, and BMI might be considered factors affecting ALL outcomes (16-19), we investigated the relationship between changes in these anthropometric parameters and the outcome in children with ALL. In this study, 8.7% of patients died, and 12.2% experienced a recurrence. The cut-off point of annual weight and height gain for poor outcomes was 14.5% and 3.8%, respectively. Besides, 60% of patients with weight loss had poor outcomes, and it was revealed that weight loss of more than 12% per year causes a poor outcome.

In our study, most of the patients had normal weight, and only 3.5% were overweight, which was inconsistent with the study of Browne et al. They reported that about 25% of their patients at diagnosis were overweight or obese (20). Also, 17.5% of our patients were underweight, much lower than that reported by Guatemala. In that study, almost 54% of patients with ALL were

moderately or severely undernourished (21). These differences may be due to the sample size, patient cytogenetic features, eating habits, diversities between rich and developing countries (22), and ethnicity or race.

Our results showed no significant relationship between BMI status at the diagnosis and poor outcome. This finding was consistent with those of Aldhafiri et al. (23) and Hijiya et al. (24). On the other hand, Butturini et al. (25) indicated that being overweight (BMI>95%) is associated with poor outcomes. However, Orgel et al. (26) suggested that both overweight and underweight are predictors of poor outcome. Our result may be attributed to the low sample size and the fact that most of our patients (71.05%) had normal BMI. While Den Hoed et al. suggested that baseline BMI was not associated with the outcome due to small sample size in BMI subgroups or analyzing the impact of overweight on survival (27), a meta-analysis suggested that it may not be attributed to sample size, since significant or insignificant associations were observed in studies with both large and small sample sizes (10)**.** To address these conflicting results, it is prudent to organize a large multicenter prospective study covering various ethnicity/race populations.

We assessed this issue regarding the shortage of evidence on the effect of weight and height changes on the outcome. We found that gaining weight and increasing in height are associated with better prognosis; conversely, weight loss is associated with poor outcomes. Based on our findings, an average monthly 1.2% increase in body weight (14.5% annual weight gain) during the treatment period was associated with a good outcome. This finding should be interpreted with caution, especially in the underweight and overweight patients, due to the small sample size and few cases in the abovementioned groups and the fact that this study is retrospective. It is noteworthy to bear in mind that weight gain during the treatment period is related to many factors such as steroid therapy, socioeconomic status, and successful management of nausea and vomiting, psychological support, and procedures to inhibit or treat gastrointestinal disorders. Therefore, a considerable weight gain, at least in the normal BMI group, should be indicated as an indicator of successful leukemia management. As a rule, maintaining the growth and development of patients with cancer can and should exist during anticancer therapy (28).

We found that decreased weight also negatively impacts and may lead to a poor outcome. An average of monthly 1% decrease in body weight (12% per year) was associated with a poor outcome during the treatment period.

This result was consistent with those of the studies by Molly et al. (33) and Browne et al. (20). However, Barr et al. (36) showed that both weight gain and malnutrition reduced survival in children with ALL in low- and middle-income countries.

Chemotherapy per se, radiotherapy, periods of infection, nausea and vomiting, mucositis, and decreased liver protein synthesis after asparaginase administration lead to a catabolic state with nutrient depletion, exacerbated by decreased oral intake and subsequent micronutrient deficiencies. Interventions should be practical and used before the occurrence of malnutrition. In the case of malnutrition, interventions should be applied to treat the malnutrition and inhibit further recurrence. It has been indicated that weight loss of more than 5.0% from baseline weight needs proactive interventions; weight loss of more than 10% should be evaded and needs more serious nutritional intervention and close follow-up (28). However, this finding should be interpreted with caution,

especially in underweight and overweight patients.

We noted that a monthly increase in height, regardless of the height status, may prohibit poor outcomes. In other words, during a successful treatment, height gaining would not be affected significantly. In a study by Browne et al., height Z-scores decreased during treatment and improved after completion. They also noted that the growth spurt in adolescents could be affected by chemotherapy, which is more intensive for patients in higher-risk categories and those with higher WBC counts at diagnosis. This could result in a lower final height when compared with patients treated at a younger age. The frequent intrathecal chemotherapy given to patients with CNS disease at diagnosis and the CNS disease itself may have direct effects on linear growth, so they recommended addressing this risk of short stature. They also mentioned the importance of implementing early interventions by a multidisciplinary team, including oncologists, nurses, dietitians, physical therapists, psychologists, and endocrinologists, preferably starting from the remission-induction phase (29). Although a previous study indicated the common effect of IGF-1 on leukemia progression (30), our results showed that height gain is related to decreased mortality rate. This may be due to the impact of the nutritional regimen, minimizing the drugs' unwanted side effects and complications that allow the patients to have a relatively normal growth pattern. This finding should be interpreted with caution, especially in the underweight and overweight groups, due to the small sample size and few patients in underweight and overweight groups, and its retrospective design.

Preliminary studies have suggested that obesity may increase the likelihood of MRD-positivity by affecting the pharmacokinetics of drugs, which has been questioned in more recent studies (20, 22, 32, 34). In our study, there was no significant relationship between BMI and MRD status with poor outcomes. This is inconsistent with the results reported in a review by Molly et al., who showed that obesity and increased body mass profile were associated with increased morbidity, decreased survival rate, and increased risk of MRD positivity (33). Orgel et al. assessed 198 children with B-cell ALL and found that children with ALL who were overweight or obese at the start of treatment had increased MRD-positive, which contradicts the result of our study (32).

4-1. Strengths and limitations

Although we defined the cut-off points for weight and height gain based on the outcome, we had significant limitations. The main limitation of our study was the short follow-up period. As we had limited cases with poor outcomes, we only assessed patients with ALL, and we assessed patients retrospectively; further multicenter studies with larger sample sizes, including various ethnicity/races with different malignancies, are strongly recommended.

5- CONCLUSIONS

According to the results, weight and height gain during the treatment period would be related to a better outcome in children and adolescents with ALL, irrespective of weight, height, and BMI at the diagnosis. Therefore, anthropometric indices, either static (weight, height, and BMI) or dynamic (changes of these parameters during the treatment period), may be associated with outcomes in children and adolescents with ALL.

6- ETHICAL CONSIDERATIONS

Written informed consent letters were obtained from guardians or patients. Ethical approval was obtained from the ethics committee of the Vice-Chancellor of

Research at Guilan University of Medical Sciences (Number: IR.GUMS.REC.1400.092, Date: 2021-06-02).

7- COMPETING INTERESTS

None.

8- AUTHOR CONTRIBUTIONS

Adel Baghersalimi, Afagh Hassanzadeh Rad, Bahram Darbandi, and Setila Dalili contributed to the study of conception and design. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by Adel Baghersalimi, Afagh Hassanzadeh Rad, Shahin Koohmanaee, Bahram Darbandi, Rouzbeh Alishahi, Seyede Tahoura Hakemzadeh, Amir Mohammad Ghanbari, Setila Dalili, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

9- DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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